

INNOVATOR INSIGHT

The importance of fill & finish in the commercialization of your cell & gene therapy



Jean-Sébastien is Head of Sales at Aseptic Technologies, a company he joined in 2007. His role is to manage and direct global sales efforts of Aseptic Technologies; accelerating growth and creating tighter connections between customer requirements and innovation, along with increased service levels, with a special attention to advanced therapy medicinal products since 2009. Jean-Sébastien is also a member of the Process and Product committee of the International Society for Cell Therapy (ISCT).

Q Can you tell us a little about the background of Aseptic?

Aseptic Technologies was founded in 2002 with the aim of developing a new primary packaging concept for biological drugs – namely the AT-Closed Vial container and associated filling technology. As this was a completely new concept in primary packaging, it required a great deal of development effort and we took advantage of that time to create strong relationships with the regulatory authorities, which helped guide our designs. By 2008 we had started to commercialize this solution and started working with our first cell and gene therapy company a year later.

Q What are the main differences for fill and finish for cell and gene therapy products compared with more traditional biologics?

The key difference is batch size and time to process the batch. For cell and gene therapies the batch size is still relatively small compared with a 'regular' biologic.

In addition, the processing time is also a major difference as a cell and/or gene therapy typically has to be processed in a 2–3-hour time window due to its inability to withstand storage at room temperature. Therefore, it's critical the fill and finish operation is completed rapidly, without compromising the quality of the product. Thus, equipment that has been designed for relatively large biologics campaigns can meet this criteria of high speed fill and finish within the timeframe of 2–3 hours. This is why it was an obvious strategic move for us to supply the cell and gene therapy space, having already developed fill-finish capabilities with traditional biologics.

Q Why is fill and finish such an important part of the manufacturing process?

It's such an important step in the process, primarily because the product container is going to be used for the long-term storage of that product and therefore it needs to be robust and maintain product integrity at the defined storage conditions (mostly vapor phase of liquid nitrogen). It also needs to be the right container to work within a scalable process, and must be compliant with all the regulatory requirements of the intended market. Ideally, the container needs to be selected during Phase 1 or 2 of clinical development of your cell/gene therapy, with the final goal of commercialization in mind. This is such a crucial point – developing a therapy without commercialization in mind can lead to huge problems and delays. So it's very important when selecting your container that you do so early enough in the development process to ensure it's suitable for commercial-scale production of your product. In our experience, most companies are aware of the importance of fill and finish and engage us at the right phase of development, but a number of these discussions are still only happening when the company is closer to Phase 3 and commercial production.

As a supplier we often work with a company from the lab stage all the way through to commercial production so we develop an in-depth understanding of their product and manufacturing processes, which enables us to provide guidance on how to integrate the fill and finish steps as seamlessly and cost effectively as possible.

What's great to see now is that as the field matures, we are seeing a trend towards much greater recognition of the importance of fill and finish in the development and commercialization of cell and gene therapies. This is primarily fuelled by the greater number of products moving towards the clinic and out of the laboratory setting – and as that transition occurs, it becomes very apparent that the fill and finish solution utilized in early stage development has to be selected with the commercial production in mind.

Q What are some of the key challenges faced in the industry when it comes to fill & finish, and what are some of the steps taken to address this?

A great deal of the industry's knowledge and regulations around fill finish is derived from the blood industry. Whilst the regulatory agencies expect biopharmaceutical standards to be applied to cell and gene

therapies, there are of course some adaptations due to the very nature of these therapies.

The key requirement is of course that the manufacturing process is current Good Manufacturing Practice (cGMP)-compliant to ensure the safety of the product to be injected in the patient. When we look at the methods of fill and finish used in the lab settings, these will typically involve screw caps and bags, and as such very open or not scalable processes which of course cannot be used in later phases of development.

Given the importance of fill and finish, we carried out a study to quantify the relative reduction in contaminant risk from viable particles in air supply between aseptic filling technologies: open vial, ampule, blow-fill-seal (BFS) and prefilled syringes, compared to the AT-Closed Vial technology. This study demonstrated that BFS and AT-Closed Vial technology significantly reduce the risk of contamination due to exposure to the environment, in some cases by a factor of more than 100 [1].

Product contamination at the point of fill and finish would potentially disqualify your entire batch, which would be incredibly costly for any company. Furthermore, in terms of risk to the patient, it is estimated that 2% of patients affected by outbreaks leading to infections were contaminated by badly manufactured injectable drug products. Therefore, it's essential that cell and gene therapy companies understand the difference that the fill and finish solutions they employ can have on product quality, patient safety, and ultimately their costs.

Another challenge when considering your fill and finish processes is that whilst the glass vials, syringes and ampules can reduce the risk of contamination, they can present problems when cryopreserving your product by losing their integrity at the critical step of cryo storage.

As we started discussing the fill and finish requirements with cell and gene companies one of their critical questions concerned the potential impact the vial could have on the freezing profile of their product. For example, when working with Celgene, they were using bags for their product but were looking to move to 20 ml AT-Closed Vials. To assess the potential impact of the change in container on the cryopreserved profile of their product they carried out extensive testing, which was presented in a poster during an ECI conference in 2012 [2]. It was great to see that the impact of the change in container on the freezing profile of their product was almost negligible, which made the transition from bags to our vials a very reliable process.



Q Aseptic have developed a new robotic system for fill and finish, the L1. Can you share some insight into the technology and how it differs from conventional technology on the market?

The robotic system we have developed allows the effective scale-up of the fill and finish operations with our AT-Closed Vial technology. As with any automated system, the primary benefit of moving to a robotized system is the increase in speed of processing and the removal of

operator variability; this system being able to process up to 600 AT-Closed Vials per hour. For any company, being able to reduce contamination risks whilst also reducing your production times is a crucial part of developing a commercially viable therapy, with a scaling up or scaling out strategy. We've seen adoption of the robotic system in Korea (e.g., Kolon Life Science) and Japan and would hope for broad adoption across the industry.

The equipment can now come completely closed and H₂O₂ decontaminated; product transfer, empty vials and caps entry and connection to the bulk, is all integrated therefore maximizing the simplicity of operation.

This new system can also positively impact the cost of goods of your cell or gene product by reducing capital and operational expenditure. As a small, closed, self-isolated system it indeed removes the need for Grade B clean room and reduces your footprint, thus enabling you to save on CapEx and OpEx.

Q What implications does the automated system have in terms of regulatory considerations?

As with any other equipment utilized in your manufacturing process, the Isolated L1 robot needs to be approved by the authorities as part of the complete process. It's not the equipment itself, rather the process it undertakes within your manufacturing pathway that needs to be approved by the regulatory body. Our experience in the field, with more than a hundred companies using our technology, makes us very knowledgeable about the approval of the AT-Closed Vial technology while we've been working closely with SKAN AG, the leader of isolation technology since the outset of developing our integrated robotic concept and presented it to the FDA last year, who provided really positive feedback. It was very rewarding to see that our efforts to support the cell and gene therapy community in the development of safe and affordable therapies offer the potential to change the face of healthcare.

REFERENCES

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2. Engineering a Process Change from Cryobags to Cryovials. DeWitt D, Murphy B, Russotti G. Poster Presentation. www.aseptictech.com/sites/default/files/publications/eci_poster1_-_dan_dewitt-updated.pdf

AFFILIATION

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