INTERVIEW

Product and Process Development: Considerations around Validation and Control

Michele Myers is Senior Director of Validation and Lifecycle Management for Cell and Gene Therapies within GSK's Platform and Technology Sciences Department with responsibility for technology transfer, process validation and product lifecycle management. She played an important role as part of the team responsible for gaining approval of Strimvelis™, an ex vivo gene therapy product for the treatment of ADA-SCID. Before joining the Platform and Technology Sciences team, Michele worked in GSK's Global Manufacturing and Supply organization where she supported commercial biopharmaceutical production, development of production control strategies and process validation. Michele was previously an associate director at Johnson & Johnson where she worked in support of commercial biopharmaceutical production, managed a group responsible for process development for a cell therapy product and prepared regulatory filings in support of cell therapy programs. Michele is a certified Six Sigma Black Belt and holds a BA in biology from Temple University and a Ph.D. in biochemistry from the Pennsylvania State University.

Q As more cell and gene therapies move toward the clinic, what do you see as the key challenges in moving to commercial scale manufacturing of these products?

There are numerous challenges for commercial production of *ex vivo* gene therapies. I'd characterize the critical challenges in three categories.

First, the technical hurdle of how to produce lentivirus (LV) vectors at a scale sufficient to treat patient numbers beyond those of an ultra rare disease. Many companies working in the field are developing LV vector production utilizing suspension-adapted, stable vector-producing cell lines, which will allow scale-up and negate the need for plasmid production in the future. This change will move production of LV vector to a process that resembles that for a monoclonal antibody and make more production capacity available.

Second, we must find ways to automate *ex vivo* cell processing. Automation of *ex vivo* cell processing will require a move to completely closed systems to minimize contamination risks, control each unit operation to the greatest extent possible and ensure process robustness. The inherent variability of the starting material makes automation of the entire process a challenge. Development of these automation systems will be achieved using healthy donor-derived material. The systems will then require extensive testing in the clinical setting to ensure the processes are robust for patient-derived starting material.

Several companies are working to develop closed, automated systems for cell processing. GSK has entered into a broad collaboration with Miltenyi Biotech to advance our cell and gene therapy pipeline and develop systems that will move our current platform for cell and gene therapy production to an integrated, automated process. The goal of the work is to simplify the supply chain for potential treatments and increase access to our cell and gene therapy pipeline.

Thirdly, the analytical methods used to control and release *ex vivo* gene therapies are complex and highly variable, so focused effort will be required to find ways to automate the analytical methods and minimize their variability. In addition to the technical challenges associated with automated process development, there are regulatory hurdles that must be overcome to allow use of automated systems and treatment of large patient numbers because thousands of patients equates to thousands of batches requiring release. In Europe, QP release for thousands of batches using currently available processes will create a bottleneck for patient access. It is anticipated that regulatory expectations for these products will evolve in parallel with, or in response to, changes in the technical capabilities of cell processing systems.

Finally, before leaving the topic of the key challenges, it's important to point out that companies working in this space face a challenge in identifying, employing and training individuals who understand the technology, the cell biology, virology and molecular biology and who also have experience in development of medicines. We find that we need to upskill and train our workforce once they're recruited into the team and, of course, this takes time.

Q What are the key considerations when considering a process change late in development or after licensure?

Before we can consider process changes, it's absolutely critical that we effectively define the control strategy for production to minimize the sources of variability to the greatest extent possible. As with the manufacture of any other medicinal product, we can apply concepts of quality risk management as described in ICH Q8, Q9 and Q10 to systematically define the risks with respect to the manufacturing process and identify effective controls in production to mitigate those risks. That is, we need to define the critical quality attributes (CQAs) for the vector and cell product and then identify the critical process parameters and critical raw materials that must be controlled to ensure those CQAs are as expected.

DOI: 10.18609/cgti.2017.034

It's this last step of identifying the controls that's typically more challenging for cell and gene therapies than for other medicinal products. It can be far more difficult to define robust controls for the raw materials used in the production of cell and gene therapies given that not all raw materials are supplied as GMP grade and some are known to vary from lot-to-lot. In addition to the variability contributed by the off-the-shelf raw materials, we need to also consider the variability associated with the patient-derived starting materials used in the process. We need to understand and control the variability of these raw materials to the greatest extent possible to ultimately control the production process for, and the quality of, our cell and gene therapy product.

For *ex vivo* gene therapies we're essentially required to develop control strategies for two processes. We need to develop the control strategy for the vector process as well as the cell process. Because the vector process is inherently linked to the cell process, both processes need to be fully characterized. Once we have a well-defined control strategy it's easier to consider process changes.

When making any process change the first step is to assess the impact on the CQAs of the product. Given the nascent state of the technology, process changes during or after clinical development are inevitable. By starting with a risk assessment to define the impact on CQAs, developers can focus their efforts to generation of data that will provide an understanding of the potential risks associated with a process change and measures required in the control strategy to mitigate the risks.

At GSK, we try to minimize process changes late in development to avoid the associated risks. When changes are necessary, development data have been used to understand the impact before consideration for implementation in the process. For example, we are working to implement automation for cell processing. To date, the work has been focused on one unit operation and its characterization to ensure process understanding prior to automation of additional unit operations. Any product differences we've seen as a result of the intended automation have to be fully characterized before implementation in any clinical production.

Q With so many variables that can impact the end product, what analytical tools are needed to minimize risks associated with process development and validation?

We've identified a number of CQAs for our viral vector and cell products. We must, however, continue to characterize them to further our product understanding and look for additional CQAs. We need to use orthogonal methods to further study the attributes that contribute to safety and efficacy. We have a unique opportunity with an autologous therapy to directly correlate product quality with patient outcomes. As more data are generated, we have to mine the data to find the relationships and further our understanding of the process, product and mechanism of action.

Development of new tools will be important moving forward but we also need to optimize and control the analytical methods we are

currently using. One of the biggest risks to process development is the changes to the analytical methods that happen over time during product development. For example, if the viral titer assay changes while process changes are happening, it makes it challenging to stitch together the development history for the vector. We need to define the critical methods like viral titer, vector copy number, transduction efficiency, and put robust controls in place as early as possible in product development. The controls will ensure continuity throughout development and are critical to enabling technology transfer and demonstrating product comparability.

Putting reference standards and controls in place is challenging but it is important to think ahead to envision how the development results will fit together to support a regulatory filing. At a minimum, it should be standard practice to maintain process retains from throughout clinical development to the extent possible without impacting the efficacy of the product and potential benefit to the patient. Potency assays are typically most challenging and likely to evolve throughout product development.

Q Looking specifically at your experience with ADA-SCID, can you share any examples of where you had to manage process changes on both the gene/vector and cell manufacturing sides?

The gene therapy for treatment of ADA-SCID, Strimvelis™, was in-licensed to GSK in 2010 after most, if not all, of the clinical data had been generated and already showed significant clinical effectiveness. This created a sense of urgency to move the product forward and file a manufacturing authorization application (MAA) in Europe as quickly as possible.

Before we could do this, we had to mitigate certain process risks that we had identified. We introduced changes to increase the scale of vector manufacture, decrease the use of animal-derived raw materials, increase process efficiency, consistency and robustness and, of highest priority, increase sterility assurance. However, we made a conscious effort not to radically redesign or over-complicate the process given that the clinical data were already available.

The changes to ensure sterility assurance in the vector and cell processes were highest priority. Changes were made to close the processes wherever possible, implement a sterile filtration step for the viral vector, and introduce rapid microbiological testing of process intermediates to identify any potential contamination as quickly as possible before administration of the product, which currently has a shelf life of six hours. Coming from a large pharmaceutical company like GSK with expertise in sterile product manufacturing, it took time for our internal understanding, alignment, and development of the release process to ensure that our internal stakeholders were in agreement with the processes developed and our risk mitigation strategies for this novel type of therapy.

DOI: 10.18609/cgti.2017.034

In addition to managing changes to the vector and cell process there were also changes to the analytical methods. Ultimately, we found that the analytical changes needed were among the most challenging as they required us to go back and test retains to fully understand the product and processes throughout clinical development.

Q How do you approach the critical issue of product comparability?

Managing comparability starts with the assessment of the process changes we discussed earlier. It's defining the impact of the process changes on each CQA and generating development data to support our proposed assessment of the risk. With the development data in hand, we can take a science- and risk-based approach to comparability. We've been fortunate to have had very open and productive conversations with regulators as part of scientific advice about our plans for demonstrating product comparability.

Demonstrating process and product comparability is challenging for autologous therapies because the variability associated with the processes is confounded with the variability of the starting material. For Strimvelis we completed two studies. First, comparability of the vector processes and product was studied. Those CQAs we'd assessed as potentially being impacted by implementation of the process changes were tested side-by-side to the extent possible to evaluate differences in the product from the clinical and commercial production processes. Once we were convinced the vector from the commercial process was comparable to that used in the clinical study, a second study to assess the comparability of the cell process was conducted. To evaluate comparability of the cell process and products, bone marrow from a pool of healthy donors was divided in half to supply two arms of the study. One arm of the study used the clinical production cell process and vector generated using the clinical process. The other arm of the study used the commercial cell production process and vector generated using the commercial vector production process. Conducting the study in two parts and using the clinical and commercial vector provided an opportunity to evaluate the cumulative impact of the vector and cell process changes. Again, the risk assessment used to identify CQAs that may be impacted by the process changes was used to define the list of characterization testing performed for the final product from both arms of the study.

Splitting the donor material to support side-by-side evaluation of processes is the ideal approach to improve the ability to detect any potential impact of process differences, but it's admittedly logistically difficult to manage this type of study to demonstrate comparability between manufacturing sites on different continents. We're currently working to transfer cell processing for the treatment of metachromatic leukodystrophy from Milan to Philadelphia and working out the logistics and possibilities for how we'll demonstrate comparability of the production processes at the two sites.

Q What opportunities are there to achieve a reduction in cost of goods when considering process development in the move towards commercial-scale production?

For most medicinal products, decreasing cost of goods is important to achieve a return on the upfront R&D investment. For cell and gene therapies, being able to decrease the cost of goods is critical to achieving the long-term promise of the technology and enabling patient access for these new therapies.

We can go back to the discussion we had earlier about the critical challenges for commercialization of cell and gene therapies. As we overcome the challenges for large scale LV vector production, automation of the cell production processes and the analytical methods used to test the products, we'll impact the cost of goods. The costs associated with the LV production are high because we're currently limited to production of relatively small batches and analytical testing of each batch is costly. We need to get to a point where one batch of vector can be used for treatment of a larger number of patients to reduce the costs associated with the vector for each patient treatment.

After we've scaled-up the LV production processes, automation of the cell process and integration of the analytics with the automated system will help reduce the cost of goods and allow greater patient access. In the future if we're able to automate the production processes, understand all the potential sources of variability, put robust controls in place and demonstrate consistency of the product, we could potentially argue to reduce the level of testing necessary for routine release and thereby reduce the costs of goods and improve patient access. We will, however, need a great deal of data to reduce the testing requirements for these products.

Q With the shift towards more automated closed system processes, what are the major analytical challenges and opportunities that this presents for process control?

A great deal of effort is typically taken to ensure process technology transfers are robust and generate comparable final product. It's important that the same focused attention is given to the transfer of each analytical method used to control the process and/or test the final product. Demonstrating that an analytical method is performing comparably between two manufacturing sites is a fundamental requirement prior to attempting to demonstrate the product comparability.

There are efforts to standardize test methods used for cell and gene therapies. The US National Institute of Standards and Technology (NIST) and other agencies are working with industry to define the methodology and put controls in place where possible to help facilitate development. Ideally new analytical methods in the future will be able to be integrated with the automated production process.

Michele Myers, Sr Director, Validation and Lifecycle Management, C&GT Platform Technology & Sciences, GSK

DOI: 10.18609/cgti.2017.034