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REVIEWS

Managing particulates in cell therapy: Guidance for best practice

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Abstract

The intent of this article is to provide guidance and recommendations to cell therapy product sponsors (including developers and manufacturers) and their suppliers in the cell therapy industry regarding particulate source, testing, monitoring and methods for control. This information is intended to help all parties characterize the processes that generate particulates, understand product impact and provide recommendations to control particulates generated during manufacturing of cell therapy products.

Key Words: *cell therapy, disposable, injectable, parenteral, particle, particulate*

Background and introduction to particulate challenge

The cell therapy community is currently engaged in more than 2500 clinical trials around the world, with 15% of those being industry-sponsored clinical trials and the remainder sponsored by leading academic centers [1]. In addition to commercially available cell therapy products and those in development, cells have been used as a standard of care for decades in the medical practices of hematology and oncology. Stem cell transplantation, for example, continues to be routinely used in, and investigated for, an increasingly diverse and growing list of malignant and nonmalignant diseases. More than one million stem cell transplants have been performed globally to date [2]. When stem cell transplantation is used as a form of cancer treatment, the requirements for particulate control in the material used for the transplant have been limited to aseptic techniques used during production, visual inspections at release and immediately before administration and in-line filters utilized at the bedside.

Cell therapy products do not undergo final filtration steps (e.g., sterile filtration) as is routinely done for many biologic products; consequently, companies developing commercial cell therapy products and suppliers need to consider the potential risk of particulate matter contamination from the external environment, during the manufacturing process or related to cellular or protein degradations. The presence of particulates in cell therapy products currently represents a quality challenge and may pose safety concerns. The challenges of particulates include difficulties identifying the nature of the particulates found in the final or injected product, limited or no understanding of the impact of particulates on the cells and difficulty defining relative contributions of different types of particulates to any *in vivo* toxicity or immunogenicity effects. Together these issues mean that control of particulates is likely to require a combination of analytical methods [3].

The current pipeline of cell-based therapies represents a maturation of the science surrounding these products. As such, the next generation of products carries enhanced expectations of quality, safety, efficacy and commercial viability. Compared with the first generation of cell therapies, the products currently in clinical development must be better characterized to

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understand the contribution and potential impact of particulates.

A number of articles addressing particulate matter exist for the pharmaceutical and bioprocessing industries [4–6], but references to particulates and cell therapies have been limited [7]. As highlighted by Clarke *et al.*, there are many reasons the regulations, guidelines and practices used to manufacture traditional pharmaceutical drugs or biologic products do not apply equally well for cell therapy products. Traditional injectable products are sterile filtered before the final fill. These clarified solutions are much easier to assess with current visual inspection methods [7]. Efforts have also more recently been held directly or indirectly by academia with research and development–driven competences to aid in addressing the particulate contamination issue for cell therapies. One example, is the implementation of bioprocessing integrated strategies as mentioned by Cunha *et al.*, in which process integration can reduce the potential source of personnel contamination [8].

To build on the general awareness brought forth in Clarke's publication, this article describes the current challenges and understanding in the industry. Challenges discussed here include risks to patients, risks to product quality and compliance or regulatory risks. Current understanding includes particulate characteristics, measurement methods, composition and sources of particulates that can be discovered in the final formulation of a cell therapy product. This article also provides guidance and recommendations for elements to be included in particulate management programs for suppliers and companies developing cell therapies. The information is intended to assist companies with their characterization of the manufacturing processes and products to minimize particulate contamination in the final products and suggests a means for suppliers and companies developing cell therapy products to work toward improving manufacturing quality and minimizing risks to products and patients.

Particulate risks to patients and products

It is critical to the success of cell therapy products in development that they be both safe and efficacious when used to treat a specific indication in relevant patient populations. Goals of product development are to understand the risks and benefits specific to the intended use of the product and, ultimately, to reduce the risks as the product evolves. Particulate risks related to a product's final formulation are important for many reasons. The most obvious risk is the potential for adverse events due to particulates that occur after a product is administered to a patient. The second risk is the impact of particulates on the product quality itself, both during production and in a product's final formulation. Particulates discovered in final products also increase a product's risk of being recalled, leading to potential clinical trial delays or failure to maintain commercial inventory.

Patient safety and medical risks

Although the expectation is always to produce safe and effective products, a variety of criteria should be evaluated when trying to determine possible patient risks. Despite the different sources and composition of particulates, there are several common types of pathogenic mechanisms for potential harm to patients. These mechanisms include inflammation due to infections caused by viable organisms, inflammatory responses caused directly or through associate leachates that trigger direct tissue injury, normal and abnormal immune responses to cellular debris, and tissue damage from thromboembolism [9]. Most of the adverse events in the literature related to particulates in parenteral drugs are based on animal studies, *in vitro* studies or human case reports. The nature of the injury and degree of risk depends on several factors, including the route of administration, frequency, particle size and number, particle composition and patient population [4].

The routes of administration mainly considered for this discussion are intravenous (IV), intra-articular and intrathecal because most cell therapy products are administered via these routes. The size of the veins changes as blood flows to the heart and then to the lungs. Most particulates administered intravenously will follow this route until they are trapped in the pulmonary capillaries within the lungs, the diameter of which is approximately 12–15 μm. Many of the cells used for cell therapy purposes are often greater than 20–30 μm in size. Their size often leads to significant entrapment. Unlike many of the intrinsic and extrinsic noncellular particulates discussed in this article, many of the cells will eventually pass through after multiple passes by the blood through the lungs. Cells are more flexible when it comes to moving through smaller diameters through amechanism called "deformation." Inhibitors of cellular adhesion molecules (CD49d) on the cell have also been created to reduce the number of passes it takes for cells to clear the lungs [10]. The most common consequences from these trapped intrinsic and extrinsic noncellular particulates are compromised oxygen transfer and impaired respiratory function. Another clinical complication potentially resulting from IV or intra-arterial product administration is granuloma formation, with symptoms of dyspnea and reduced pulmonary function. For example, a report by Garvan describes postmortem pulmonary vasculature granulomas due to cellulose fibers. In another report, a large pulmonary granuloma formed in a patient when a particle became lodged in an arteriolar wall and eventually eroded through to form a