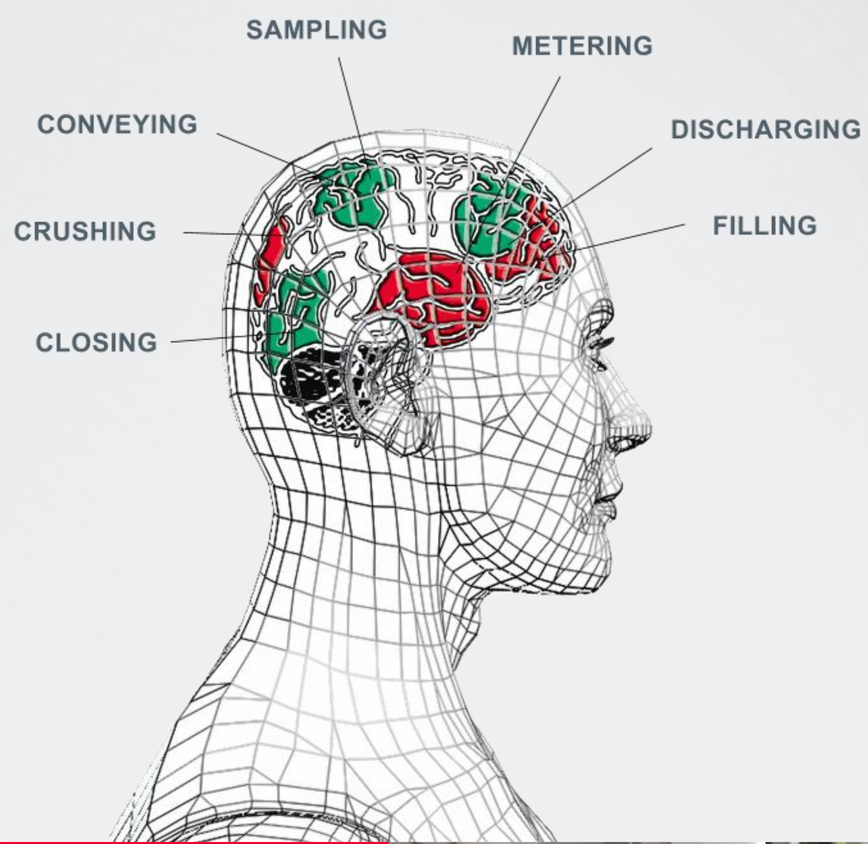
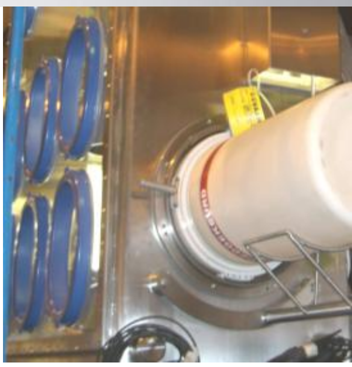


REPORT 02



Total Containment of highly potent or extremely hazardous Substances in the Production of Active Pharmaceutical Ingredients

HECHT technologie

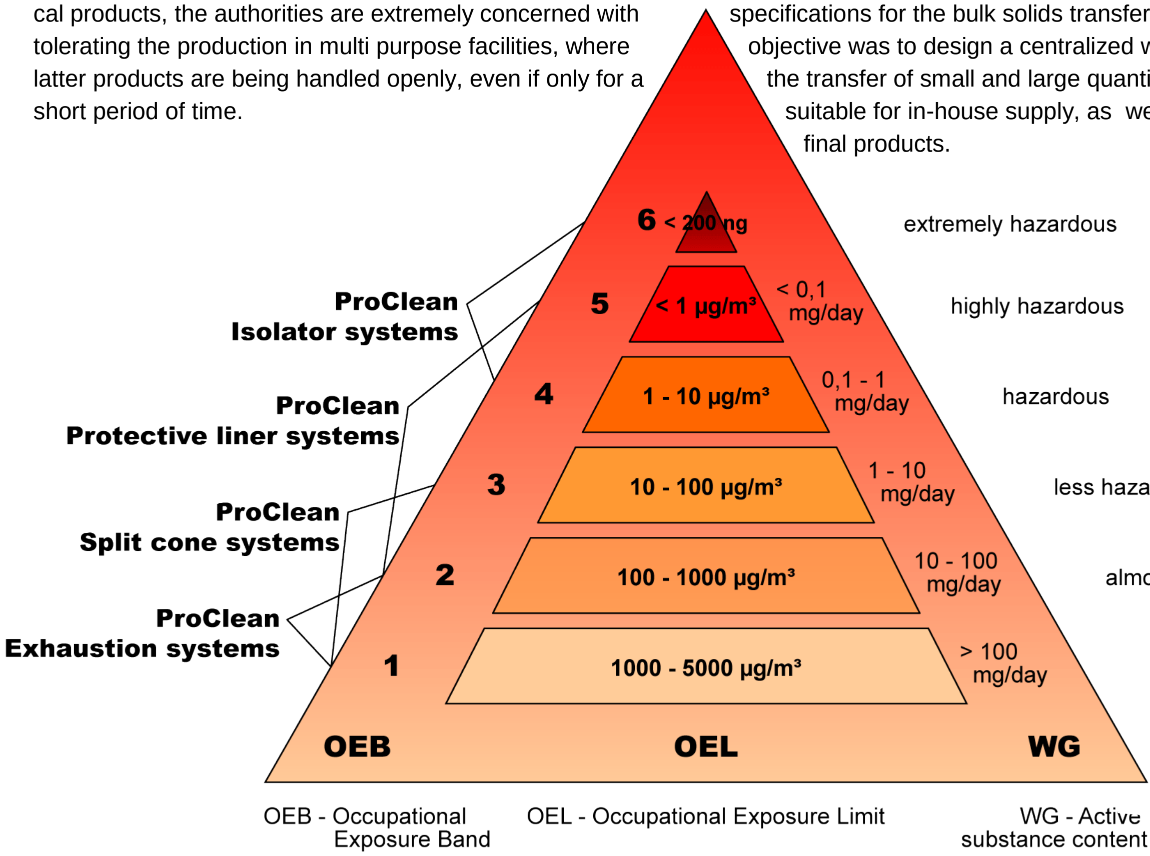
Product and operator protection

An active pharmaceutical ingredients (API) manufacturer rises to the challenge of production and handling of API and implements a flexible containment solution, together with HECHT.

Due to the increasing number of products in the API and pharmaceutical industries that are classified as high potent or high risk, the authorities are more demanding in terms of product and operator protection. Especially in the production of cytostatic and teratogenic substances, antibiotics and other critical products, the authorities are extremely concerned with tolerating the production in multi purpose facilities, where latter products are being handled openly, even if only for a short period of time.

Customised solutions by HECHT

The expansion process involved the development of technology that was specially tailored to the customer's needs. The fact that the API manufacturer was unable to find the appropriate technology on the market led to HECHT Technologie GmbH to be commissioned to develop an appropriate containment system. The maximum Occupational Exposure Limit (OEL) was defined at 370 nanograms/m3, the maximum batch of product was set at 350 kg. Along with the client, requirement specifications for the bulk solids transfer were developed. The objective was to design a centralized weighing system for the transfer of small and large quantities into bundles, suitable for in-house supply, as well as weighing the final products.



HECHT Containment Pyramid

The cleaning of equipment in multi-purpose facilities constitutes another challenge. To be equipped for the production of highly hazardous substances, it was a priority of the API manufacturer to be provided with the utmost degree of flexibility and containment (closed systems). Together with HECHT, they had already been able to gain experience in the field of API containment before, when they had implemented the initial stage of expansion of the manufacturer's facility. The cleaning and maintenance, as well as the enormous servicing costs for the containers posed another challenge.

The production facility consisted of a total of six reactors, which were supposed to be charged in three separate rooms. After the drying process, the substances needed to be filled into a safe container. The different concepts were evaluated in a matrix using carefully generated risk assessments. After two months of preliminary planning, the decision was made in favor of FIBCs to be the suitable containers. These FIBCs were custom-made with specially designed inlet and outlet connectors to be safely coupled with the isolators.

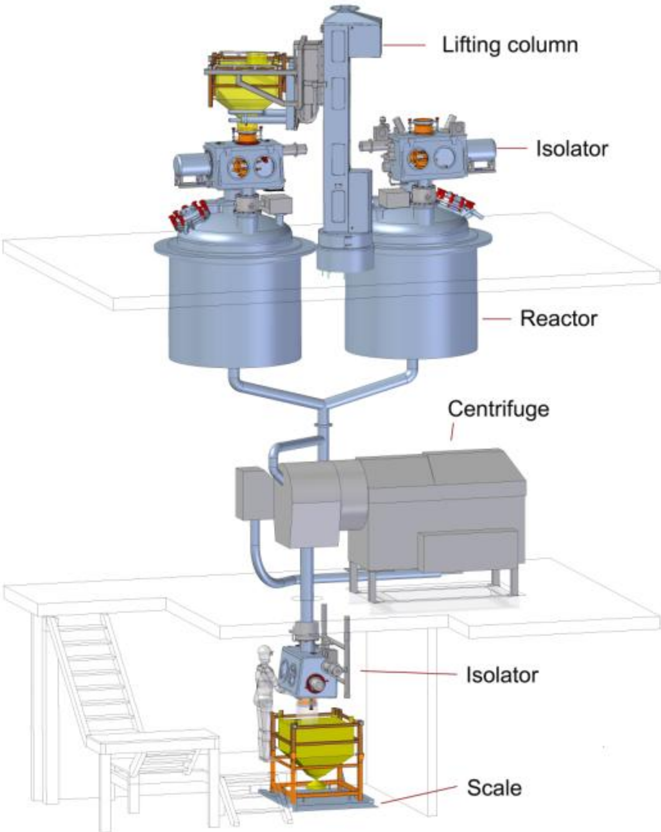
Flexible containment solution using FIBCs

The decision to use flexible single-use systems (i.e. FIBCs) proved to be the correct decision throughout the entire project. The crucial reasons were:

- The product output from the FIBC is guaranteed, even with products that display poor-flow characteristics.
- FIBCs do not have to be cleaned after use, as they are only used as single-use systems.
- Acquisition of FIBCs means lower prices compared to the costs of cleaning rigid receptacles, e.g. containers.
- When using FIBCs, there are no costs that come up for maintenance and repair.
- FIBCs use up less storage area compared to other receptacles.

The deployed FIBCs consist of an outer liner and a dual anti-static foil inner liner. A crucial point in the development of this innovative containment technology was to allow for the FIBCs to be filled and emptied in a contained manner. Extensive tests followed to determine the design of the FIBCs. To comply with the OEL of 370 nanograms/m^3, it was decided to add a second inner liner connection piece to both the inlet and outlet systems of the FIBC. These specifically designed FIBC inlet and outlet systems are connected using isolator technology.

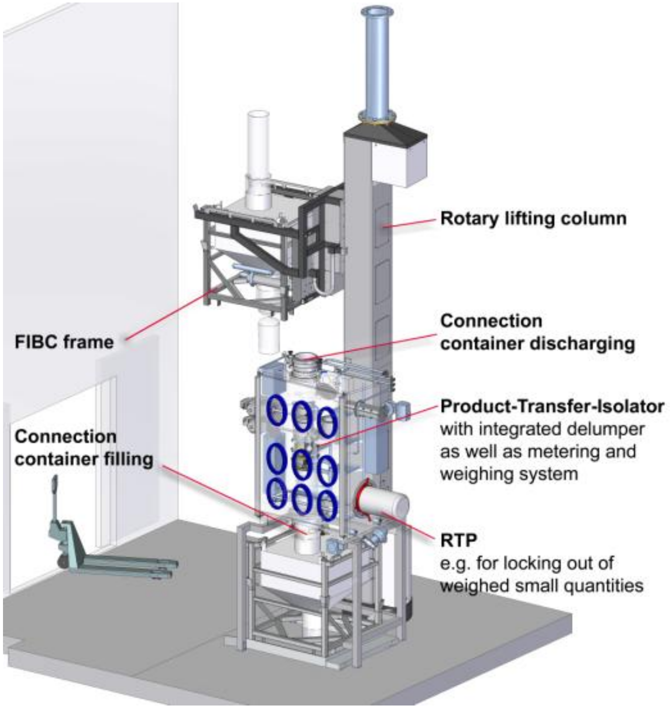

FIBC in a frame



Overview of production facility


API production facility

Transfer



Isolator for transferring the product into various containers

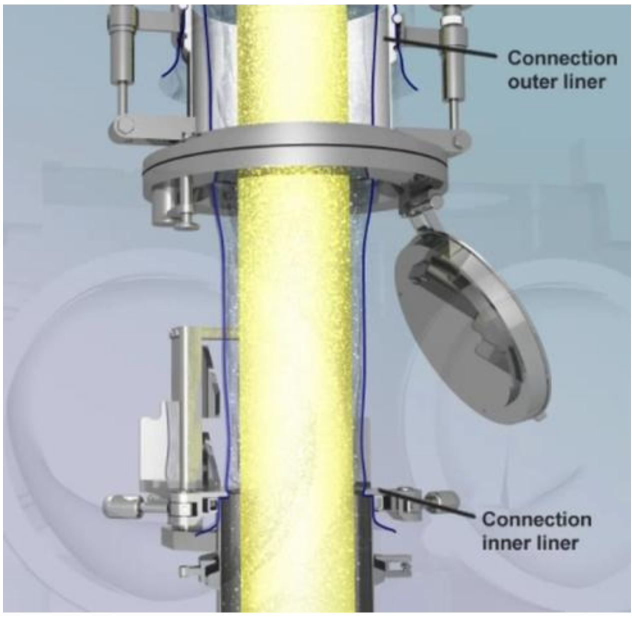
A product transfer isolator was installed in the transferring room. This isolator transfers the final product from the production plant into smaller intermediate containers, which are then hauled to the pharmaceutical production company for formulation. The product transfer isolator is also used to transfer the product from one intermediate container (i.e. FIBC) into another intermediate container (i.e. FIBC). This transfer is necessary due to the fact that the dryers have to be completely evacuated, and only the actual product is registered in the intermediate container (FIBC). Subsequently, the exact quantity for the next production step is provided by the transfer isolator in another intermediate container (FIBC). In order to perform all these tasks with the transfer isolator, a wide variety of features had to be integrated:

- A product metering system for weighing both large and the smallest of quantities. For weighing small and extra small quantities, a weighing system had to be integrated into the isolator. For filling larger quantities in to FIBCs, a scale was installed, located underneath the isolator.
- A communition system was required in the isolator, in order to be able to break up product agglomeration, to allow further dosage.

In order to provide maximum flexibility, all features had to be modular. Both the metering system and the communition system had to be exchangeable, to guarantee flexibility for product changes or varying product characteristics.

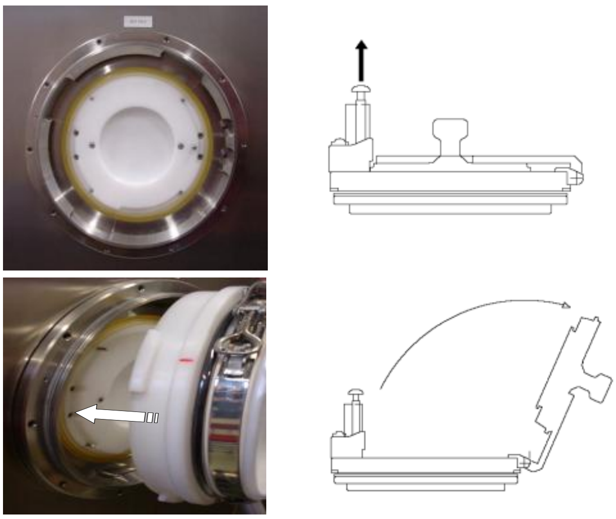
Customised solutions by HECHT

To connect the exterior outer liner of the FIBC, a connection adapter was installed in the upper area of the isolator. The inner liner (product liner) is connected from within the isolator.



HECHT patented solution: docking the FIBC with two liners to the isolator

The isolator is protected through a RTP (Rapid Transfer Port) from inside out.



RTP (Rapid Transfer Port)

Similar to the discharging process, the same technology was used for the filling process of the FIBCs underneath the product transfer isolator - only in mirror-inverted version. The RTP is used to lock components in and out of the isolator. For the filling of smaller quantities, a scale for small quantities is locked in through the RTP to enable the product to be weighed and filled it into small bags. Furthermore, a container is docked to the RTP in order to remove the packed bags from the isolator and to transfer them safely to the pharmaceutical production facility for further processing. A small mobile carriage inside the isolator is used to slide the sealed product bags into the canister that is attached on the side of the RTP.

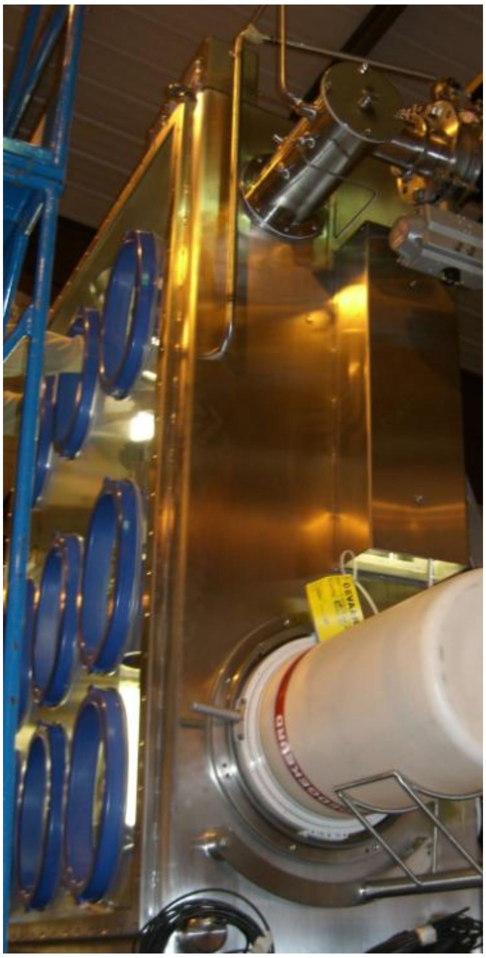
All parts in the isolator have to be easily removable. The weight of each component is limited to 10kg, the size and construction of each part must allow for safe handling from and to the RTP port, using the gloves attached to the isolator. The RTP port sets the standard for the maximum size of each component used. The maximum diameter of any component must not exceed 350mm to ensure that they fit through the RTP into the canister for locking out. All drivers (metering system and communition) are located outside the isolator. For this purpose, plug-in connections in hygienic design are attached at the rear side of the isolator. To meet all these requirements, computerized feasibility studies, as well as other intensive studies were carried out, using both 3D models and models for testing with operating personnel. Different body heights of the personnel had to be considered to ensure convenient access to the isolator. Accordingly, a height-adjustable operating platform was provided, that allowed all procedures to be accurately and ergonomically executed. This meant that all gloves of the isolator were accessible for all operators, regardless of height. For security reasons, the platform was framed with safety glass. This enabled the operator, as well as other personnel from outside the room, to have a clear view on the isolator.

The isolator is also fitted with cleaning nozzles and additionally integrated hand spray guns. The position of the nozzles was specified using computer software. The corresponding CIP system (Clean In Place), together with the tubing for the cleaning medium and the drying air, was planned and supplied. The unit was installed outside the room in the technical department. The drainage for the cleaning fluid is located at the bottom area of the isolator.

The FIBCs used for the transportation of the products are provided in frames and kept ready for further use. The frames are utilized for better handling of the flexible containers using manual lift trucks, as well as for damage protection during handling.

The frame also features a pick-up and positioning device for the FIBC to be elevated using a lifting column. For easier connection of the FIBC outlet system to the isolator, the frame is split in two parts. This has the benefit that only the top part of the frame, with the FIBC attached, is lifted, whereas the bottom part remains on the ground. This offers more space to operating personnel when connecting the FIBC outlet to the isolator.

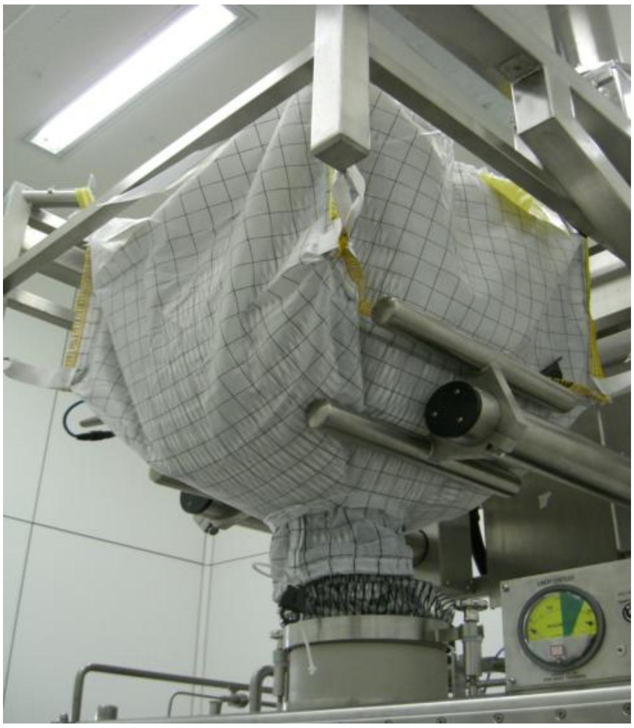
The FIBC is then lifted up to the connection adapter of the isolator, using the lifting column that is mounted alongside the isolator. The lifting column is equipped with a pneumatic massaging mechanism, to be used with poor-flowing products. This mechanism can be adjusted in height. The height adjustment comes to use when flexible containers deform during discharging, meaning that the pneumatic massaging mechanism must be readjusted. The lifting column had to be manufactured from stainless steel, due to the frequent cleaning of both the equipment and the work space.



Product Transfer Isolator

API production ranging from charging the reactor to discharging the dryer

Charging a reactor using a lifting column



FIBC connected to isolator for discharging

A total of six reactors are installed in the production facility. One compartment respectively contains two reactors. For the process of filling, each reactor was equipped with an isolator. To protect the connection from the isolator to the reactor (pressure tightness, smooth product flow and solvent-resistant), a specially designed ball segment valve was installed.

A central lifting column is located between two reactors, that lifts the framed FIBCs and places them on top of the respective isolator. Similar to the design in the transfer room, the lifting column is equipped with a pneumatic massaging mechanism to ensure secure and accurate discharging, even when handling products with poor flow characteristics. The connecting systems for docking the FIBC outlets are identical to the systems used in the transfer room. As a result of the mock-ups conducted prior to the installation of the equipment, the size of the isolators was kept to a minimum to allow for simple and fast cleaning. Additionally, a hygienic metering rotation flap was installed to discharge the product in a controlled manner.

Discharging a dryer into FIBCs

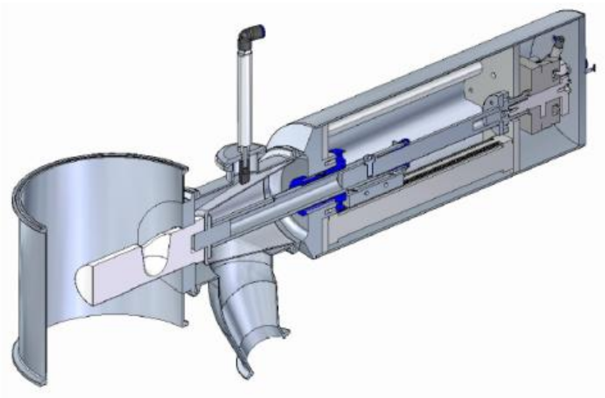
Another isolator, that is used for charging the FIBCs, is installed underneath the dryer. The same method as for discharging the FIBCs was used. Since the FIBC filling system is located one level below the dryer, the isolator was installed as close as possible to the dryer outlet. This does not only minimize the product drop height, but also simplifies the cleaning of the down pipe. It was important to reduce the size of all parts to be cleaned to a minimum, even if additional equipment had to be used.

As a result of the short down pipe, staff was not able to operate the isolator from the ground anymore. Furthermore, the FIBC had to be lifted in order to be connected to the isolator outlet. Therefore, an operating platform became necessary for the operator. For the precise positioning of the FIBC, a lifting column, with a loading platform for the frame was installed underneath the isolator. The lifting column lifts the loading platform with the empty FIBC already in place, and moves it in position for connection. A weighing unit was integrated in the loading platform to allow for the FIBCs to be weighed after filling.

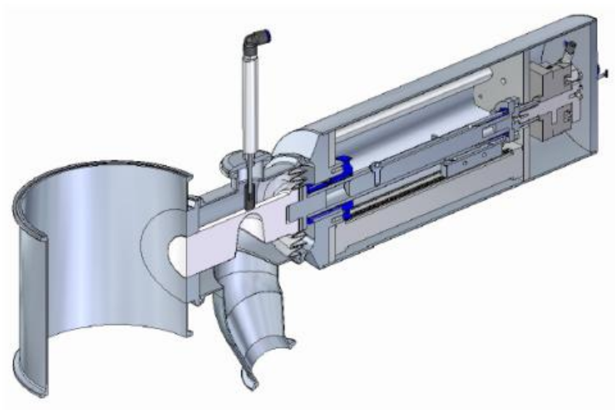
Filling a FIBC connected to an isolator

Integrated automatic sampling

Automatic and validated sampling was required during the process of discharging the dryer. Therefore, a sampling system was installed in the down pipe. For product extraction, the sampling system contains a small pan that is moved into the down pipe using a positioning unit. Once the sample pan is filled, the unit retreats into the sampling system and, with a rotation of 180°, empties the content into a sample container located in the isolator. This process is repeated until the sample container is full. The filling of the pan is controlled by the discharging process of the dryer. This allows for selective sampling, which reflects a representative cross-section of the entire product in the FIBCs. The sampling system also features an integrated cleaning unit.



Taking samples



Dropping samples

FAT with measurement of the Occupational Exposure Limit

Measuring room

During the planning of the project, preparations were made to test the engineered systems in a Factory Acceptance Test (FAT) and to verify the specified Occupational Exposure Limits (OEL). A lactose free environment had to be set up in the final assembly hall, in order for the measurements to be conducted according to the ISPE-SMEPAC-baseline guide. Lactose is listed as a reference product in the ISPE baseline guide. The installation conditions resembling those of the projected API factory were simulated using a wooden construction. The wooden structure was surrounded by another wooden construction, constituting the measuring room. After all components had passed quality control and various performance tests, the wooden construction was sealed with foil. All openings, for example cable feedthroughs, were sealed. After that, the ventilation unit was connected. As described in the ISPE guidelines, multiple air exchanges had to be conducted inside the measuring room, using H14 (HEPA14) filtered air. An airlock was also installed, where operators had to put on protective clothing before entering the measuring room, to prevent any lactose contamination from the outside into the measuring area. The equipment inside the measuring room was cleaned using purified water.

Two rooms were built altogether. One room with two isolators represents the compartment for charging two reactors, the other room is used for discharging the dryer. After the rooms had been cleaned thoroughly, no personnel was allowed entry before measurements started.

A surge drum was installed on top of the room in order to be able to fill the lactose into FIBCs. The discharging system for the FIBCs filled with lactose was established outside the final assembly hall to prevent contamination inside the building. Before measurements were launched, the lactose was transferred into the surge drum using a pneumatic conveying system. The surge drum served as a dryer.

The measuring process was documented using video recording. According to the ISPE guidelines, IOM-Samplers were used. These samplers were positioned close to the operator's respiratory system, on the operator's gloves, on the filters in the isolator at both docking stations and in the room itself. The first measurements were conducted without any lactose in use, in order to be able to measure the concentration of lactose at hand. Afterwards, three consecutive measurements with the lactose stored in the surge drum were carried out. The FIBCs filled with lactose were then transported into the other room for discharging. After that, the same measurements were conducted. After all measurements were carried out, critical areas in each compartment were tested using wipe tests, in order to document any lactose deposits on the different surfaces. Thereafter, all samples were sealed and sent off for analysis to a laboratory in the US, which, at the time, was the only laboratory that could analyse lactose with an OEL of up to 5 nanograms/m^3. The results that were received after six weeks exceeded all expectations. Almost all samples were below the limit of 5 nanograms/m^3, meaning an OEL of less than 100 nanograms/m^3 for the operator (see test record).

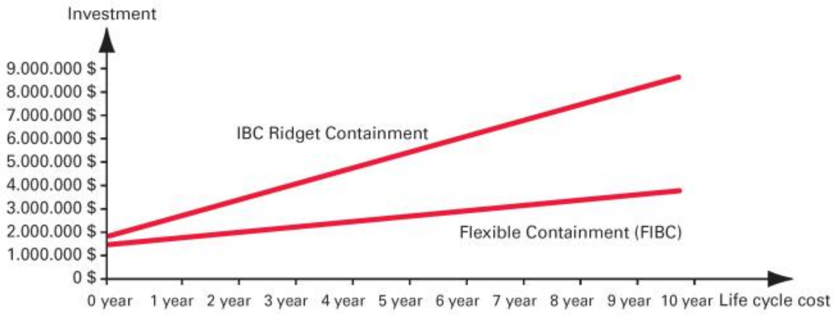
Monitoring point

Custom-made FIBCs provide High Containment

The FIBCs, designed and engineered by HECHT Technologie, are the result of a nearly two-year-long study, conducted on adequate container systems to be used for the API industry. The inner liners used in the FIBCs meet the CFR (Code of Federal Regulations) and thus are in conformity with the FDA, meaning they are electrically conductive and resistant to most commonly used solvents. Furthermore, the FIBCs were examined using a patented foil-welding method and found to be 100% leak proof. This ideal solution allows to fill, discharge and transport even the highest of hazardous substances in the safest way possible.

Exemplary planning reduces overall planning and manufacturing costs

On the basis of end-to-end planning from one source, acquisition costs could not only be reduced dramatically, in contrast to the costs estimated by the client, but implementation and installation were also completed earlier than scheduled. The fewer instances involved in planning a containment facility, the more efficient and cost-effective the performance. No information is lost between the client and the planning administrator, and fewer or no errors are being made. This is due to the direct communication between the expert and the client, where the overall plant concept is thoroughly reviewed. The planning and implementation costs originally calculated by the client had been undercut by about 30%.



Comparison of the total investment and life cycle cost

Task	Sample Location	Sample Number	Flow Rate (l/min)	Sampling duration (min)	Sample Volume (litres)	Loading (ng)	Atmospheric Concentration (ng/m^3)
Test 5: Background before charging	Beside collar that attaches to FIBC	25008446	2.00	41	82.0	10	122
	Beside HEPA port	25008389	2.01	39	78.6	7	87
	On top of control panel	25008398	1.99	40	79.7	9	109
Test 6: Charge 1 (101kg)	Personal – Wolfgang Holzer	25008447	2.00	55	110.2	<5	<45
	Beside glove port	25008457	1.99	55	109.3	<5	<46
	Beside collar that attaches to FIBC	25008408	2.00	55	109.9	<5	<45
	Beside HEPA port	25008385	1.99	55	109.6	<5	<46
	On top of control panel	25008422	2.00	54	107.8	<5	<46
Test 7: Charge 2 (91kg)	Personal – Wolfgang Holzer	25008415	1.99	64	127.4	<5	<39
	Beside glove port	25008410	2.00	65	129.8	7	55
	Beside collar that attaches to FIBC	25008472	2.02	65	131.2	<5	<38
	Beside HEPA port	25008432	1.99	65	129.2	<5	<39
	On top of control panel	25008460	2.01	65	130.9	<5	<38
Test 8: Charge 3 (84kg)	Personal – Wolfgang Holzer	25008465	2.02	48	96.8	<5	<52
	Beside glove port	25008413	2.01	48	96.4	<5	<52
	Beside collar that attaches to FIBC	25008463	2.01	48	96.7	<5	<52
	Beside HEPA port	25008431	1.97	48	94.9	7	70
	On top of control panel	25008474	2.03	48	97.5	<5	<51
						Target Concentration	370

Test record

MASCHINEN • SYSTEME • IDEEN

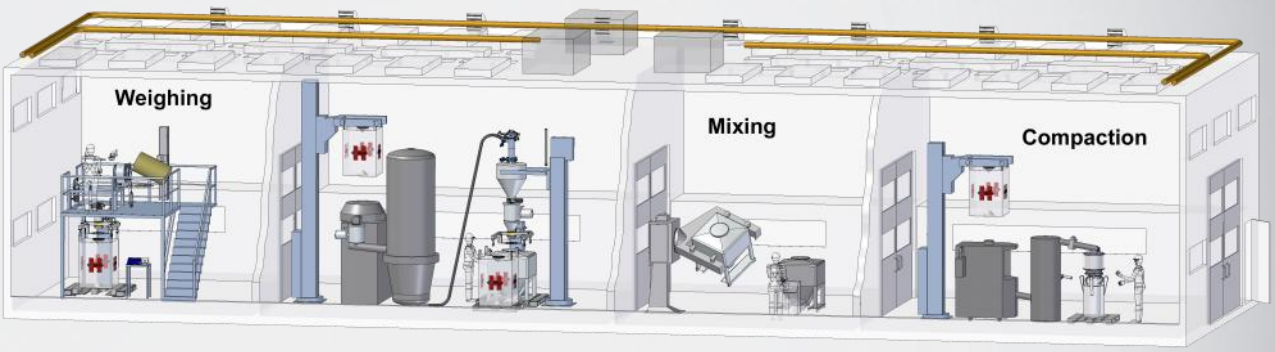
Additional Containment Solutions by HECHT

High-Containment **Liner Connection System LAS** for the discharging of FIBCs

Containment Sack Discharging Station with endless-liner-ports for contamination-free discharging of sacks

Modular Filling Station with endless liner for clean and safe filling into small containers

Flexible **Expendable Weighing Isolator EWI** for transferring and weighing small quantities



Planning, providing and installing complete containment solutions - from one source

Alongside single components, HECHT is, on the basis of many years of experience and know-how in the field of containment, your competent partner for complete solutions of various processes in the chemical, pharmaceutical and API industry.

Status: 10/2011

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