

Cool Tool – Particulates in Cell Therapy Products – An important issue for commercialization

The presence of particulates in cell therapy products is an issue that is becoming increasingly important as potential cell therapies move through the clinical pipeline. I recently read a very informative paper on this topic titled, “Managing Particulates in Cell Therapy: Guidance for Best Practice,” published in *Cytotherapy* and written by the International Society for Cellular Therapy (ISCT) Process and Product Development Subcommittee (Clarke, et al.). The paper was written to provide guidance for cell therapy developers, manufacturers and also suppliers regarding the management of particulates in cell therapy products. This paper is particularly valuable, since currently there are no set limits or standards specific to particulates and cell therapy products.

The authors begin the paper with a brief background on the issue surrounding particulates. The primary challenge is that cell therapies, unlike most other biologic drugs, do not undergo a final sterile filtration step prior to final product packaging. This is because the cells are the final product and thus wouldn't pass through a filter that could capture the particulates without also capturing the cells. As a result, particulate matter is not filtered out of the final product prior to release and this presents a potential risk to patient safety and product quality.

Particulates in Cell Therapy Products

Particulates can be introduced in a variety of ways including through the external environment, manufacturing/packaging materials, and from the cells themselves. Since it is unlikely that particulates can be kept out completely, cell therapy developers and manufacturers must conduct a risk based assessment to determine the level of risk present in each manufacturing scenario. This evaluation requires identifying the particulate type and the particulate load as well as the impact of these to patients, product quality and regulatory compliance. In addition it is important to understand the particulate characterization, i.e. its composition and source. The paper states, “It is the responsibility of the cell therapy sponsor to characterize and understand the load, source, composition and potential impact of particulates in the final formulation of the product.” In particular, particulate size, number, source, and infusion route are key to understanding the risk to patients and product quality.

In order to understand the makeup of particulates in the final product, companies will look to quantify and characterize the particulates. Quantification can be done visually for larger particulates, but for smaller particulates other methods must be used and these are destructive to the cells. Hence, smaller particulates can only be identified in process development or validation but not as release criteria in the final formulation.



Characterization involves determining the type, source and composition of the particulates. The source of the particulate is important as this helps to create controls and if needed, mitigation steps. Particulates can enter the cell therapy manufacturing process at many different steps and can accumulate throughout the process. To reduce the introduction of particulates, the paper points out the importance of the relationship between cell therapy developers, manufacturers and suppliers in working together to both identify and to reduce the introduction of particulates.

By understanding the particulate profile of the final product, a risk assessment can be performed and quality tools such as process flow diagrams, fishbone diagrams, and failure modes and effects analysis (FMEA) can be used to both assess the risk each type of particulate poses as well as identify controls, and if needed mitigation strategies, to reduce the introduction of particulates during the process. After controls or mitigations are implemented the effectiveness of these methods then must be evaluated.

After reading the paper, I was fortunate to be able to interview Dr. Dominic Clarke, Global Product Manager for Cellular Therapy and Bioprocessing at Charter Medical and corresponding author of the paper. I asked Dominic about his involvement and about particulates in cell therapy. Here is the summary of our interview:

Question:

How big of a challenge do you think particulates and their impact on quality is to large scale commercialization of cell therapies? Where are we now and where do we need to go?

Answer:

Particulates could be a real issue for commercialized cell therapy products if they aren't managed appropriately. The industry is actively addressing the challenge of particulates. The risk of

particulates is dependent on a number of factors as described in the paper. The industry needs to maintain awareness and actively monitor and control particulates through risk-based approaches. Removal of all particulates is likely not possible or necessary as long as the potential risks are assessed.

Question:

Can you explain the absence of a sterile filtration step in cell therapy manufacturing and the impact of that on quality?

Answer:

For cell therapies, the cell is the product. Since the cells can often times be larger than many of the sub-visible particulates, a final filtration step is currently not an option, as the cells would be removed along with the particulates. Furthermore, cell-based solutions aren't typically clear which makes visual particulate inspections of the final products difficult.

Question:

As you point out in the article, particulates aren't just an issue in terms of quality and patient health, but also greatly impact cell culture and production. What are the key impacts of particulates in cell culture?

Answer:

Studies have demonstrated that particulates could affect the adhesion properties of cells, which can lead to cell lysis or promote cell aggregation for example. Particulates can also be cytotoxic, causing inadvertent activation and ultimately impact the viability and functionality of the cells.

Question:

I think that there is a feeling that materials such as disposables, packaging, and various primary contact materials make up a large portion of the particulates, however in the article you present data showing that in clean rooms, personnel are the source of 70% of the particulates. While manufacturers are working to create products that reduce the levels of particulates, what can be done about the particulates humans introduce?

Answer:

The source of particulates can be misleading at times so you highlight a good point. We (the authors) want to stress that particulates in cell therapy are cumulative throughout the entire process making the inability to final filter even more critical. Since cell therapy manufacturing is predominantly performed using single-use components, a percentage of the particulate load does originate from the disposables/packaging, etc. Particulates are also introduced during the manufacturing of the CT product with contributions from the starting material, environment (personnel) and process (tube welding for example). Indeed, evidence does support that the personnel can contribute significantly to the particulate load. This is why it is important to perform some level of particulate characterization to determine likely sources so that a risk analysis can be performed and improvements can be made. As a single-use supplier, we perform these types of analyses on a regular basis. In addition to performing 100% visual inspection, the ongoing analysis has led to improvement in our raw material sourcing, personnel gowning procedures and even optimizing process flows.

Question:

In the paper you provide several good resources for evaluating both the type of particulate and the associated risk. As well as providing suggestions for identifying the particulate source and mitigation solutions. What advice would you have for

cell therapy companies that are beginning to think about commercial manufacturing of their cell therapy product with respect to particulates and quality?

Answer:

Currently there are no limits or standards specific to particulates and cell therapy products. Companies would benefit from performing an initial risk-based analysis to determine the potential impact of particulates. Awareness of the particulate load (number and potential sources) in the final product will contribute significantly to possible mitigation steps if needed and aid in continuous improvement efforts.

Question:

How important is it for companies to work with their suppliers on particulate issues and what do you see as the role of each?

Answer:

Collaboration is always important as it can help address any immediate requirement or concerns and help with potential long-term needs resulting in product testing or design.

Question:

Why was it important to you to become involved in this project?

Answer:

Cell Therapy is an exciting industry with products that have the promise to provide life-changing results. Charter Medical and myself, the team of authors on the paper, and the ISCT Process and Product Development (PPD) committee are invested in the growth and future of Cell Therapy. Charter Medical viewed this as an opportunity to learn and contribute to our internal continuous improvement efforts and in turn assist with the evolving needs of the industry.

Question:

If you had a crystal ball, with respect to manufacturing trends for cell therapy, what would the future hold?

Answer:

As more and more CT products gain commercial approval, I expect established guidance documents and standards (particulates for example) will be developed specifically for the industry. These documents will aid in the manufacturing and quality of the raw materials and CT product manufacturing. Processes will become more and more automated which will reduce manual handling and exposure which will lead to more efficient and cost-effective manufacturing and likely aid in reduction of overall particulate load.

References:

1. **Managing particulates in cell therapy: Guidance for best practice**, Clarke, Dominic et al., Cytotherapy, Volume 18, Issue 9, 1063 – 1076

