CELL & GENE THERAPY RAW MATERIALS:
GETTING IT RIGHT FROM THE START

SPOTLIGHT

INTERVIEW

Scope and challenges of managing particulates in cell therapy manufacturing

Dr Jean Stanton joined Johnson and Johnson (J&J) in 2008 after more than 20 years in the healthcare industry, developing cell-based therapies. Jean is responsible for leading the integration of cell and gene therapy regulations into Janssen's internal quality standards. Jean works closely with the business and development organization, establishing compliance strategies relating to cell and gene therapy products as well as supporting due diligence activities, regulatory agency interactions and health authority inspections. Jean's current responsibilities also include the deployment and maintenance of the R&D compliance program for all GMP aspects within the J&J Pharmaceutical sector, which includes the development and maintenance of the quality and compliance strategies to support all novel products that are in-licensed or developed within Janssen.

Q Managing particulates is seen as one of the biggest challenges in cellular therapy manufacturing. Could you tell us a bit about particulates and the risks associated with their presence in cell therapy products?

For cellular therapeutics, the active ingredient of the product is the cell. That prevents any type of final clearance or filtration step prior to the final product packaging, unlike traditional biologic drugs. This is because cells cannot pass through a filter that could capture the particulates without also capturing the cells. Whatever particulate is there in the final product cannot be removed.

For developers in this field, there is very limited information in literature regarding the impact of particulates on their specific product attributes. One of the biggest challenges associated with it is understanding the risks involved to those patients from a cell therapy perspective. Currently, we are extrapolating information from other industries. For instance, if we want to assess the risks of particulates to patients, we look to the healthcare industry and the literature on the impact of particulates for people who are infused with large volumes of IV fluids. To understand the impact of particulate on the cells themselves, we refer the medical devices industry and look at the work they've done understanding implantable materials in the body and its impact on cells. Currently there is no study that has looked at the specific cells and materials we are working with. We're taking data and making inferences, trying to theorize what would be the risks in our patients or our cells.

Q How do particulates and their impact on quality affect the large-scale commercialization of cell therapies?

Particulates and their impact on safety and efficacy does not necessarily change as you progress from early-stage development to large-scale commercialization. What changes are the volumes of consumables and equipment.

Problems can arise for developers who have not started to characterize their particulate load, early in development. When changes are made to scale up the process, it gets harder to understand the sources of these particulates or the ingress routes. It also gets more difficult to justify the impact of any process changes to the particle load. Managing both change management and investigations becomes more challenging. If companies aren't starting early, it becomes difficult to defend process controls related to particulates.

> Currently there are no cell therapy-specific guidance documents related to particulates. We're working with what exists for other biologic drugs.

Q How are particulates introduced to cell therapy products and where do they typically originate during a cell therapy manufacturing process?

What we find is pretty much aligned with what you see in the general drug manufacturing literature. Particulates can be introduced in a variety of ways including the external environment like the personnel, equipment, manufacturing/packaging materials and materials like buffers and cell culture media. It is hard to get rid of all particulates completely; cell therapy developers and manufacturers must conduct assessments to determine the level of risk present in each manufacturing scenario and what controls can be implemented to mitigate the risks.

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Q What are some of the current methods available for their detection and how effective are they?

There have been no methods developed specifically for cell therapy. What's currently being used in the pharma industry is what we're using now. Visible inspection is the primary test performed routinely. However, cell-based solutions aren't typically clear, which makes visual particulate inspections of the final products difficult. Techniques like the light microscopy, flow cytometry and dynamic light scattering assays are used for the detection of smaller particulates. And possibly for detecting very small particulates in the nano range, SDS-PAGE can be used but it has not been used in the industry yet.

The effectiveness of these techniques is dependent on the context in which they are used. It depends on whether it's adequate for the material being tested and it has to take into account whether the method is destructive to cells. Developers also need to evaluate who is performing these tests and the capabilities of the lab. Are they able to work with complicated method or simpler ones? Some type of qualification is necessary to ensure that the method selected is adequate.

Q How relevant are the current guidance documents and what are some of the challenges associated with setting limits specific to particulates and cell therapy products?

Currently there are no cell therapy-specific guidance documents related to particulates. Again, we're working with what exists for other biologic drugs. For example, in the USA we work with USP 788, 790, and the relevant EP and JP requirements for Europe and Japan.

The greatest challenge is the basic assumption that the final product is clear and transparent. Cell therapy products on the contrary are opaque, because they are cells.

The other thing to remember is testing for visible particulates. The result 'no particulates detected' gives no guarantee that there are no particulates present. It could be that these particulates adhere to cells or hide in aggregates or be engulfed by cells and this could in turn impact safety and efficacy.

Q Could you share your thoughts on the potential strategies being developed to address and control contaminating particulates in cell therapy products?

From an industry perspective, I think it's been very limited. In cell therapy conferences, it's very rare to see topics related to particulates. It's very different compared to that of other biologic drugs, which have had entire conferences dedicated to particulates.

I think the type of strategies deployed to control particulates tend to be company specific. I've seen where some companies are very proactive, they're working up front with suppliers, characterizing particulates very

early in development, and then establishing controls and working to improve the process for optimization and lower the number of particulates.

There are others who don't get into the details, beyond basic descriptions of particulates identified upon visible inspection of the final product. There are still some others who wait for regulatory agencies to indicate a need, if they don't hear it they may not do it.

Q How important is it for cell therapy developers, manufacturers and suppliers to work together on particulate issues and what do you see as the role of each stakeholder?

If you think about basic drugs, on average about 20–25% of recalls are related to particulates. If you look at the sources of these particulates, 25% of them originate in the consumables and materials. It is critical to the success of developers and suppliers to forge a path together when it comes to controlling particulates. All stakeholders have a role to play to resolve this issue. Working together is the only way to understand where they come from or how to improve it or make it better.

> All stakeholders have a role to play to control particulates in cell therapy products. Working together is the only way to manage them effectively.

The sponsor is ultimately responsible for what's in their product and the regulator will hold them accountable. Product developers need to start early to characterize what's in their product, the source, ingress route, composition, morphology, size, number etc. Once the information is transferred to the manufacturers, it's their responsibility to maintain control of particles, via environmental monitoring programmes, managing complaints, looking at visual inspection procedures and making sure adequate training is available.

Suppliers are responsible for managing the particulate load of their supply. Many of the controls put in place for drug products can and are applied to materials.

You can't improve the process without the involvement of all three stakeholders and they can't operate in isolation to improve process. I've seen the most success when all three parties are working together to improve controls, and reducing the potential for particulate contamination.

Q With respect to particulates and quality, what advice would you have for cell therapy companies that are beginning to think about the commercial manufacture of their cell therapy product?

I've seen presentations from companies where they have been very aggressive. You can really see the difference between Phase 1 and Phase 3 where they have paid attention to particulates and focused on

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efforts to reduce them. The more the suppliers are engaged in understanding their particulate load, the better it is for the company. I haven't yet seen any supplier who has responded negatively to such a request. Even if they do, it's not beneficial in the long term if they want to remain as a supplier in the cell therapy industry. Being willing to work on this effort jointly is important for the success of all parties.

Therefore, I think starting early during product development is the critical step. The more work done upfront will help developers in the long term with investigations and process changes. The key factor to optimizing a process is having the ability to identify what is a critical change, and when have they gone too far. If they don't know it at the beginning stages, it's going to be difficult later on.

It's important for the industry to start asking some of those standards setting organizations like USP and ISO to start thinking about this topic. I think there are limits to working with the more general guidance documents. As the industry moves forward, I think it's important that it has standards that better support cell therapy products.

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