Achieving a Successful Drug Product Technology Transfer



Catalent® BIOLOGICS

Within the pharmaceutical product development life cycle, technology transfer is a critical step towards a successful product launch. Technology transfer is a challenging and multi-faceted endeavor, with multiple variables that must be carefully considered. In addition, when the technology is transferred to a 3rd party (for example, a contract provider), there can be an added layer of complexity. Planning and communication among stakeholders are required to achieve a successful manufacturing process transfer for any potential drug product (DP).



TECHNOLOGY TRANSFERS — A CDMO PERSPECTIVE

A contract development and manufacturing organization (CDMO) can be engaged by a sponsor company at any point in the drug product development process to help advance a DP to clinical trials and eventual commercial launch. That hand-off of product and process knowledge from the sponsor to its partner is referred to as a *technology transfer*.

In an ideal scenario, sponsor companies will seek out a CDMO at the beginning of the process – shortly after a therapeutic candidate is identified. This way, a CDMO can be a part of the journey at the outset and will be able to develop the process to seamlessly work into its own manufacturing environment, potentially shortening the overall timeline.

The timing of a technology transfer is specific to the nature of each drug candidate and the sponsor company's outsourcing philosophy. Quite often the decision to engage a CDMO takes place in Phase II or Phase III of the development journey.

Typically, before the CDMO takes over the DP development effort, much of the following preclinical work has already been completed:

- Phase I proof-of-concept
- Safety studies
- Outline of preliminary quality parameters
- Selection of the container/closure system

Regardless of where in the drug development journey the CDMO is engaged, the groundwork needs to start at the same place: with a well-organized plan.

PLANNING A MANUFACTURING PROCESS TRANSFER

The first step in a technology transfer is to perform a *Gap Analysis*.

When a newly-discovered drug candidate and the proposed manufacturing process are transferred to a CDMO, an assessment must be made to ensure that the DP in question can be developed within the CDMO's manufacturing standards.

To prepare for a smooth transition, stakeholders will look at the following during a gap analysis:

- What is the current process definition?
- How can the process be transitioned to the CDMO's own manufacturing standards?
- What impact will the observed gap(s) have on the transfer process?

Once the necessary information has been gathered via the gap analysis, it is time to develop a transfer plan.

Planning: Vital Considerations

Once a gap analysis is completed, a CDMO can move on to developing a plan and timeline for an effective manufacturing process transfer.

The process is not the sole responsibility of the CDMO, but a collaborative effort amongst all required stakeholders from the sponsor company and CDMO. Effective communication is crucial to ensure all variables are factored into the plan, including:

- Timeline for various milestones
- Regulatory guidelines
- Resources needed including new equipment and materials
- Operation and maintenance of existing equipment

When these factors are discussed and evaluated upfront, the technology transfer team will have a clear understanding of time and resource needs. The sponsor company and CDMO will be able to align their expectations, and the process is less likely to result in unexpected delays or issues.

Focus on Commercialization

When pharmaceutical/biopharmaceutical companies and their development partners begin to organize a blueprint for the manufacturing process, the main focus should be future commercial scale.

The CDMO must always look toward the future with the end goal to develop a robust commercial process. They should have a clear idea of what will be needed for commercial-scale manufacturing as they develop the transfer plan.



A DEEPER LOOK: FILTRATION CASE STUDY

The following is a real-world example of a manufacturing process transfer, which presented a unique set of challenges. The approach used by the technology transfer team not only resolved the challenges but also resulted in process improvements.

Formulation

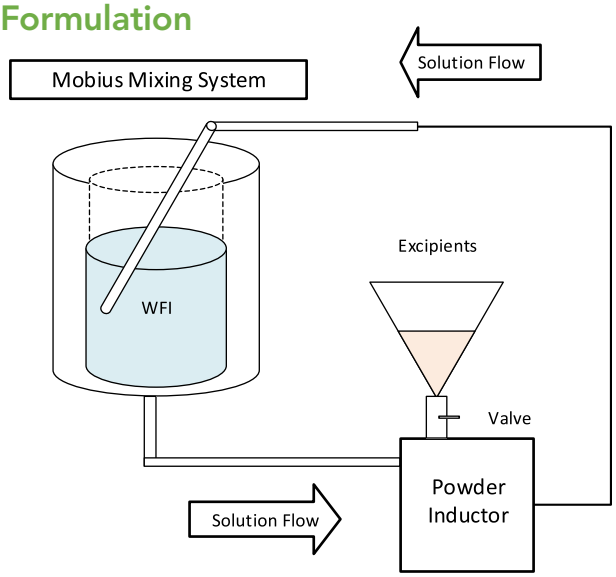

Figure 1. Formulation process provided to Catalent by the sponsor company. WFI denotes water for injection system and provides pharmaceutical grade water suitable for injections.

The Product

Catalent Biologics, a leading development and manufacturing company was approached by a sponsor to transfer a manufacturing process developed by a third party.

The DP in question was a sterile diluent. The proposed manufacturing process required a piece of equipment which was new to the Catalent manufacturing site, a powder induction system for high shear mixing. A major component of the diluent formulation had low solubility, and the high energy mixing provided by the powder inductor was required to ensure that a homogeneous solution could be produced. The resultant solution was then passed through a mixed membrane pre-filter prior to final sterile filtration (*Figure 1*). The pre-filters provided additional mechanical energy to break down and/or remove any undissolved material to protect the sterilizing filters.

Process Performance Qualification (PPQ) was successfully executed by Catalent. Based on the PPQ, the maximum number of pre-filters was limited to three (3) for routine processing, and the powder induction time was fixed at 15 – 20 minutes (*Figure 2*).

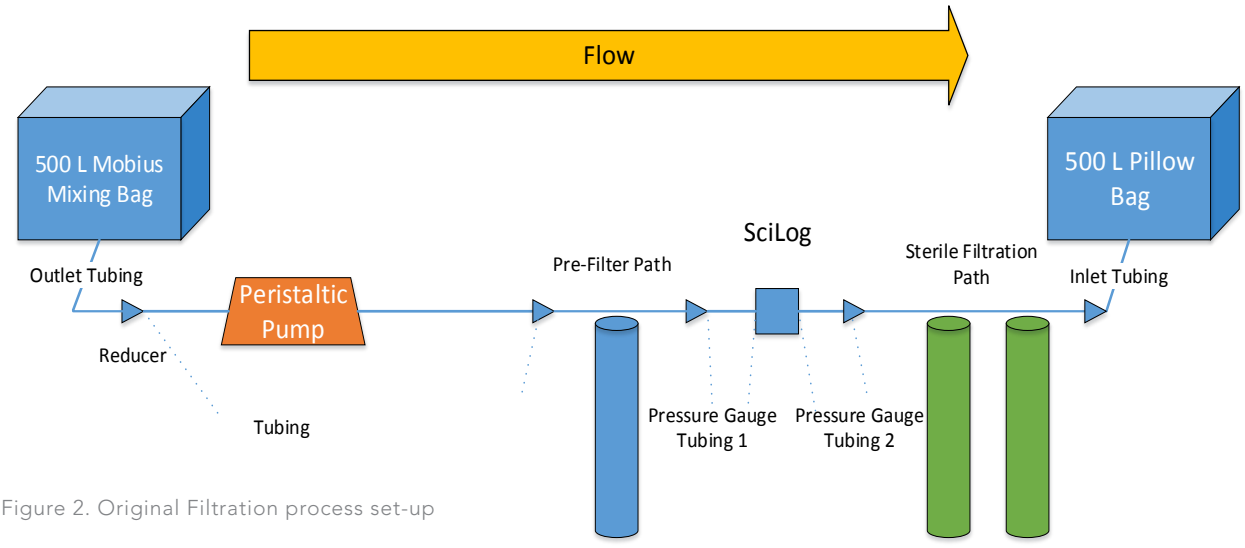

Figure 2. Original Filtration process set-up

The Challenge

Post-PPQ, Catalent successfully produced several commercial batches using the validated manufacturing process for the sterile diluent. However, filtration performance suddenly declined and barely half of a full-scale batch could be moved through the filter train.

The sudden deterioration of filtration performance was unexpected.

Faced with this unanticipated complication, the team at Catalent had to devise a solution. They started by identifying the root cause.

The Analysis

To find out what was causing poor filtration, the team collected all relevant information about the filtration process (*Figure 3*):

- **Literature Search:** The team combed through published literature related to the material in question.
- **Client-Provided Resources:** The team reviewed all client-provided information and requested additional information that wasn't provided upfront.

The process development (PD) group at Catalent Biologics also assisted in the analysis.

After evaluating the information gathered, the team developed two hypotheses for the source of the problem:

1. The powder addition process - the duration of time the material passed through the induction system may not have been adequate to consistently achieve a homogeneous solution.
2. The pressure monitoring mechanism - the issue may lie in *where* and/or *how* the filter train was monitored.

The Investigation

Catalent's team designed two studies to test their hypotheses:

To determine whether the powder induction process was adequate, the team executed two at-scale engineering batches to evaluate:

- the method used to add the powder through the funnel of the powder induction system.
- the mixing times.

To determine whether the filtration parameters were adequate, the process development group built a small-scale manufacturing model. Using the model, the team was able analyze the validated filtration process, along with its pre-set parameters.

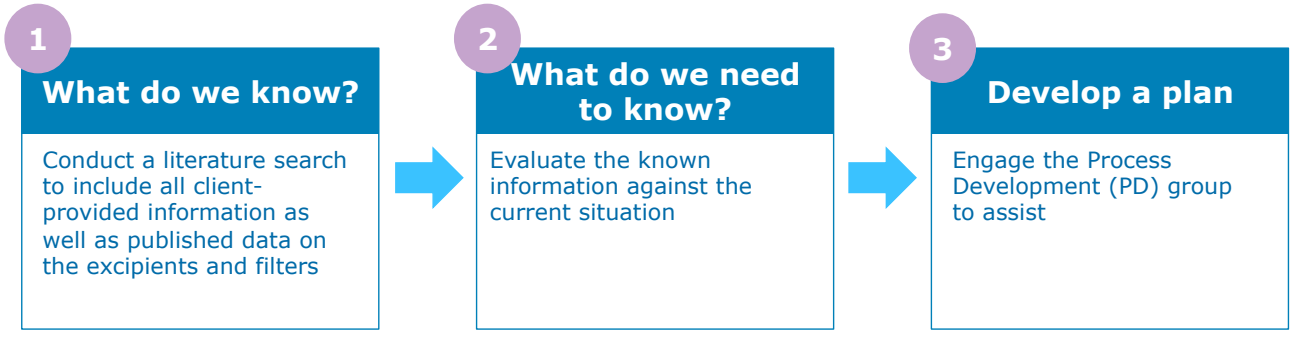

Figure 3. Analysis of the filtration process

Isolating the Problem

After performing both studies, the project team determined that both of their hypotheses were correct. The powder induction processing time was inadequate to allow for lot-to-lot variability of the excipient. Additionally, the placement of the filtration pressure sensors was inadequate to detect the decrease in pre-filter performance.

The pre-filters are an adjunct to the high-shear mixing provided by the powder inductor, helping to ensure that a homogeneous solution is presented to the sterilizing filters. Due to the insoluble nature of one of the key excipients, it was known that multiple pre-filters would be required. During PPQ, the pre-filters were exchanged when the pressure of the sterile filters increased and the flow decreased. Using this process, no more than three pre-filters were required in the PPQ batches. However, the sensors were only monitoring downstream of the pre-filters. Monitoring in this manner did not provide a true picture of the flow through the pre-filter.

The Solution

After successfully determining the root causes that compromised filtration, Catalent's team then analyzed the results to identify potential process improvements. They evaluated the high-shear powder induction mixing and found that increased time did not have an adverse impact. Next, they determined the maximum volume that could flow through the pre-filter and predicted the number of pre-filters that would be required based on the batch size.

Once analysis was complete, the team implemented three process improvements (*Figure 4*) resulting in a robust, repeatable process:

1. Increasing the time allowed for the high-shear powder induction mixing.
2. Setting the exchange point below the maximum volume that could flow through the pre-filter.
3. Adding an additional pressure sensor to monitor the pre-filter as a process control.

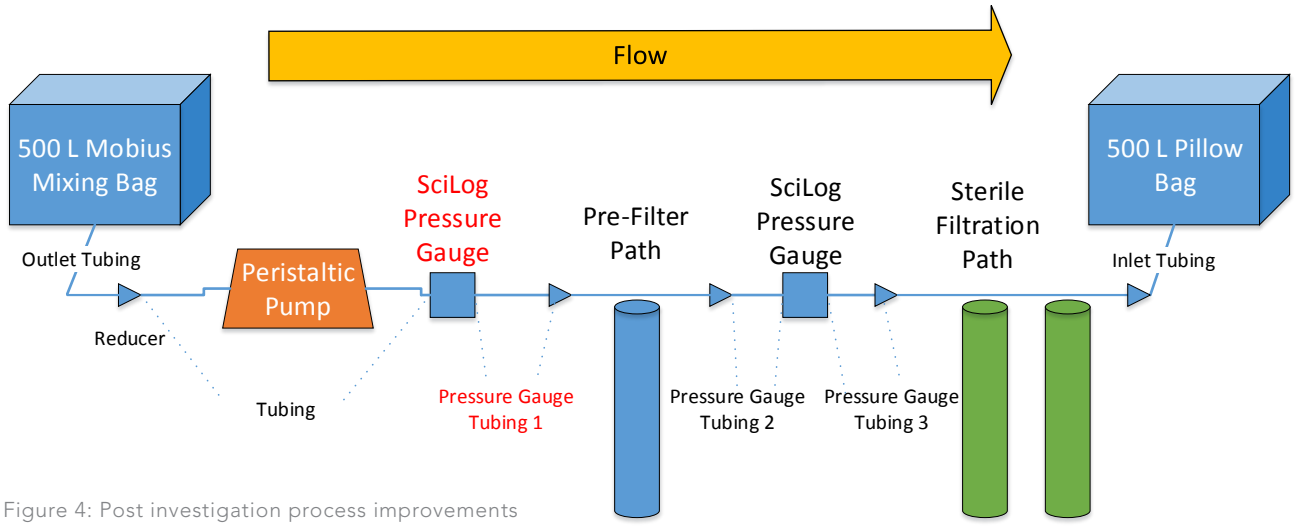

Figure 4: Post investigation process improvements including additional pressure sensor indicated in red.

TAKEAWAYS

To be successful, manufacturing process transfers must be collaborative with continuous two-way communication between the drug sponsor and the CDMO. Each stakeholder has different, valuable expertise that they can contribute to the process, and when unexpected challenges surface, it's important to continue to have a collaborative partnership to keep your program on track. Moreover, both parties should consider what is required to develop a robust commercial manufacturing process. A strong partnership combined with shared expertise will ensure that a technology transfer is set up for the best chance of success.

To learn more, view our webinar, "Critical Steps for a Successful Tech Transfer."



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Catalent Biologics provides advanced technologies and tailored solutions for biologic and biosimilar development, from DNA to clinical supply. With a technology platform including GPEx® cell line engineering and SMARTag® protein-conjugate technology, combined with comprehensive analytical services, biomanufacturing and fill/finish supply, Catalent is the catalyst for your biologic development success.

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