Considerations for Multi-Product Manufacturing Facilities

Trishul Shah, Associate Director Business Development at PolyPeptide Laboratories Inc, reviews the considerations for the manufacture of active pharmaceutical ingredients at a multi-product facility.

Introduction

The regulatory standards for approval of new drugs have increased as companies and agencies raise the bar and their expectations. In particular, regulatory agencies have become more stringent as more information and understanding on the impact of drugs and their interaction with biological systems becomes available. With the increased hurdles to approval and the necessity to extend the product knowledge base, more focus is being placed on specific areas of the drug approval process.

The manufacture of many active pharmaceutical ingredients (APIs) are outsourced to contract manufacturing organizations (CMOs). These have to cater to multi-product manufacturing at their manufacturing sites. As a multi-product manufacturer, the CMO can choose to dedicate equipment for each single product or use shared equipment. In some cases if a campaigning modus is used for a small number of products of similar scale and same equipment type; a single equipment type can be dedicated and shared between these few products.

The PolyPeptide Goup is one such CMO that routinely faces this choice. Both approaches have their own unique challenges and will be discussed in the ensuing article.

Figure 1: Multi-product facility at the PolyPeptide Group

Dedicated Manufacturing Equipment

Cross-contamination is always a major concern in multi-product facilities, particularly for highly potent molecules and at early stages of development when the potency of a molecule may not be known. The use of dedicated equipment reduces concerns about cross-contamination between products. With less risk of cross-contamination, validation of cleaning procedures between batch change-over is simplified because of the lower concern of residual potent product carry-over from a different product using the same equipment. With less exhaustive cleaning procedures necessary, resource utilization is reduced bringing improved efficiency to the manufacturing process and reduced overall manufacturing cost. Duplicating dedicated equipment improves the production flow. There is less disruption in production planning, less waiting for equipment because it is not otherwise used.

Use of dedicated equipment comes at a cost. In a multi-product manufacturing facility, purchasing dedicated equipment for specific products is expensive for the CMO. Therefore the cost of the dedicated equipment is usually passed on to the sponsor. Besides the original purchase cost, the equipment has to be maintained on an on-going basis, with the additional cost of maintenance contracts that are usually borne by the CMO. Over and above expense, the use of dedicated equipment adds logistical challenges. Secondary (back-up) equipment is important as mitigation in the event of a mechanical failure to the primary equipment. Storage areas are required for all the dedicated equipment. Maintaining a storage area adds cost and uses valuable real estate that could potentially be used as additional manufacturing space.

Disposable equipment is another approach to dedicated equipment saving on expensive upfront costs and storage costs; however disposable equipment may not always be feasible with chemical manufacturing because they are made from material that may degrade and leach during processing.

Shared Equipment

The use of shared equipment by a CMO greatly reduces the expense of duplicate equipment and multiple maintenance contracts. Having the ability to use the same piece of equipment for various products reduces the amount of equipment needed to be housed and therefore alleviates this logistical challenge and additional storage expense. It also frees up space to build supplementary revenue generating manufacturing suites.

On the other hand, the use of shared equipment brings its own set of unique challenges. The manufacturing flow at the CMO may be slowed down because a new manufacturing campaign has to wait for availability of equipment that is already being utilized. Use of shared equipment necessitates the need for change-over procedures which incur additional resources, time and costs. The biggest concern with the use of shared equipment is cross-contamination between products used in the same equipment. Therefore, as per the principles in numerous guidance documents that include ICH Q7 to Q10, FDA's cGMPs for the 21st Century, FDA's PAT Initiative and the FDA Process Validation Guideline; an appropriate cleaning validation strategy has to be established.

Cleaning Validation

Cleaning Validation is an important systematic set of procedures to control product cross-contamination, ensure product quality and ultimately patient safety; however it does require resources, time and investment. The guidances listed above encourage the use of a risk and science based approach to cleaning validation. A risk analysis is performed to evaluate the level of risk of the cleaning procedure by looking at various factors, such as:

- What are the potential risks of the residual product?
- Does the cleaning process have an impact on the risk of the residual product?
- How difficult is to clean the residual products?
- Are all areas of the equipment (potential dead legs) subjected to the cleaning process?
- How potent is the residual product and is it below a safety limit?
- How is the safety limit determined?
- How effective are the analytical methods in detecting the residual product and their degradants after the cleaning process?

Based on this evaluation, a risk score is applied to the product and cleaning process. This forms the basis of a control strategy to develop a cleaning process specific to the product, equipment and process. As part of the control strategy and risk analysis, it is essential to use scientific means to determine product risk (e.g. API, degradants, and intermediates), cleaning agent risks and bioburden/endotoxin.

Once the residual products are identified, a toxicological review should be performed by a toxicologist to determine an Acceptable Daily Exposure (ADE). The ADE is used to calculate the maximum safe carryover limit to evaluate the level of risk posed by the residual product. In many cases for early

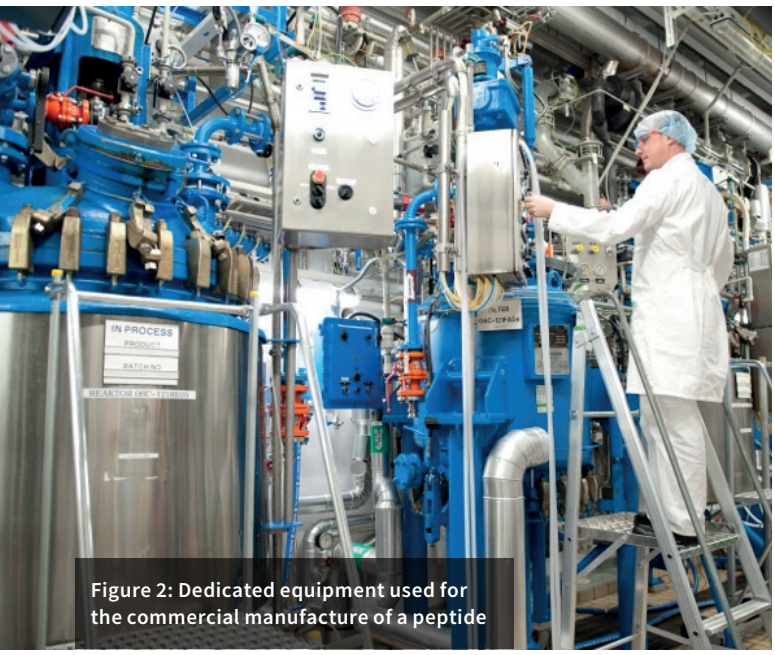

Figure 2: Dedicated equipment used for the commercial manufacture of a peptide

phase projects, the ADE may not be available. In these cases a conservative Threshold limit should be used instead.

Caution should be taken when choosing the cleaning agents i.e. it is preferable that the cleaning agents are Generally Recognized as Safe (GRAS). If a non-GRAS cleaning agent has to be used, then a similar ADE for the cleaning agent can be used to determine the maximum safe carryover limit. The cleaning agents may bolster proliferation of microbial contaminants stemming from a previous product, obliging the need to appraise microbial risk as part of the cleaning process. This is especially important for sterile manufacturing processes.

After determining the maximum carryover limit, a Failure Modes and Effects Analysis or another risk management tool can be used to perform a risk assessment of the cleaning procedures and their effectiveness at removing the residual product. During the cleaning process development, the residual product data should be obtained and compared by statistical analysis against the maximum safe carryover limit to evaluate the relative risk of cross-contamination. Based on this information the risk assessment maybe revised. The assessment and analysis would form the basis of a cleaning program and cleaning master plan.

An important part of the cleaning process is the ability to detect a potential source of contamination and the effectiveness of the cleaning process. There are several methods that can be used for determining residual product, and each method would be appropriate for different levels of risk. Typical detection methods used during cleaning validation include visual inspection, conductivity, Total Organic Carbon (TOC) analysis and HPLC. Visual inspection is an active observation of the visually accessible product contact surfaces of the pharmaceutical manufacturing equipment and is the first measure of equipment cleanliness. Conductivity can be used to detect the presence or absence of ionic or charged compounds. Conductivity is very useful in determining the presence of the cleaning agents used in the cleaning process. TOC analysis can be used for any drug compound or cleaning agent that contains carbon and has reasonable to limited solubility in water. HPLC is used for detecting very specific residual process impurities/degradants.

In general, a life-cycle approach should be used for a cleaning validation program that consists of Cleaning Process Design and Development, Cleaning Process Performance Qualification, and Continued Cleaning Process Verification.

Perspective

Multi-product manufacturing facilities operate on a fee-for-service basis with multiple clients, multiple projects and multiple needs. Each project has its own unique set of challenges and in most cases the projects are in the early phase of development. Early stage projects are at high risk of "survival" and therefore investment in dedicated equipment at the early stage would not be practical. Use of disposable dedicated equipment depends on the manufacturing process and the availability of such equipment. For most chemical synthetic processes requiring organic solvents, disposable equipment is not available. In addition – with numerous projects – CMOs would be challenged to store dedicated equipment for each client and project. The question would also arise as to who should bear the costs of the dedicated equipment and who owns the equipment once a project is terminated.

Once a product reaches a late phase of development or commercialization, use of dedicated equipment may be more advantageous. At this stage, use of dedicated equipment would mitigate the need for an exhaustive cleaning process and therefore reduce the long-term cost of manufacturing. Use of dedicated equipment at this stage of the life-cycle approach would improve the manufacturing flow by alleviating the need for product change-over and waiting times for available equipment. This would result in improved efficiency and reduced manufacturing costs that would benefit both sponsor and CMO.

Figure 3: Shared purification equipment

To limit the cost of dedicated equipment, the scale of equipment required for manufacturing should be carefully considered. The standard thinking is that for large annual product requirements, large equipment should be used for manufacturing. Large equipment cost substantially more and a failure in equipment would result in the loss of a bigger batch of product. Downscaling to smaller equipment requiring multiple smaller batches but automating a continuous process could be an attractive alternative. Downscaling would mitigate the risk of losing a single expensive batch and the purchase of smaller equipment would require less upfront investment. Automation would enable savings in the overall manufacturing costs.

It seems practical for CMOs to use shared equipment for manufacturing of products in development and early clinical phase projects even though this necessitates extensive cleaning validation processes. At late clinical or commercial stages it would be favorable to utilize dedicated equipment with mutual benefit to both the Sponsor and CMO.

The author would like to thank Rodney Lax, Business Development Consultant at Rodney Lax Consultancy, and Jon Holbech Rasmussen, Global Director of Development at the PolyPeptide Group for their comments and review.

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