A CASE STUDY

Automating Aseptic Manufacturing of Autologous T-Cell Therapies

An Aseptic Process Simulation (APS) clearly demonstrates that the closed-system Cocoon® manufacturing platform results in a sterile end product

According to the National Cancer Institute, immunotherapies that enlist and strengthen the power of a patient's immune system are the "fifth pillar" of cancer treatment adding to surgery, chemotherapy, radiation therapy, and molecular targeting. Autologous CAR T-cell immunotherapy is one approach that is changing the lives of many patients with blood cancers. To date, the FDA has approved six CAR T-cell therapies to treat leukemias, lymphomas, and myelomas.

However, manual or partially-automated manufacturing processes contribute to the high cost of this potentially life-saving immunotherapy. Manufacturing involves several segmented steps—sample separation, cell selection, activation, transduction or transfection, expansion, harvest, and final formulation.

"An autologous product is manufactured on the scale of one product for one patient. Traditionally, this manufacturing has been done in a piecemeal, labor-intensive manner," said Nicholas Ostrout, PhD, Senior Director Strategy and Implementation of the Personalized Medicine Business Unit at Lonza. "You perform a step, and then transfer the cells to another piece of equipment, often through a biosafety cabinet, to go to the next step. This works fine for a small number of patients but is unsustainable for commercial scale up."

Automating the Manufacturing Process

To incorporate and automate all manufacturing steps in a single system, Lonza developed the Cocoon® Platform. The Cocoon® Platform is a closed-system, patient-scale bioprocessor. Cells are loaded into a sterile, single-use cassette, within which all the manufacturing steps take place. As such, Lonza's Cocoon® technology significantly increases quality, reduces labor and costs, and facilitates efficient scale up of CAR T-cell products.

"Not only can the Cocoon decrease the cost of autologous CAR T-cell products, but it can also bring manufacturing closer to the point of care," said Ostrout.

Demonstrating a Process is Aseptic

"Gene-modified cell therapies cannot be terminally sterilized by filtration," said Laura Sands, Head of Regulatory Affairs, Personalized Medicine Business Unit at Lonza. "The entire process must be run aseptically to ensure that it produces a sterile product on the back end." To this end, Lonza manufactures the Cocoon® Platform to applicable ISO 13485 standards, and actively engages with regulatory bodies to validate the platform's capabilities. This includes proof of the capability for sterile manufacturing by aseptic process simulation (APS).

Key regulatory guidelines with similar language are applicable to APS, also referred to as aseptic process validation (APV): the FDA guidance for industry on sterile drug products produced by aseptic processing, the EMA guideline on GMP for ATMPs (Advanced Therapy Medicinal Products), EU GMP Annex 1: Manufacture of Sterile Medicinal Products, and the PIC/S Validation of Aseptic Processing PI007-6 guidance. PIC/S also provides inspection guides for auditors that manufacturers can use to facilitate their study design.

"To satisfy regulatory requirements, you need to demonstrate that a manufacturing process can result in a sterile product," said Sands. "Sterility testing is probabilistic since microbial contamination is not uniformly distributed across a batch. A representative sample from an end product could provide a negative result even if contamination exists elsewhere within the product volume."

A combination of controls ensures a sterile drug product including management of the clean room environment, environmental monitoring, and an APS.

All drug product manufacturers are required to perform APS studies in-house with their operators and specific processes. This validation step is required in triplicate prior to the start of manufacturing, every six months thereafter, or earlier if a change to the process, equipment, procedures, or environment is deemed to have the potential to impact the aseptic process.

In an APS all of the starting materials, in-process reagents, and additions to the process are replaced with sterile microbiological growth medium, such as Tryptic Soy Broth, to easily encourage the growth of contaminating microbes. "An APS incorporates all the process steps and manual interventions (routine and non-routine) to simulate the entire process," said Sands. "At completion, the media samples are incubated and checked for growth."

Including all variables means manufacturers can spend a significant amount of time running the APS. The closed-system Cocoon® Platform automates the majority of the manipulations, thereby simplifying the study. "The Cocoon® Platform reduces the number of manual interventions and, therefore, the length, duration, and complexity of the APS study," said Sands. The closed-system also provides the ability to run the process in a lower classification Grade D environment, reducing facility management needs. Typically aseptic manual processes are run in a Grade B background with access to Grade A environments through biological safety cabinets.

"An appealing feature of the Cocoon® Platform is that the interactions with the single-use cassette are the same regardless of the product – loading the cassette, connecting the fittings to do the sampling, extracting material from the cassette, and so on," said Sands. "Potentially, an organization could run a single APS with the Cocoon® Platform and cover multiple products, another opportunity for time and cost savings."

The APS Design and Results

To demonstrate that the Cocoon® Platform could reproducibly generate a sterile product, Lonza performed a worst-case scenario APS.

The APS was carried out in an internal non-GMP biology laboratory, not in a clean room. "We performed the study in a regular biology laboratory where air quality is not controlled as demonstrated by environmental monitoring particulate data included in the APS documentation appendix," said Michele Vicentini-Hogan, Research & Development Scientist at Lonza.

The study was performed in triplicate and used three separate cassettes. All typical manual interactions were maintained and non-routine interventions, such as having to change out a fitting or take an extra sample, were included to mimic a worst-case scenario.

"Our process is usually 10 days long, but for the APS we accelerated it to 2 days by reducing long incubation periods that did not involve manual manipulations," said Vicentini-Hogan. "During a regular run we take samples from the culture and inject media into the cassette. Since we wanted a worst-case scenario, we added more non-routine interventions to the protocol to really test the system and prove that it could keep its sterility."

Operators were scientists experienced in using the Cocoon® Platform. "We had multiple operators using the same cassette and changing the reagents to add even more risk than having each operator use a different cassette," said Vicentini-Hogan. "We showed that even though we did a lot of manipulations to the cassettes they maintained sterility."

The samples collected during the study were divided into two, half of the volume was kept for the internal analysis performed at Octane Biotech, a Lonza Company, and the other half of the volume was sent to a third party, SGS Life Sciences, where the test was repeated. The Growth Promotion Test was performed solely by SGS Life Sciences.

"We stacked the odds against the Cocoon® Platform and tried our hardest to see if it would fail and it did not," said Vicentini-Hogan. "Auditors request the results of the APS. It is a simple yet effective test to prove that a process maintains sterility."

Summary

The worst-case scenario APS undertaken by Lonza utilized the Cocoon® platform, a closed-system, patient-scale bioprocessor for the manufacture of autologous immunotherapies. The APS clearly demonstrated that using the Cocoon® Platform for manufacturing processes results in a sterile product, even when performed in an unclassified space.

The Cocoon® Platform's journey has just begun. Lonza continues to innovate and integrate new technologies, such as magnetic selection capability to address the challenge of high variability in the cellular starting material, and enhanced analytics to allow for in-depth product characterization.

"We have big plans and have processes for other cell-based immunotherapies, in addition to CAR T-cells," said Ostrout. "We will continue to broaden the Cocoon® Platform's applicability to additional gene-modified cell therapy modalities such as those using NK cells, hematopoietic progenitor cells, dendritic cells, and monocyte-derived cells." ■

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