

Excellence In A Small Space



Centocor Schaffhausen Creates An Advanced Fill Finish Pilot Plant Facility In A Tight Spot

By Mike Auerbach, Editor-In-Chief

Several years ago, after determining it would not have enough manufacturing capacity to meet the future needs of its growing pipeline, Centocor in Switzerland embarked on an ambitious plan to design and build a new vial and syringe filling facility at its Schaffhausen campus.

The design, construction and integration into the existing campus has earned the company a coveted category award for Facility Integration in the annual Facility of the Year Award (FOYA) program and has put it in the running to win the overall award announced in November.

The FOYA program, sponsored by ISPE, INTERPHEX and Pharmaceutical Processing magazine, recognizes and rewards outstanding facilities from around the globe. Six facilities are selected as winners in individual categories and the overall winner is announced at ISPE's Annual Meeting in November.



WHO IS CENTOCOR AND WHAT DO THEY DO?

Centocor Inc. is a US based, wholly owned subsidiary of Johnson and Johnson. In Schaffhausen, Centocor R&D is a division of Cilag AG and is responsible for fill finish operations and analytical testing of clinical supplies, for tech transfer activities, and for marketed product support to the commercial plants.

The new R&D fill finish plant replaces an older existing facility and offers a state-of-the-art technology portfolio that mirrors the set-up of commercial facilities to ease process comparability and scale-up. The facility strengthens the strategic focus of the Johnson & Johnson global biological supply chain for clinical material and marketed products.

Centocor R&D and Cilag's team approach is one of the main reasons why the facility has been so successful as

Equipment operators were trained as Subject Matter Experts (SME's). This enabled Centocor to realize efficiencies and cost savings through subsequent reductions in equipment support staffs.

Claudio Thomasin, Ph.D, Director BIO PD EU Drug Product Tech Support, at Centocor R&D Schaffhausen explains, "The excellent team work and also the management support and guidance from over the pond was certainly one of the highlights. Considering the fact that the team had to juggle two balls in parallel - manufacturing clinical supplies in the old pilot plant whilst designing, building and qualifying in parallel a brand new facility - points to the commitment, expertise and accountability of the crew."

This project was no small task as evidenced by Centocor's list of "musts" for the new facility:

- An R&D dedicated plant, fully integrated into the Cilag site campus and linked to commercial operations, QC testing and development labs and offices.
- A facility shell construction to allow addition of subsequent levels.
- High level of autonomy for utilities to minimize dependency from commercial plants and downtime schedules.
- Install fill finish equipment in a way that avoids duplication with other Johnson & Johnson plants while providing flexibility to integrate new technology to meet future needs (e.g. combination products).
- Provisions made for contained infrastructure supporting manufacturing of high potent compounds up to class OEL-3A.

- Good fit with the scale-up rationale and process comparability from lab to late stage development and commercial production.
- Integrated automation concept to minimize different types of software/hardware architecture and Human Machine Interfaces. Avoidance of complex SCADA systems to the best extent possible.
- Leveraging of existing freeze drying process equipment in old plant.
- Leveraging of campus quality standards and validation approaches.
- In-parallel phase-in/phase out concept from old facility to maintain robustness of the clinical supply chain.

TURNING A PLAN INTO A FULLY FUNCTIONAL FACILITY

To meet its needs for more capacity and incorporate its list of "must haves" Centocor constructed a new 670 m² fill finish pilot plant facility (F2P2) on its campus. This facility produces biological drug products for early- and late-stage clinical trials and also plays a key role in the transfer of fill finish operations into a commercial plant, also located on the Schaffhausen campus.

With its capability for compounding and final formulation, vial and syringe filling, and lyophilization, this highly



Above: Glove ports for the syringe line are integrated into the clean room wall; the human machine interface (HMI) displays process and environmental data for operators inside the clean room.

Right: Semi-automated loading of the freeze dryer under laminar airflow.

integrated facility provides flexibility for new product development and clinical manufacturing, as well as an efficient operational platform. The F2P2 was designed and built in a way that maximizes interactions with other key groups such as Quality Assurance, Quality Control, and commercial manufacturing.

As in many projects where new facilities must be integrated with existing facilities the company faced some challenges. One of the main challenges was the space limitations imposed by the existing buildings and their structure. While this may have posed a challenge to some, to the team at Centocor it was an opportunity for innovation, as Thomasin explains, "Most of the filling lines were integrated into the clean-room walls to save space and to provide access for maintenance outside the aseptic core. The Vaporized Hydrogen Peroxide material locker was sized and installed in a way that flexible machinery such as the syringe denester could be wheeled-in and out from the aseptic B-grade corridor. The lyophilizer loading room was designed as a classical clean-room allowing us to conduct manual fills or other aseptic activities based on less frequently used technologies, for example in the exploratory

device area. The new building was interconnected by a hallway with the adjacent one, to keep offices and labs as close as possible to the manufacturing site, and, given the height restrictions of the clean rooms, most of the HVAC infrastructure was installed in the basement of the building."

LIKE FITTING THE PIECES OF PUZZLE TOGETHER

The design of F2P2 posed a challenge to the company, as it required the integration and installation of many high-tech processes in a comparatively small space. The project team realized early on that while the design might look good on paper, it might not work in "real life". To assuage any fears, the decision was made to do a facility mock-up study. This effort was initiated once the preliminary layout approached its final stage for approval and prior to starting construction of the clean room and building services.

The purpose of a complete facility mockup study was to cover the entire manufacturing process at actual scale in order to anticipate unforeseen difficulties and design flaws. As Thomasin explains, this study was important for two reasons: "First, it provided the necessary comfort level to the end-user that the layout on paper will work on a day to day basis later on as well. Since everyone was concerned about the limited space, the early mock-up was "psychologically" important to get the voice of the customer to the engineering department. Second, some design flaws, for example the opening of doors, size of interlocks to wheel in and out equipment without bumping into the walls or the position of benches to allow a logical material and process flow could be corrected right at the beginning."



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AUTOMATION AND EXPERTISE - KEY TO EFFICIENT OPERATION

A number of features enable the facility to be run efficiently and with a limited staff. Automation of process equipment, data acquisition and documentation retrieval all contribute to this. A single automation architecture for all process equipment and utilities simplifies running the various systems. As Thomasin further explains, balancing automation and flexibility can be a challenge, "In general, a high automation level was put into well standardized processes such as vial or syringe filling and into labor intense activities such as cleaning and sterilization, whereas non-routine operations were designed with less automation efforts.

tors in as many aspects of the building fit-out and of process technology design and implementation. Thereby, they could gradually take over ownership and help tailor the facility to their needs. This concept ensured a high level of autonomy and minimized the dependency from support functions for troubleshooting. It ultimately added to developing everyone's skill-set and to establish a pool with broad expertise within their own department."

A FACILITY TO BE PROUD OF

When asked what specific details or features he's most proud of Thomasin gets right to the point. "Condensing a broad platform of parenteral manufacturing technologies into one single facility is certainly very attractive. Also, responding to the flexibility needs of a changing R&D environment while maintaining at any time the highest levels of aseptic quality, and being asked to combine RABS technology, VHP room decontamination and classical clean room features into one footprint is certainly an accomplishment to be proud of. We are particularly pleased by this smart approach."

REASONS FOR WINNING

Finally, when asked his opinion as to why the FOYA judges chose his facility, Thomasin has this to offer, "We think we did very well in integrating a multi-product and multi-format R&D fill finish facility into a crowded campus while ensuring the shortest distances to the commercial facilities and to existing analytical buildings. The building shell was constructed in a way allowing future expansion on another three levels. Besides, we managed to map all relevant technologies for aseptic processing into the new facility to ensure perfect scalability, process comparability and tech transfer conditions to the commercial plants on the campus. The design was supported by computer simulations for airflow and particle distribution- thereby reducing the risk of inappropriate clean room conditions after building erection. Finally, we limited the complexity of automation whilst keeping labor intense operations at minimum. Operator safety was equally important and was an integral design prerequisite for all machinery and processes."

On the other hand, we wanted to keep the automation concept as flexible as possible for process adaptation and 'last minute changes' of manufacturing parameters. Equally important was to build a standard architecture with the same PLC's and operator panels to allow personnel operating as many equipment as possible with the same process visualization features thereby minimizing training efforts and errors.

To ensure equipment operators were as well trained as possible, the Centocor team embarked on a program to train them to become Subject Matter Experts (SME's). This tactic was of key importance to the project as Thomasin explains, "Given the constraint in resources it was key to engage opera-