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High Potency
Handling



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STERILE PRODUCT MANUFACTURING is unique and complex. This complexity is magnified when manufacturing highly potent molecules. High Potent Active Pharmaceutical Ingredients (HPAPIs or HPAIs) compounds can present many challenges due to the complex handling required for toxic substances. Data indicates units sold of sterile, highly potent products in the U.S. and EU markets continue to have steady growth¹. This growth underscores the importance of understanding the safety considerations in this area as the increase in sales volume translates into increased manufacturing volume of HPAI compounds.

We shall consider the triad of safety considerations for highly potent manufacturing — employee/operator, environmental and product — and the related aspects of capital investment, organizational capability and strategic flexibility in the final decision to outsource high potency manufacturing. Dealing with high potency molecules requires:

- Dedicated facilities with dedicated buildings or “plant in plant” concept
- Customized equipment for manufacturing and quality control
- Monitoring of safety systems for the protection of employee/operators and product
- Comprehensive knowledge of regulatory requirements

- Experienced employee/operators
- Integrated standard operating procedures, training and risk assessments

Dedicated Facilities and Production Areas

Dedicated production areas that provide state-of-the-art cGMP manufacturing for high potency and cytotoxic compounds reduce the risk of cross-contamination between products and product classes. Furthermore, fully integrated manufacturing resources supported and monitored continuously by Lean tools like “5S Philosophy”, “Kanban Systems” and “Control Charts” can reduce variability and improve manufacturing reliability.

Customized Equipment and Systems To Ensure High Safety Level for Personnel and Product

Manufacturing processes for highly potent products require customized equipment and processes as compared with standard aseptic processing. Strategic, long-term relationships with equipment suppliers help with the translation of process know-how into reality within the manufacturing environment.

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Having this relationship allows for the collaborative development of new features and processes which helps deliver sustainable product quality, along with innovation. For example, in order to handle HPAIs, strict separation of product and personnel in all steps of manufacturing must be implemented, starting with the compounding process and ending after cleaning and decontamination. Therefore, standard equipment is not applicable. Some examples of special design features include:

- Waste-resistant electronics and balances in the aseptic core area able to withstand decontamination
- Reliable and reproducible decontamination processes in the sterile core area without compromising the aseptic environment
- Pressure controlled containment air-locks for product infeed and outfeed
- Waste water treatment on site

Additionally, the HVAC systems of the equipment and facility are specially designed. They have to provide unidirectional air-flow for the process, but the design must also ensure that the filters can be decontaminated after the processing. Furthermore, the operator and the environment must be protected from the HPAI during situations like maintenance or filter change.

The implementation and application of barrier technology provides technical flexibility in the high potency manufacturing environment, while maintaining employee/operator safety. By utilizing zones within an isolator, for example, it is possible to manage differing process parameters such as temperature, relative humidity and pressure. Zone management can improve response times during changes in the manufacturing process by focusing control on a defined area rather than the total environment.

Utilizing cRABs (Closed Restricted Access Barrier System) technology for commercial manufacturing also provides benefits as it helps to maintain the integrity of the molecule, enhances product sterility and improves the safety of the line operators by:

- Isolating operator from the aseptic core area
- Utilizing a single-wall concept with external return air ducts allowing for maximum operator accessibility
- Delivering a homogeneous air velocity distribution by using return air ducts along the whole length of both sides of the filling machine.
- Avoiding active air exchange between the inside and outside with pressure-controlled active mouse holes. Pressure zone concept keeps the critical zones in positive pressure to the grade B room, while the different zones are separated from each other by active mouse holes (pressure sink concept)
- Optimizing operator protection even during critical situations like breakage, spill of product or aerosol generation

- Providing cGMP required Class 100 with a background class 10
- Protecting the environment through material transfer systems, the product through overpressure to the surrounding room and the operator by safety locked doors

The integration of state-of-the-art resources dedicated exclusively to cytotoxic and high-potency product manufacturing provides focused experience that can help provide manufacturing reliability as products move from development to commercialization.

Comprehensive Experience with Regulatory Governance

Good manufacturing practices apply to the production of sterile, highly potent products with additional employee safety requirements integrated into the manufacturing process. The following tables list key regulations that apply to sterile manufacturing as well as worker safety regulations, specifically OSHA 18001 and DIN 14001, that provide minimum worker safety standards.

The following guideline table relates to all sterile products:

US 21 CFR 210/211	Current Good Manufacturing Practice for Finished Pharmaceuticals
ICH Q10	Pharmaceutical Quality System – April 2009
US Drug Quality System Guide	Quality Systems Approach to Pharmaceutical cGMP Regulations - September 2006
EC cGMP	The European Community (EC) Guide to Good Manufacturing Practices (cGMP) for Medicinal Products
ISO 13408	Aseptic processing of health care products
ISO 14664-1	Clean rooms and associated controlled environments
ISO 11134, ISO 11137, ISO 14937	Sterilization of health care products
FDA, CDER, CBER, ORA	Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice – September 2004

In addition, the following guidelines directly refer to EHS aspects:

DIN 14001, OSHAS 18001	Certification of implemented EHS processes in the facility
ISPE RiskMapp Guideline	Verification of Containments Integrity

Complying with these environmental and regulatory requirements corresponds to a potentially significant capital investment. Building the necessary high potency manufacturing is potentially a cost prohibitive, or inefficient, use of capital for a drug developer. An assessment needs to be made weighing the relative return for capital invested in manufacturing capacity vs. the competing capital requirements required during development and commercialization. Continued investment to maintain manufacturing compliance and worker safety in a dynamic marketplace must also be considered. One additional important factor is the implementation of a sustainable industrial hygiene program. A specially trained team uses qualified methods to monitor, according to the hygiene plan, air and surfaces for toxic residues in areas where HPAI is processed. Continued demonstration that the equipment and the processes are qualified is required to ensure a safe work environment.

Integrated Standard Operating Procedures, Training and Risk Assessments

In addition to specialized equipment and systems, other critical features of a highly potent manufacturing facility include integrated standard operating procedures, mandatory training protocols, documented risk analysis for processes with a focus on cGMP and EHS, as well as regularly scheduled risk reassessments.

While installation of barrier technology can be challenging, visualization exercises, control charts and standard work processes can be useful tools. Prior to installation, training operators as early as possible and having employees visualize it as part of the manufacturing process is important. Using these tools and processes can assist in the clear understanding of expectations for operators, and potentially improve the safe work environment.

Involvement with regulatory agencies, professional societies, educational resources and industry thought leaders seeking to improve manufacturing practice is an important aspect of continuing improvement in this complex area. Development of an organizational capability to seek out these resources and disseminate valuable information within the manufacturing organization is an aspect of safety that also needs to be considered.

Understanding the Advantages Partnering with a CMO Can Offer

Drug developers have realized that outsourcing is an opportunity to leverage capabilities and capacity that exist outside the core competencies of their organization. This concept is particularly important when considering outsourcing of high potency molecules, as there are advantages associated with partnering with a CMO. When evaluating partnering decisions, some critical factors include:

- Evidence of effective safety (i.e. # of days since last accident)
- Regulatory agency inspection track record
- Implementation of a industrial hygiene program



- Application of barrier technology in manufacturing and quality control
- Robust and visualized descriptions for all steps processing HPAI

A CMO should be able to clearly articulate its experience and its plans to support the drug developer with the appropriate design for the manufacturing processes, while ensuring that all cGMP, environmental and safety approvals for the product are in place. In addition, it is important to consider a CMO's certifications and other achievements as a means to assess its ability to deliver on commitments.

An effective outsourcing solution identifies quality, technical expertise, delivery, service and speed to market as aspects of the collaboration that can provide value for the drug developer. Maximizing the unique aspects of each partner's contribution to the collaboration is critical to the overall success of the partnership. That's why it is important to choose a partner who has the proven capability of delivering on commitments, who offers a depth of services and is able to effectively harness the relevant expertise within their organizations to support their partner's objectives. CMO partners that provide access to specialized technology and expertise in such areas as high potency are able to provide enhanced value for their pharmaceutical partners, while achieving product and employee safety, so patients can ultimately be served. ■

Reference

- 1 IMS Data; 2006-09 MIDAS unit volumes for US and EU5 in hospital and retail channels.