A Case Study

Building the Future: Using Simulation Effectively

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Baxter's BioPharma Solutions facility in Halle/Westfalen, Germany manufactures primarily cytotoxic and highly potent drugs, with over 60 years of experience supplying to global markets from this site. Baxter works closely with SafeBridge, and is the only company worldwide with facilities certified by SafeBridge doing both parenteral drug substance synthesis and parenteral drug product manufacturing and testing. SafeBridge verifies how high-potent drugs are handled to ensure that operator safety and environmental safety are a high priority in the development of processes and manufacturing processes.

This case study provides an in-depth look at Baxter BioPharma Solutions' latest expansion at their Halle, Germany cytotoxic facility, offering insight on:

- Handling of complex expansion projects
- Elements of process design
- Application of different simulation and visualization tools
- Innovations for manufacturing of parenterals
- Effective team building

Process Design: Simulation and Visualization of Core Processes

A typical process to be performed at the approximately 2,000-square meter Halle/Westfalen Facility expansion involves four main steps: compounding, filling, lyophilization (more than 80% of the products are lyophilized), and unloading. There are two filling areas, one for small-scale products (500 milliliters up to 350 liters) and the other is optimized for a maximum throughput (50 liter to 1,500 liters).

Designing a new facility requires establishing a set of rules. First, form follows function. In this case, because aseptic manufacturing is critical, the aseptic process is considered the core of the development process. All processes in the building need to support the aseptic core processes perfectly.

Second, standardization is very important. The processes need to be defined once in every detail. Clear description of critical parameters and visualization of manufacturing steps are key to success. The process design must ensure simple and reproducible manufacturing. Minimizing variation in the process minimizes risk and increases quality.

Visualization is the third element of importance to achieve transparent processes and reliably good product quality. Furthermore, this helps to ensure that operators, authorities, customers, and quality assurance personnel can follow the process easily and share the same understanding.

The fourth element is flexibility, meaning the new facility should be able to manufacture most any appropriate product in the future, in order to meet future requirements as they arise. And throughout, EHS considerations for handling cytotoxics must be considered and included.

In order to achieve these four main elements, a process development team was put together consisting of manufacturing, quality control, and engineers. While each has a different expertise and view of the manufacturing process, the simplest way to get everyone on the same page is to develop the manufacturing processes by visualization with flowcharts. A high level flowchart is the starting point. It provides the framework of the process and defines the job for each group.

Additionally, a detailed process flow of each manufacturing step is crucial as is simulating the manufacturing process. Finally, risk analysis can be performed for each manufacturing set based on the flowchart.

As an example of how all of this comes together, consider a process development preparation area. Here, the final rinse, as well as the sterilization of pumps, houses, tubing, and clamps, takes place. Defining all handling steps in detail at the beginning of the process planning is a prerequisite to ensure particle-free and sterile manufacturing parts.

First, a high level flowchart. **Figure 1** was developed to indicate all the processes that occur in the preparation area. Second, a more detailed process flow chart, **Figure 2,** provides more information about what should occur at each stage. In total, there are 38 steps identified.

Next, it is important to simulate the process to make sure that what is defined on paper works in reality. Simulation provides a clear view of the design of the preparation area to make it usable and efficient.

FIGURE 1
High-Level Process Flow Chart

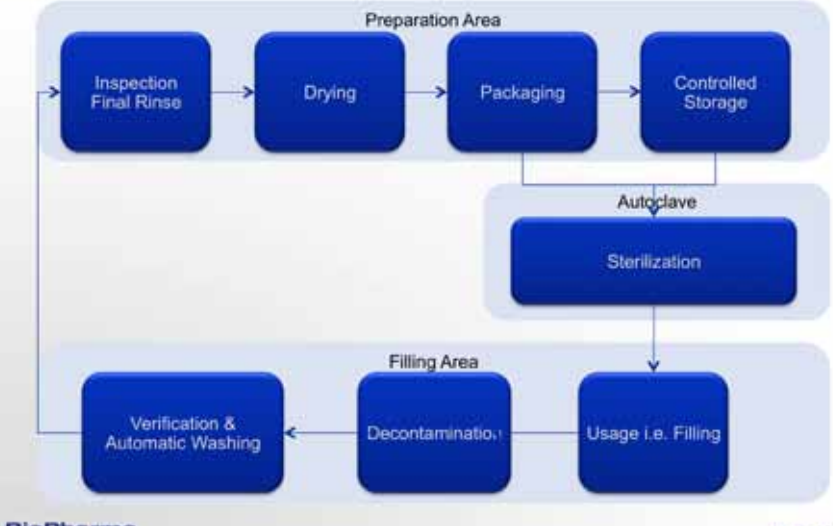
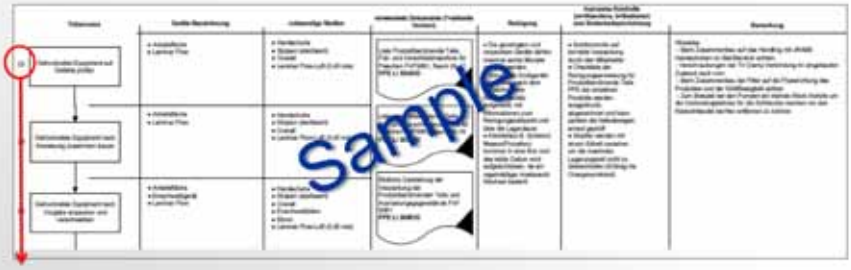


FIGURE 2
Example of Detailed Process Flow

Example of set-up of detailed process flow with evaluation of each step

Process Step	Equipment List	Infra-structure/ medias	SOP/ GMP documen-tation	Cleaning procedure	In-process controls	Qualifi-cation/ validation activities



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The same principles can be applied for designing process equipment. First, develop the detailed process flowchart, **Figure 3.** Then, a 1:1 model of the machine is built from wood or carton (mock-up) and simulations of the new process are performed. This provides a visualization in order to discover any deficiencies that may exist while presenting a good overview of all processes around the filling machine. Finally, this 3D model can be used to perform process risk analysis.

Additionally, Computational Fluid Dynamics (CFD) can be a big benefit to understand the airflow in the newly designed filling machine, identify critical points before clean room qualification, and to help the machine supplier to customize the machine to the final process requirements (**Figure 4).**

The last step in the design of process equipment is to perform the risk analysis to ensure cGMP compliance. Visualize the process flow, evaluate the risk of its detection, its occurrence, the severity, and define counteractions.

Once that determination was complete, a modular facility design, with two filling lines and one preparation area, was developed (**Figure 5).** The modular design ensures that the filling lines don't influence each other during the filling process. Each filling line has its own HVAC system. A modular design also helps to:

- Simplify maintenance
- Ensure that there is no cross contamination
- Enable facility extension for future product needs

The modular design is supported and enhanced by visualization. Baxter designed 60% of its new facility from glass. This ensures that the process is visible, comprehensible and flows in the way it was designed. The visibility offered by the glass allows for easy communication and process control for all involved, whether colleagues, clients, or authorities. It allows daylight to come into the manufacturing areas. This improves operator performance, especially in the sterile core. Color coding of walls is used to indicate where operators and processes are located, helping to improve orientation and standardization. Together, transparency and color coding can contribute to an overall improvement of quality.

FIGURE 3

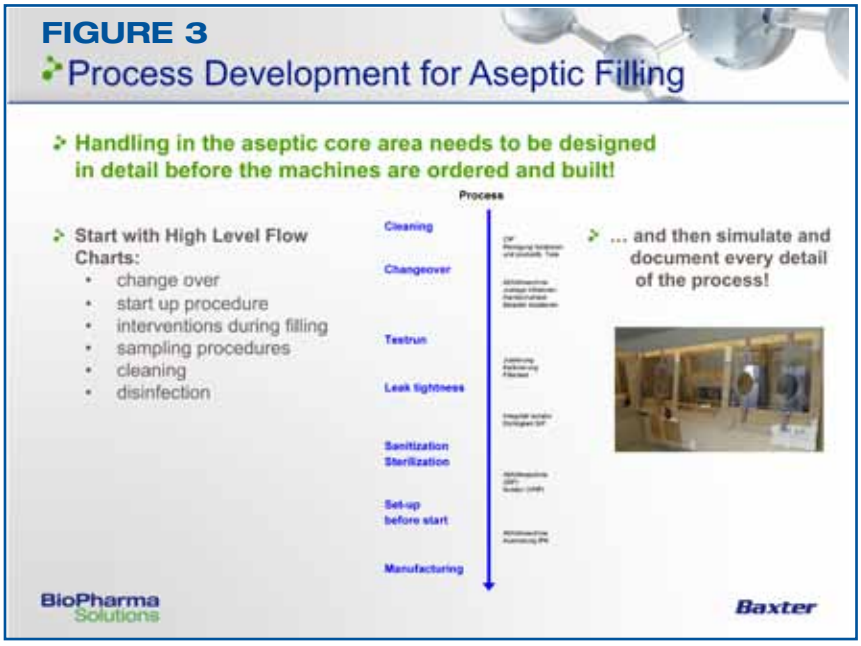


FIGURE 4

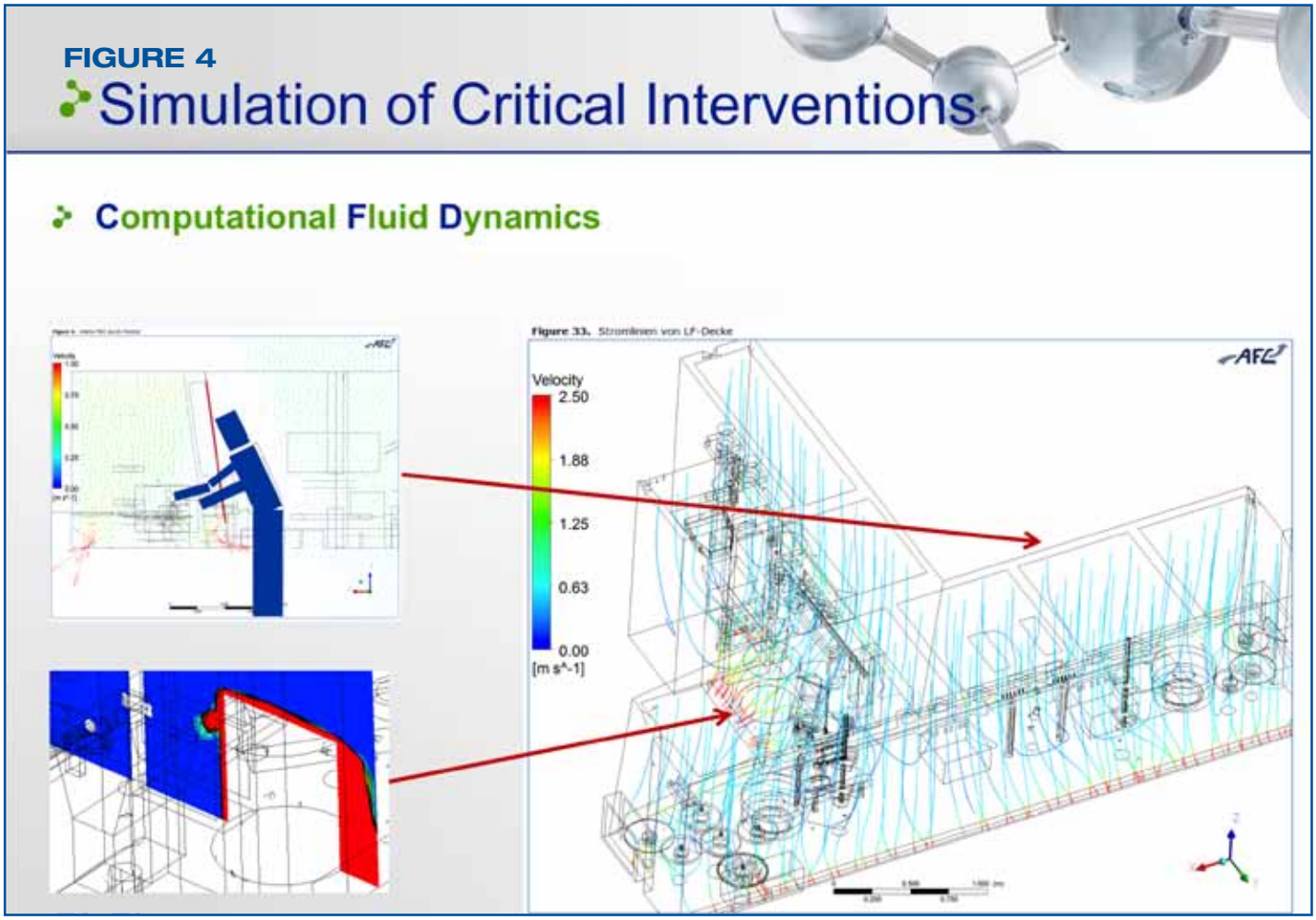
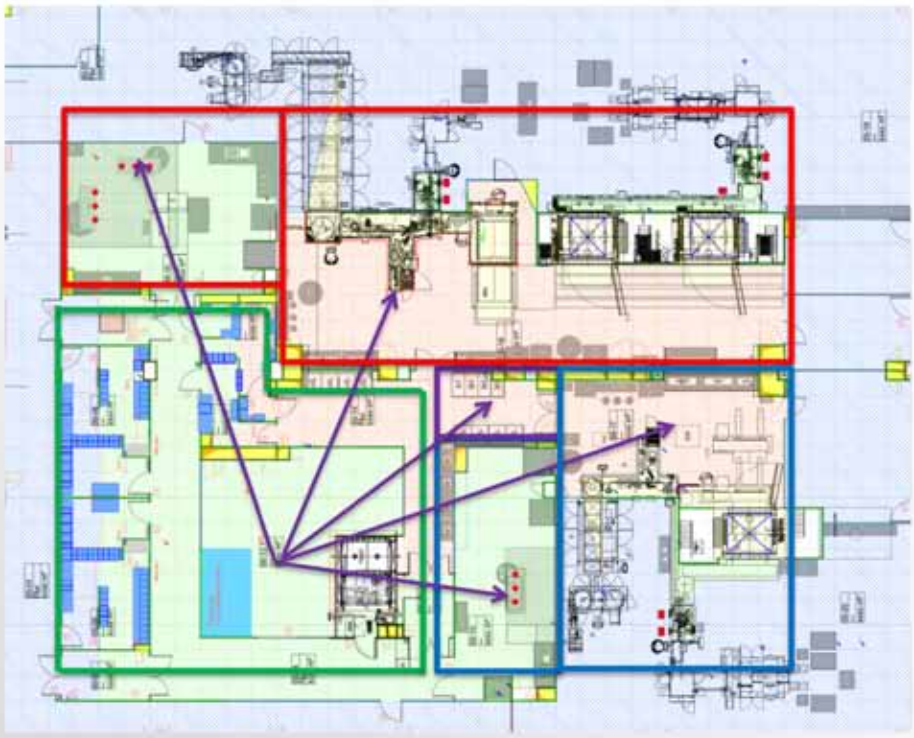


FIGURE 5

Modular Layout



Modular Design ensures:
- flexibility
- minimization of cross-contamination

Central Gowning, Washing and Sterilization Area:
- require dedication to one product class
- increase efficiency

Segregated filling / mixing:
- 2 filling lines, 2 mixing centers
- separated by isolators, rooms & HVAC

Filling LS
Large Scale

Filling SS
Small Scale

Organization of the Project Team

All of the process design work--architecture, equipment specification, risk analysis, qualification and validation, regulatory--was done by Baxter. Working on design together has the added benefit of acceptance and personal ownership of processes at an early stage.

External contractors were only used to support the non-GMP areas, and premium suppliers were called in for machines, equipment and cleanrooms.

The next step to consider is how to transfer from the project team to manufacturing. This was accomplished by setting up a project team with interdisciplinary skills. The project engineers will be the process engineers in the future. The people who have designed the isolators and the filling machines will operate them. This helps ensure a safe ramp-up from the project phase into manufacturing without loss of expertise along the way.

Results/Outcome

Baxter consistently applied Operational Excellence and Lean Manufacturing Principles end-to-end for process, personnel, material and waste flows, starting with the design phase of the project that carried through to the operation of the facility. All of this contributed to the Baxter team's successful completion of the project, on time and on budget, resulting in a facility with planned Operational Excellence and doubling output without impact to current operations. For this accomplishment, Baxter BioPharma Solutions (Halle/Westfalen, Germany facility) has been selected as the 2016 Facility of the Year Awards (FOYA) Category Winner for Operational Excellence.

FOYA 2016
Facility of the Year Awards
CATEGORY WINNER
Operational Excellence