

This article presents a process transfer case study and the significance of continued project support after the site is licensed.

Process Transfer to Contract Manufacturing Organizations: A Case Study on Process Development Support Past Regulatory Approval

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Introduction

Transferring a process to a contract manufacturing site typically follows a lifecycle model as shown in Figure 1. Contract negotiation is focused on the objectives and goals of the partnership. It is typically managed by business and project managers of each organization. Once contract negotiation is complete, the project focuses on the technical aspects of the transfer, including facility fit, process/knowledge/documentation transfer, and validation lots. The identification of any necessary process updates as part of introduction into the site and large equipment purchases are performed as part of facility fit. Following facility fit, there is a large information exchange that culminates to the execution of validation lots. These three phases require

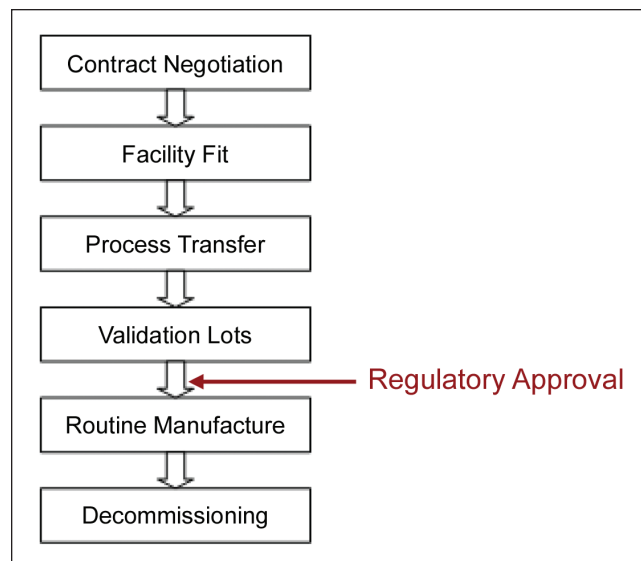
a large deal of time and effort and are usually the main focus of the process transfer. The transfer often is considered complete once the site attains regulatory approval. However, the routine manufacturing stage of the project plays an equally important role in process transfer and could be the longest duration of the transfer process lifecycle. An examination into a recent transfer of a commercial antibody purification process to a CMO demonstrates the significance of continued support from both the CMO and client during routine manufacturing at a CMO.

Background

Genentech transferred an existing commercial antibody process to a CMO to increase manufacturing capacity. The transfer to the CMO site also required a scale increase relative to the licensed process due to the pre-existing equipment at the CMO. Existing process validation work from the initial licensure was leveraged during the transfer wherever possible.

Both companies had an aggressive timeline for regulatory approval. Figure 2 shows the overall project schedule. Validation lots for regulatory approval at the site occurred roughly one year after the contract was signed. Routine manufacturing was performed on a campaign basis. When Genentech's product was not being manufactured, the facility was in use for the manufacture of other products.

Figure 1. Typical process transfer lifecycle.



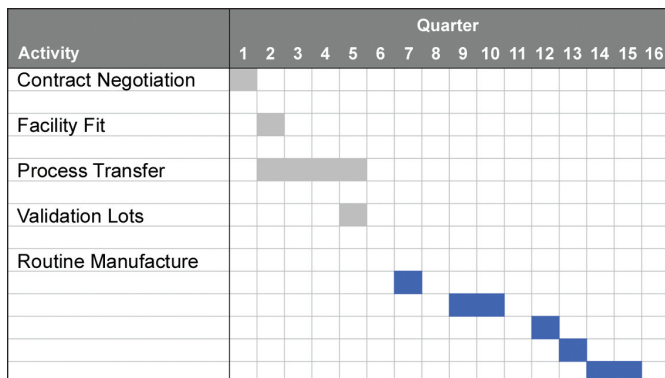


Figure 2. Timeline for the process transfer.

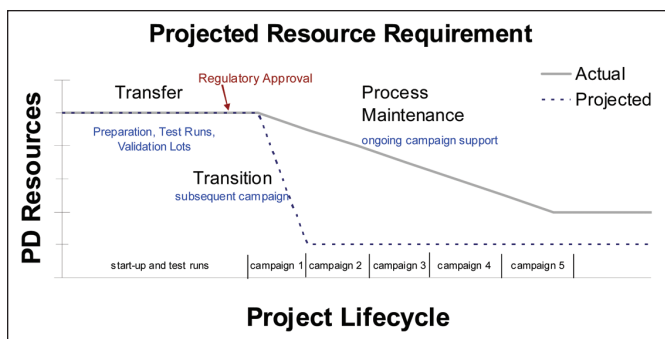


Figure 3. Project resource support during the lifecycle of the process transfer.

Genentech’s purification process transfer team included several Process Development (PD) members. During facility fit to validation lots, considerable resources were dedicated to the project with approximately four Genentech purification representatives committed full time to the project. After regulatory approval was obtained, both Genentech and the CMO immediately decreased their process development/manufacturing support staff considerably to one person full time from each site. Upstream cell culture support was similar for both Genentech and the CMO.

Manufacturing support demands proved to be more than expected. Process monitoring, deviation review, change control, and process improvements required additional staff not originally budgeted to support ongoing production. The issues seen during routine manufacturing at the CMO demonstrated the importance of continued process support, and showed the process transfer team that transfer activities do not end at regulatory approval at the site. Figure 3 compares the anticipated Genentech purification PD support for the process transfer lifecycle to the actual required resources. Relating back to timelines shown in Figure 2, the Genentech strategy for supporting the project lifecycle was to augment staff during commissioning and process transfer, and then reduce headcount for the commercial production campaigns.

Case Study Review

Soon after regulatory approval, it became apparent that considerable off-site support would be required to maintain the transferred process. Time dedicated to batch record,

change control, and deviation review was significant. Process monitoring proved to be a useful way to ensure the process was operating as originally transferred and intended. However, this exercise was time consuming and resulted in the discovery of multiple issues and process enhancements that needed to be addressed.

Case Study #1: Method Transfer

Due to tank limitations at the CMO site, an affinity chromatography buffer was prepared as a concentrate and diluted on-line prior to the column. Since this was a process change based on facility fit, the project team examined impact by investigating solubility, stability, and specifications for the buffer. The team ensured that the concentrated buffer could be prepared correctly and diluted online to meet the same specification as the neat buffer. Soon after regulatory approval, routine process monitoring noted a difference in the conductivity measurement for the online buffer. Despite the same buffer composition, the CMO consistently obtained lower conductivity readings compared to the historical average at Genentech. Figure 4 shows the historical conductivity values for the equilibration buffer at Genentech and the CMO.

Although still within specification, the lower conductivity values potentially pointed to an issue with robust processing. At the CMO, the buffer concentrate was diluted inline with Water for Injection and measured for conductivity at the chromatography skid. When conductivity was outside of range, the buffer was sent to drain until the specification was met. Since the buffer concentrate conductivity was already at the low end of the specification, the diluted buffer conductivity also was on the low end of the range. Therefore, small fluctuations in conductivity during inline dilution caused the skid to flush the system and increase overall buffer usage. The increase in buffer usage was above the planned projections for the process step. Buffer usage was a specific concern on this process step, because multiple cycles were run on the column for each lot. The maximum amount of protein processed was limited by buffer volume. Therefore, sending large volumes of buffer to drain to meet conductivity specifications negatively impacted the total amount of protein processed.

An assessment of the raw materials and the buffer preparation process did not point to a root cause for the shift in conductivity. Upon review of the method for conductivity meter standardization, the team noted slight differences in how each site accounted for temperature compensation. These differences led to an offset in conductivity measurement as

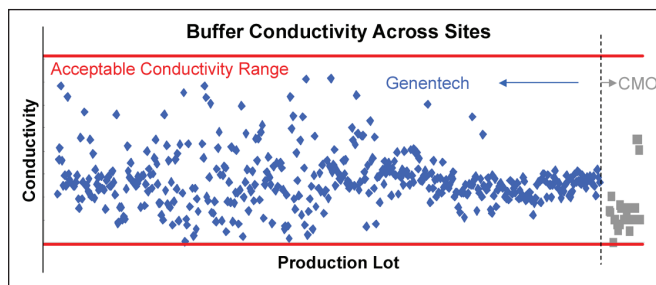


Figure 4. Historical conductivity values at Genentech and the CMO for a chromatography buffer.

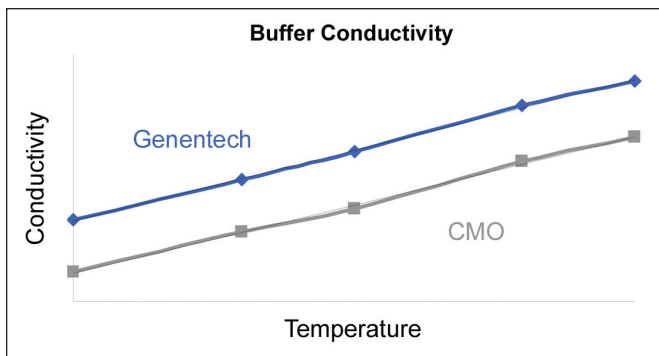


Figure 5. Conductivity correlation of a process buffer measured at Genentech and the CMO.

shown in Figure 5. Small scale studies were performed for all buffers in the process so that specifications were aligned with the measurement method.

Approximately 20 buffers were tested in total, requiring a large time commitment by Genentech PD. Small scale lab support of this project was not originally anticipated and required an additional temporary employee for three months to perform the study. When the study was completed, CMO site-specific conductivity ranges were created. Implementation of the new ranges reset the target specification so that the diluted buffer conductivity value was more centered within the range, leading to less buffer wasted. The total amount of material that could be processed increased on this step.

Case Study #2: Decrease in Process Yield

During the process transfer, Genentech provided historical in-process step yield ranges to the CMO to assess comparability of the processes. Although yields do not affect final product quality, they are used to gauge potential performance differences between sites. Typically, once the CMO has produced a minimum number of runs, the yield ranges are updated based on site specific CMO data.

Through routine process monitoring, the project team observed an approximately 10% decrease in yield on the cation exchange chromatography step as shown in Figure 6.

Column Packing	Upstream Processing	Processing Time
Buffer pH	Resin Variability	Automation
Buffer Conductivity	Load Density	Load Cell
Raw Materials	Equipment Calibrations	Assay

Table A. Partial list of potential root causes examined by CMO and Genentech.

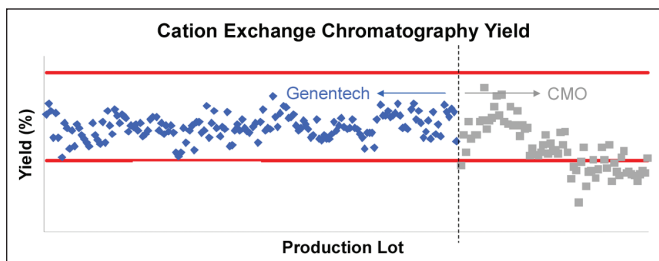


Figure 6. Historical yields on cation exchange column at Genentech and CMO.

Step yields were routinely falling below the historical values used to track step performance, resulting in deviations. These deviations were thoroughly investigated by the CMO.

Despite the low step yields, product quality was not affected and the final product consistently met all specifications. The CMO performed an extensive review of the processing data at the site to address root cause for the decrease in yields. The thorough review of historical data included, but was not limited to, the potential root causes listed in Table A.

The CMO review of the step parameters listed in Table A did not determine a root cause to the decrease in yields and small scale studies were required to further assess the issue. Studies were initiated at Genentech in purification PD to examine the decrease in yield. Small scale studies examined resin lot variability, load lot variability, and column packing variability as potential root causes. Studies performed at Genentech were able to mimic the decrease in yield seen at large scale. Additionally, the studies showed the decrease in yields was associated with a shift in the charge distribution of the load material as shown in Figure 7.

This shift in charge distribution was a result of a change in the amount of acidic and basic variants found in the load material. The change in charge distribution of the load material caused increased binding of the load to the resin. The increased binding resulted in a smaller elution profile, during the product pooling phase. Additionally, the process was

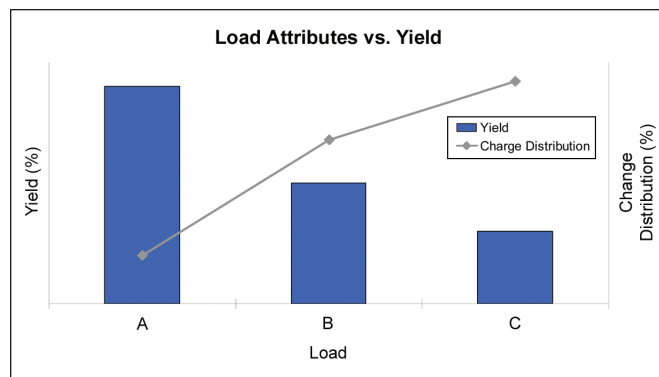


Figure 7. Small scale studies investigating the decrease in cation exchange yields at the CMO. Loads A, B, and C represent load material from the CMO during early, middle, and later lots of routine manufacture.

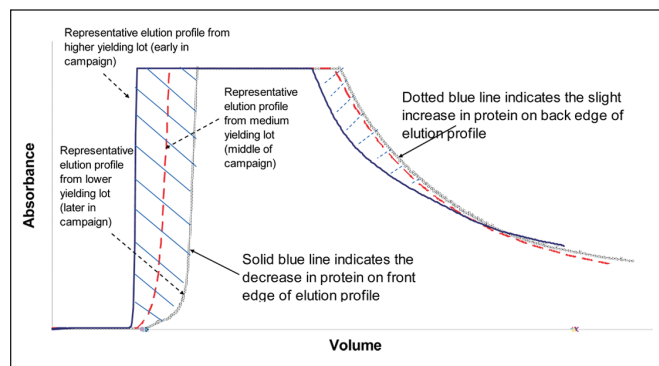


Figure 8. Change in elution profile of the cation exchange column due to the shift in charge distribution of the load. The shift in elution profile negatively effected process yield.

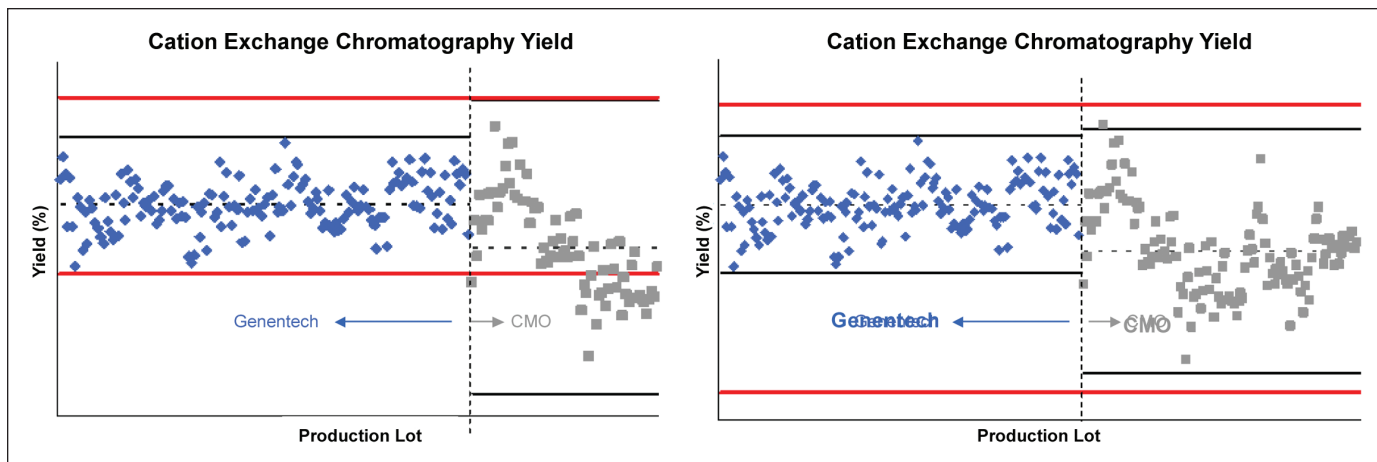


Figure 9. Yield comparison, historical Genentech yield and updated CMO yield.

pooled to a fixed volume, further amplifying the decreased yield effect. Figure 8 shows how the differences in the charge distribution of the load material affected the elution peak profile. An increase in basic variants in the load material created more narrow elution peaks, which ultimately caused a decrease in yield across the column. The solid blue lines in Figure 8 show graphically the reduction in protein yield across the column.

The change in charge distribution of the load material was attributed to cell culture variability. Further analysis within cell culture could not definitely assign a root cause. Ultimately, small scale studies were able to show the cation exchange column was performing as designed and there was no impact to product quality. Since product quality was not compromised and addressing the root cause to increase yields would require substantial changes to the production license, in this case, the team chose to maintain the current process design.

Although product quality was confirmed, the team still needed to address the multiple deviations generated from the step yield falling below the specified range. Process changes to improve the yield, such as a change in pooling strategy or buffer make-up, would have required significant regulatory involvement. Genentech and the CMO agreed to update yield specifications in order to maintain the current licensed state of the process. These updated ranges used historical data from the CMO and reflected the normal manufacturing process variability observed. The updated process yield range for this step coincided with Genentech's typical process transfer activities where yield ranges are updated for all process steps

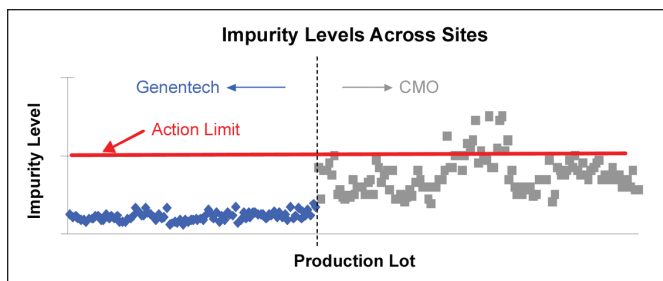


Figure 10. Impurity level comparison at Genentech and the CMO.

based on historical CMO data. The updated ranges, shown in Figure 9, were wider than the historical GNE range. However, these new ranges reflected the current expectations for the process.

Case Study #3: Higher In-process Impurity

Routine process monitoring at the CMO revealed the concentration of a process related impurity trended higher at the CMO. This impurity is measured in an intermediate process pool and has been validated to be removed to less than detectable levels with further downstream processing. Figure 10 shows the impurity values for runs produced at Genentech were lower than those produced at the CMO.

Testing of the final bulk verified removal of the impurity for all lots above the action limit. The CMO examined the out of trend results by performing root cause analysis investigation similar to the step yield investigation described in Case Study #2 - Table A. However, review of numerous parameters and step performance did not result in identification of the root cause.

Upon further analysis, the Genentech/CMO team did note a difference in the set-up of the automation recipes between the sites. Although the automation procedures were the same, the CMO loaded these procedures individually (1 process sub-step = 1 recipe) compared to Genentech's single recipe (all process steps combined = 1 recipe). Consequently, the CMO loaded seven recipes correlating to Equilibration, Load, Wash1, Wash2, Wash3, Elution, and Regeneration, when Genentech typically loaded one recipe for all of the steps combined - Figure 11. This resulted in a longer residence time for the product in contact with the resin, while the operators manually loaded the first wash recipe after the load recipe was completed.

Genentech designed small scale studies to assess the impact of residence time on impurity levels. In these small scale studies, a hold time was introduced after the load phase to mimic the amount of time the operators manually loaded the wash sub-step. The studies showed that higher levels of impurities were seen with longer residence times - Figure 12. In-process impurity levels increased approximately two-fold

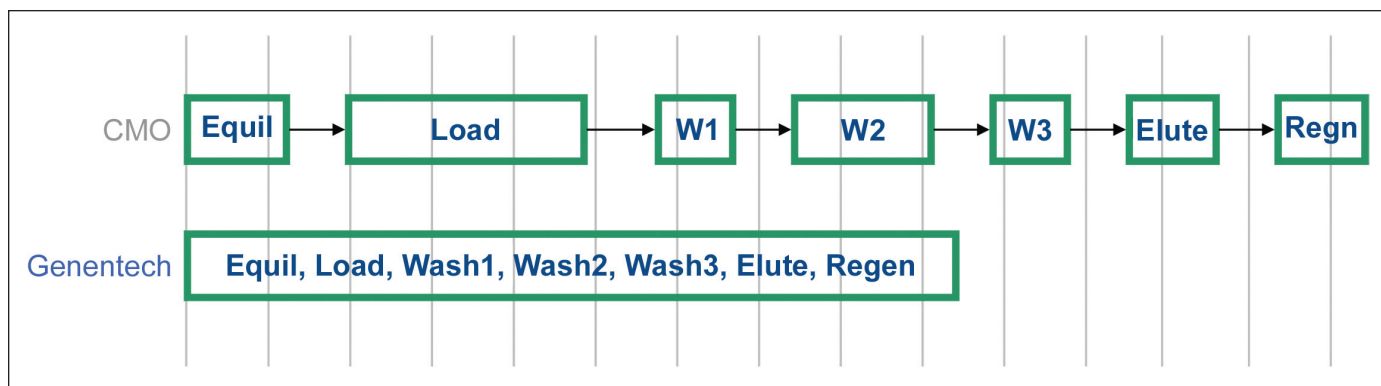


Figure 11. Automation recipe configuration at each site. The block sizes and location are roughly equivalent to process time. The CMO loaded several smaller sub-recipes and Genentech loaded one recipe to complete a given chromatography process.

with an increase in residence time of one hour.

Based on the small scale data, the CMO merged the individual automation recipes into one recipe, which decreased the residence time and also reduced overall processing time for this step by 10%. As a result, lower process impurities were seen during the next campaign.

Lessons Learned

These three case studies provide valuable lessons learned for the technology transfer team. The process transfer was regarded as highly successful to both the CMO and Genentech. The project team was able to transfer a process to a CMO, produce comparable product, and obtain regulatory approval at the site to meet business needs and ensure product to patients.

While meeting this important primary goal, the team addressed other goals including optimizing the manufacturing fit at the CMO. To accomplish this goal, process monitoring was essential for recognizing differences in manufacturing and assessing the available data for potential product impact. In all three cases presented, the optimization took time and resources. Laboratory work or equipment modifications were needed and the team worked to ensure quality product and robust manufacturing, all the while providing material for the market.

Case Study #1 demonstrated the importance of a rigorous assay transfer. In this case, both sites had methods in place to determine conductivity. A thorough review of potential

differences in these methods was not performed prior to process transfer. Because the conductivity method correlation occurred after regulatory approval, a significant amount of change control and regulatory documentation was required to implement the revised specification. Current transfer activities now require method assessment at the start of transfer.

Case Study #2 illustrated the importance of detecting data trends real-time. Early detection enabled the team to trouble-shoot the problem in multiple ways. First, the team was able to gather and analyze historical data to rule out any changes in processing. Once processing changes had been ruled out, samples were taken to perform small scale studies, which ultimately assessed whether the transferred process was aligned with the original design of the process. Had the team detected the trend later, sample collection to permit further analysis at small scale in both purification and cell culture would not have been possible.

Case Study #3 illustrated the importance subtle differences can play on the overall manufacture of a product. A documentation review of the process steps would have concluded that both sites were performing similarly. However, thorough automation recipe review and on-the-floor support from Genentech enabled the detection of more subtle differences between the sites, particularly the configuration of automation recipes. Discovering this difference in operation not only improved process performance but decreased overall processing time at the CMO.

Although the original intent of continued process monitoring was to ensure product quality, the benefits went beyond maintaining the transferred process. The case studies also demonstrate improved process economics. Although additional resources were required to further optimize production, a return on investment is dependent on other factors, including production costs, final product costs, process yields, and product lifecycle. In our case, both businesses benefited from the decrease in manufacturing time and increase in yield.

Summary

The project lifecycle of a successful process transfer does not end with regulatory approval at the site. Continued support from both the transfer site and CMO is required to ensure

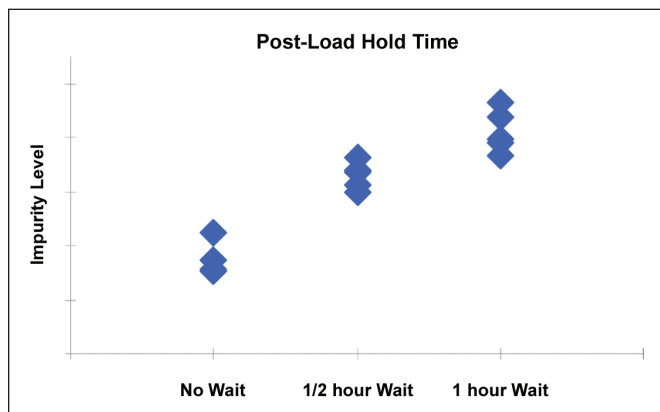


Figure 12. Effect of residence time on in-process impurity.

the transferred process runs as originally intended. In this case study, continued process support from both the CMO and Genentech was more than originally anticipated. The elevated level of support of the product not only ensured successful manufactured lots, but also provided both companies with important lessons learned for future process transfers.

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