

Optimizing Operations in Multiproduct Pharma Manufacturing Facilities

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Fixed, single-product pharmaceutical factories are becoming a thing of the past. Gone are the facilities dedicated to a handful of blockbusters. To survive, today's drug manufacturers must be agile and willing to adapt to wide-ranging and fast-changing requirements. Flexible, highly efficient manufacturing plants are in demand as a result of many factors – including the need for frequent changeover between small batches targeting rare diseases, short timelines and expedited programs, and a wide array of increasingly complex therapies. Some of these are highly potent, involve market uncertainty, or need to be scaled.

However, operations in these modern, multiproduct facilities are complex and must be carefully laid out and orchestrated for optimal results. This white paper outlines some of the key features that pharmaceutical companies should look for in the facilities of prospective manufacturing partners.

Facility Design

Centralizing operations in a single plant rather than building multiple facilities saves time and cost while allowing much-needed customization. However, manufacturing many products in parallel and in succession in the same place can also be problematic. Crucial considerations, such as cross-contamination, cleaning, and project-to-project transitions influence almost all elements of manufacturing configurations, operations, risk management, and quality control ([refer to FDA 21 CFR 211 Subpart C](#)). A proper multiproduct facility design will incorporate the following features:

Novel, Generous Layout

Controlled, adaptable environments designed to prevent cross-contamination are easiest to achieve with new construction. Retrofitting an older, mono-product facility is often difficult and costly. Such facilities were designed according to the specific needs of a single process. In contrast, multiproduct facilities are purposely designed to suit the approximately 80% of pharmaceutical manufacturing processes that have typical unit operation (UO) layouts. In these plants, commonly associated operations, such as dispensing and mixing, are usually co-located for efficiency.

To allow for flexibility, spaces must be larger than in a mono-product facility in which equipment is typically bolted down in

the most compact, efficient arrangement possible for the given process. Multiproduct production areas must accommodate not only variable sizes of equipment but also manufacturing lines that may be reconfigured depending upon the product. Smaller, auxiliary pieces of equipment, such as those for blending and milling, may be moved from room to room as needed.

Redundant Utilities & Services

Every room needs adequate electricity, cooling water, compressed air, and steam. Well-planned facilities incorporate redundancy to ensure seamless service, as adding capacity later will be very expensive. One should look for oversized services — within the limits of reason and budget — that will meet the needs of the typical UO layouts mentioned earlier.

In addition, heating, ventilation, and air conditioning (HVAC) design is critical to control the flow of air, preventing cross-contamination. For instance, corridor air handler systems must be carefully implemented to maintain air pressure cascades that prevent aerosolized materials from leaving any of the production areas and entering the rest of the facility. The right HVAC system provides for personnel and product safety and is essential for the successful operation of a multiproduct manufacturing facility.

Built-In Cleanability

In multiproduct facilities, cleaning must be foolproof and fast. Determining changeover speed is a critical step that directly affects capacity utilization, profitability, and timely batch production. A room or suite clean-out entails washing down and wiping down from ceiling to floor. Therefore, all rooms should be designed with smooth, slick, sloping surfaces that can be cleaned quickly and easily. Architectural ledges and grooves should be avoided. Utilities should be recessed in walls and sealed off to eliminate the need for cleaning when not in use.

QC Laboratories With Generous Storage

In facilities that manufacture a variety of products, the testing laboratories will be required to perform an unpredictably wide variety of tests. Over time, as new products are introduced, the need to add new testing equipment is inevitable. These areas must be designed for flexibility — with extra space to store the newly acquired pieces of equipment as they accumulate from campaign to campaign.

Efficient Warehouse Operations

For a multiproduct facility, inventory management is more complex than one might think. Each project's products, packaging, and client materials must be controlled. The early arrival of materials for future projects and bulk supplies that remain on hand from previous activities add to the logistical web. This overlap in storage needs from one project to the next necessitates careful planning.

Equipment Design

When selecting equipment for multiproduct facilities, each item should offer as much functionality as possible to accommodate varying process needs. Specifications that decrease downtime between projects and that help prevent cross-contamination should be the focus ([refer to FDA 21 CFR 211 Subpart D](#)).

Scalability

In a multiproduct facility, manufacturers must be prepared to handle your unique project. For maximum utility, equipment must be scalable for use with small or large batches. For example, a tablet coater that can be configured to process any batch size from 10 kg to 150 kg would be a good choice. A high shear granulator with interchangeable bowls that can accommodate 10 liters to 65 liters is another example of scalable equipment. One should make sure that the equipment on hand can work for the batch sizes that will be needed.

Rapid Changeover

In multiproduct facilities, minimizing changeover time between products is a huge focus — as is zero-defect cleaning. For this reason, one should look for wash-in-place (WIP) equipment. Not only can this equipment be cleaned easily and thoroughly, there will also not be a need to tear down the equipment and wash all the parts separately, which is extremely time-consuming. Clean-in-place (CIP) equipment is even faster and more convenient to clean — albeit expensive. It has automated cleaning cycles with ports for flushing and no disassembly is required. For example, a fluid bed dryer with well-designed CIP can reduce changeover times from 12 hours to less than 3 hours with minimal manual breakdown and inspection.

Fast and Easy Maintenance

Regulatory authorities mandate regular maintenance for pharmaceutical manufacturing equipment, as in [FDA 21 CFR 211.67](#). It is important to find out whether a manufacturer's equipment is designed for quick, in-place maintenance. The maintenance routine should be fast and easy with minimal teardown required. Ideally, the technician should be able to complete it during the standard changeover time. Equipment maintenance requirements are an important consideration that should not be overlooked.

SUS vs. Stainless Steel in R&D vs. Commercial Manufacturing

The efficiency requirements for research and development differ from those for large-scale manufacturing. In general, single-use systems (SUS) offer the greatest efficiencies at R&D scale while non-disposable (stainless steel) components are more practical for commercial-scale manufacturing.

Disposables Suit Small-Scale, One-Off Projects

Cleaning validation of reusable components is expensive and time-consuming: A manufacturer must show that the cleaning method is effective in the context of switching from one overall process to another. For example, performing cleaning validation/verification on a typical weigh dispense isolator can take 60 to 80 hours between protocol generation, sampling, testing, and review and approval of results. For a small R&D campaign that only involves one or two batches, investing in cleaning validation may not be practical. Since the components are small and the process is being performed a limited number of times, the expense of SUS are not prohibitive. In addition, SUS enable very quick changeovers as they minimize setup and cleaning time. In these cases, SUS are a great choice.

Stainless Steel Suits Large-Scale, Repeating Projects

Disposable components may not be cost-effective for commercial-scale processes that will be manufactured repeatedly. In these situations, cleaning validation is worthwhile and one should expect that stainless-steel components will be used.

Containment Follows Suit

When processing toxic materials — high-potency APIs, controlled substances, or anything else with low acceptable operator exposure levels — equipment must be contained to control any substance that might escape from the system. A glove box is the typical containment device for this purpose. Again, your manufacturer will likely recommend a cost-effective, disposable unit for your R&D campaigns and hard-shell, cleanable containment for your commercial projects. Disposable containment may also be used in the commercial environment for convenience and to minimize post-processing cleaning requirements. However, it can increase expense.

Personnel Training and Safety

The spaces and equipment must be flexible and adaptable in a multiproduct manufacturing facility and so must the process and maintenance technicians, QA analysts, and other employees responsible for day-to-day plant operations. Records of all training should be carefully maintained.

Cross-Training Is Key

In a mono-product facility, having expert, specialized operators running the equipment for a single process step ensures the greatest productivity and product quality. In a multi-use facility, however, process and maintenance technicians must be cross-trained to work with multiple types of equipment and to run a variety of processes. The best technicians will be able to operate almost all the equipment. For safety and to avoid errors, ensuring all personnel are appropriately trained to fulfill the requirements of upcoming campaigns must be an ongoing focus.

QA analysts should be well-informed for each new project. In a facility that constantly produces a single type of product, batch records seldom change, so technicians can more easily identify anything amiss. In a multiproduct situation, QA analysts need preparatory training to understand what each new product's batch record includes so they can review it effectively.

Flex Hours May Be Required

For maximal efficiency and optimal capacity utilization, the manufacturing team must be prepared to shift working hours as needed — depending upon the unique schedule of each manufacturing campaign. While it may be possible to minimize these disruptions to the schedule, manufacturing demands often require staggered shifts and the manufacturer's staff must be willing and able to accommodate the needs of the project.

Planning and Scheduling

Planning optimal setups and production schedules while managing timelines and other priorities is a challenge in multi-use facilities. It takes a specialist to know all of the durations of all possible process steps. This information, along with the number of batches per day and the desired output, determines production schedules. A good manufacturer will have a scheduling expert to ensure smooth operation of the facility. Changing material needs, delivery schedules, and efforts to maximize capacity utilization and minimize equipment downtime are key.

Regulatory Considerations

At multiproduct facilities, regulatory inspectors are particularly focused on verifying the adequacy of cleaning and on the prevention of cross-contamination. Proper Good Manufacturing Practice (GMP) documentation is essential for approval and traceability. Knowledgeable personnel should be monitoring operations closely to guarantee compliance.

Cleaning Validation and Measures to Avoid Cross-Contamination During Cleaning

A facility carefully designed for multiproduct use, with easy-to-clean work areas and equipment as described above, along with appropriate cleaning validation reports, will reassure inspectors. In addition to the cross-contamination-preventive HVAC measures described above, processes should be in place to ensure that cross-contamination does not occur during cleaning. For example, dirty items must not enter a cleaning area before cleaned items are removed. Procedures should also be in place to verify that cross-contamination is not occurring during maintenance, via contaminated tools.

Redundant Controls to Prevent Mistaken Identity

In a facility with multiple ongoing manufacturing projects, similarly packaged materials could be accidentally exchanged in the warehouse or elsewhere in the facility. Careful labeling practices and redundant checks must be in place to avoid errors.

Great Design Fosters Efficient Operation and Regulatory Compliance

Facilities flexible enough to manufacture multiple products have become a cornerstone of our industry, crucial for meeting changing market and regulatory expectations. With careful planning, they can be extremely efficient and eliminate the need to build new facilities for every new drug product. This allows for even drugs needed in small quantities, such as orphan drugs, to be manufactured cost-effectively.

Numerous considerations must factor into the design, equipment, and operation of these facilities, which require more space and different architecture than traditional pharmaceutical manufacturing plants. When you are investing in products that can change lives, accepting mediocrity is not an option.

Demand More

Choose the CDMO with facilities expertly designed to ensure flexibility, efficiency, safety, and regulatory compliance for your products. No matter the phase of your project, Recro Gainesville will deliver — exceeding your expectations for developing new oral solid dosage formulations from concept to clinic to commercial scale.

In summary, one should consider the following checklist for multiproduct facility design:

Multiproduct Facility Design Checklist

Building Design

- Custom built for multiproduct
- Generous, flexible layout
- Redundant utilities and services
- HVAC designed for personnel and product safety
- Built-in cleanability
- Generous laboratory space
- Generous warehouse space

Equipment

- Scalable
- Enables rapid changeovers
 - Clean-in-place
 - Fast, in-place maintenance
- SUS for small scale; stainless for large scale
- Containment, either SUS or stainless

Personnel

- Cross-trained
- QA analysts trained for each project
- Training records available
- Flexible hours

Planning/Scheduling

- Scheduling expert available to answer your questions

Regulatory and Quality Considerations

- Proper documentation
- Knowledgeable personnel
- Expert cleaning validation
- Measures in place to avert cross-contamination
- Redundant controls to avert material mix-ups

About Recro Gainesville

Recro Gainesville provides solid dosage form development, clinical and commercial manufacturing, and packaging and logistics services to the global pharmaceutical market. Specializing in modified release solid dose and DEA controlled substances, Recro has the experts to deliver clients' most complex pharmaceutical development and manufacturing projects in its best-in-class, 120,000 square feet of manufacturing space. For more information about Recro's flexible CDMO solutions, visit recrogainesville.com.