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Managing particulates in cellular therapy

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Abstract

The concept of particulates, while common to many in the pharmaceutical and blood transfusion disciplines, represents a distinct challenge in the field of cellular therapy. With newly discovered products advancing through clinical trials, the focus has shifted to ensuring products are manufactured in a reliable and safe manner. Given the unique manufacturing processes and resulting products (i.e. the cell being the active ingredient of the product), the way in which particulates are viewed and subsequently tested needs to be reviewed. No specific test or method for particulates will apply to all products, and guidance documents will be generated over time as more cell therapy products are approved. The details of the processes, testing methods used and acceptance criteria established for particulates will play a major role in generating the guidance documents. This will ultimately allow for the manufacture and administration of safe and effective products without thwarting advancement of the cellular therapy field. The intent of this review is to bring awareness to the topic of particulates with respect to cell therapy, and encourage a more open dialog and exchange of examples within the industry. We have reviewed the concept of particulates, where they originate and how they are introduced to cell therapy products, and the current methods available for their detection. We have also reviewed the relevance of current guidance documents and present potential strategies to move forward and address and control unwanted contaminating particulates in cell therapy products.

Key Words: *cellular therapy, disposable, injectable, parenteral, particulate*

Scope

Cellular therapy is a constantly evolving field within biotechnology and is filled with excitement and challenges. As numerous potential products advance through clinical trials, we recognize that there will be an increasing focus on overall product quality and subsequent manufacturing processes. There are unique challenges to developing manufacturing processes for cell therapies, where the living cell is the active ingredient in the product and what is added inadvertently during processing may be difficult to remove by the end of production. Part of the challenge with respect to particulates and cell therapy products is that specific publications available for investigators are currently very limited. The intent of this paper is to bring more awareness to the concept of particulate contaminants in cellular therapy: what they are, how they get introduced into the product, how to measure and control them, and their potential impact on product quality and safety.

It should be noted that, given the unique and emerging nature of cellular therapy, the scope of the topics discussed here have been limited. While the emphasis in this paper is on intravenously administered cell therapy products and USA standards, numerous alternative product types and documents

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exist with relevance to particulates. As the field advances and the manufacture of cellular therapy products continues to scale up, particulate cleanliness requirements, detection methods and guidance documents will evolve. It is the hope of the authors' that one outcome of this paper will be to initiate further discussion on particulate contaminants within the cell therapy community, potentially leading to additional dialog and encouraging retrospective studies as new analytical tools are made available to cellular therapy.

Definition of terms

Particulate

A particulate is a discrete undissolved object or foreign material found in a solution that is unintentionally present in the final product. Note: based on the nature of the product itself, a cell is a particulate.

Foreign particulate

Foreign particulates are materials that are not intrinsic to the product and therefore typically are not cells or of cellular origin (secreted by cells).

Non-viable particulate

A non-viable particulate is a particulate that is not or does not contain a living micro-organism.

Viable particulate

A viable particulate is a particulate that is or contains one or more living micro-organism. This can include a foreign cell (different from an intended cell) or a cluster of cells.

Visible particulate

A visible particulate is a particulate that can be visualized with relevant inspection aids and means, such as light, rotation and magnification lenses, with an adequate background size ≥ 50 μm (more typically > 100–200 μm). Visibility may depend on a number of factors.

Subvisible particulate

A subvisible particulate is a particulate that cannot be visualized easily, having a size between 1 and 100 μm, and so not yet visible.

Submicron particulate

A submicron particulate is a particulate of a size less than 1 μm.

Parenteral

Parenteral refers to medicine taken into the body or administered in a manner other than through the digestive tract, such as by intravenous or intramuscular injection.

Disposable

Disposable is a term that loosely encompasses all single-use contact surfaces, including flasks, bags, bottles, pipettes, tubing, syringes and vials.

Introduction

Cell therapy is a hybrid of therapeutic platforms with origins and processes stemming from both the transfusion/transplantation and pharmaceutical industries. This blending of disciplines has helped cell therapy advance rapidly in many areas but has also highlighted an area of non-overlap on the topic of particulates derived during cell processing. For cell therapy, the concept of particulates has generated some critical questions, specifically: are there safety concerns regarding particulates and, if so, how do we address these concerns? The answer to the first part of the question is yes: everyone is aware of particulates as a medical concern, but there may be a significant difference in focus with respect to the actual size and number of the particulates. For individuals coming from a blood transfusion background, particulates are generally a concern that is addressed with the use of filters, typically in the range of 170–260 μm, used to remove transfused cellular aggregates. Medical safety concerns probably focus on vessel occlusion in the patient, and the consequences thereof. Other than visible inspection of the product, no specific tests or regulations for particulates are described for blood products (1). In many of these clinical situations, only one product or unit is available for the patient, and therefore discarding the unit because of particulates is not an option.

In the pharmaceutical industry, particulates represent a different set of concerns. Most injectable small molecule formulations, and nearly all protein-based biological products, seek to maintain solubility of the product to ensure a rapid and even distribution in the blood pool after administration. An observation of particulates is often the first sign of an inadequate process or container/closure cleaning, formulation incompatibility or product instability. Thus particulate is a commonly used term within the industry and standard testing formats are in place for final injectable dosage forms. It can be appreciated that the pharmaceutical concern for particulates is focused more on the subvisible size

range (much smaller than particulates currently encountered during blood transfusions) and most often revolves around ensuring that no large particulates threaten an immediate vessel occlusion and avoiding a patient immunogenic response to any foreign particulate. Therefore, within the pharmaceutical industry, particles are observed at a much higher frequency than in blood products because of the more complex manufacturing processes, which involve multiple product manipulations and include many different components and raw materials, as well as the transparent solution properties of injectable drugs. In contrast, routine whole blood collection is split into different components within a closed system, as well as a clarified solution where the end product is not by definition considered to be a particulate. Given the inherent and obvious differences regarding how particulates are considered within the collective disciplines, choosing one set of requirements is not sufficient for cellular therapy products as a whole.

Background

Regulations

In order to begin addressing the types of questions posed above, a good starting point is to review the history of regulatory requirements regarding particulates and the relevance to cellular therapy products. This review aims to give an overview for both visible and subvisible particulate requirements in the USA for particulates in injectables and parenteral infusions. Although the emphasis here is on the requirements that apply to parenterals, it is important to highlight that other particle standards do exist, for example United States Pharmacopoeia (USP) 789 Particle Matter in Ophthalmic Solutions (2). The USA standards (USP) initially focused on the appearance of a solution. From there, the focus moved to the methods used to evaluate the solution, then the visual inspection process itself, and the limits for visible particle matter. Additional standards were developed for allowable particle burden in products.

The first requirement of 'solution clarity' and freedom from contaminants for parenterals occurred in 1936. This requirement for clarity in injectable solutions specified: 'Aqueous ampule solutions are to be clear; i.e., when observed over a bright light, they shall be substantially free from precipitate, cloudiness or turbidity, specks or flecks, fibers or cotton hairs, or any undissolved material'(3). The additional requirements issued from 1936 until 1948 focused on visible particulates and visual inspection of products. From 1949 to 1965, no changes to compendial requirements occurred, although there were many reports in the literature regarding particulate medical events related to particulate matter injection. One exception occurred in 1959, with the Fed. Std. No. 00142, Parenteral Preparations, issued by the United States Navy Bureau of Medicine and Surgery (BuMed (4)), which became mandatory for all federal agencies. The standard was applicable to sterile parenteral preparations in final containers intended for human consumption. It provided requirements for the clarity of solutions as well as limits for visible particulate matter. Section 6.2.1 of the standard, Clarity of Solution' included: Solutions of parenteral preparations shall be clear and free from undissolved or particulate matter within the limits permitted in the classification of defects and the applicable acceptable quality level (AQL), via a specific method'. The significance of Fed. Std. No. 142a (4) is that it provided government- endorsed acceptance limits for the presence of 'visible' particles. Parenteral product quality acceptance levels were based on the limitations of the sterile-product manufacturing capability at that time.

In 1965, the National Biological Standards Laboratory, Canberra, Australia (5), published a particulate standard. The publication of this standard stimulated compendia and regulatory activities in the USA, leading to a period of great activity in the USA and abroad, starting with an Food and Drug Administration (FDA) symposium on the safety of large volume parenterals. In 1974 standards for particulate matter in large volume products were issued in both Great Britain and Australia. Later in the same year, USP published standards for particulate matter in large volume products following studies conducted by the Pharmaceutical Manufacturers' Association and Pharmaceutical Drug Association (6).

From 1986 to 1995, changes to the compendial requirements included 'Particulate Matter for Large Volume Injections', for products with final fill volumes greater than 100 mL. Other changes included differentiating methods for large and small volume products as well as the addition of a new method, light obscuration. The most dramatic change to USP 788 (7) occurred in 1995, identifying light extinction as Method 1 and the membrane method as Method 2 for quantifying the number of particles observed.

In 2007, USA, European and Japanese pharmacopoeial organizations, through the Pharmacopoeial Discussion Group, harmonized the USP 788 methods, definitions and limits. This chapter is seen in the respective pharmacopeia as USP 788, EP 5.5 and JP XIV, XV, and is the current standard. Table I provides the current limits for subvisible particles from USP 788.

Table I. Current USP 788 Particle Matter in Injections: Limits for Subvisible Particles (2).

Volume	Particle size, microscopic limits	Particle number, microscopic limits
Large parenteral volume (>100 mL)	>10 micron	12/mL
	>25 micron	2/mL
Small parenteral volume (≤100 mL)	>10 micron	6000/container
	>25 micron	600/container

USP General Chapter 1 was issued in 2008 (8). It states: 'Each final container of all parenteral preparations shall be inspected to the extent possible for the presence of observable foreign and particulate matter (also termed visible particulates) in its contents. The inspection process shall be designed and qualified to ensure that every lot of all parenteral preparations is essentially free from visible particulates'. No inspection method is specified.

Origin of particulates

The manufacture of cell therapy products, whether at very small scales or larger scales, requires exposure to a large variety of raw materials and disposables. Given the number of materials that could come into contact with the cell therapy product during upstream and downstream processing, the level and variety of particulates are significant. As traditional (0.1–0.2 microns) filtration of the final cellular product is not feasible, it is easy to see how particulates can accumulate. Understanding this is critical to the strategy a manufacturer should develop to control the introduction of particulates to the production process. Particulate controls include sterile filtration of raw materials immediately prior to use, container closures, equipment qualification (e.g. heat sealers) and final product containers approved for administration of the products.

The raw materials, along with disposable single-use components, used for cell therapy applications are often produced for the research market and are composed of a wide variety of materials. Because of this, the manufacturing processes vary considerably. Particulates associated with these types of components can vary immensely, as determined by the origin of the raw material itself and the manufacturing process used for the component. Particulates typically found with standard cell culture flasks, dishes, disposable bags, etc., are likely to be quite different to those found in culture media or sera. Some of the more common types of particulates noted include plastic and metallic fragments, synthetic and organic fibers, and protein aggregates. Table II provides a more comprehensive list (generated from the authors' experiences). Many of the particulates found are remnants of the raw material or disposable product. An additional particulate load can accumulate as a result of the manufacturing process and the number of open manipulations that occur in the manufacturing process. The size and number of these particulates can vary depending on the manufacturing process and quality programs established. It is because of the variability that manufacturers need to establish quality assurance programs to evaluate suppliers and the materials themselves, understand the potential ingress routes of particles during manufacturing, and ensure operators are trained appropriately.

Table II. Commonly Observed Particulates and Sources.

	Raw material	Disposable	Final product
Source	Culture media	Flasks/tubes	Biological (from original cellular starting material)
	Storage media	Plates/dishes	Raw materials
	Serum	Bags/vials	Process disposables
	Buffer solution	Tubing sets	Operators
	Reagents, etc.	Filters	Primary containers
		Pipettes	
		Syringes	
		Sterile gloves	
		Beads	
		Stoppers	
Type	Protein aggregates	Synthetic fibers	Cell (aggregates)
	Minerals (salts)	Glass	DNA
	Organic fibers	Organic fibers, gowns	Extracellular matrix
	Plastic fragments	Plastic fragments	Organic fibers
		Cardboard	Plastic
		Metallic	Cellulose
		Rubber	Inorganic particles

While the manufacturing process is different for each of the raw materials, certain aspects are common to some, although certainly not all. Most often, these products will be manufactured in an International Organization for Standardization (ISO) 14644-1 class 8 or better cleanroom, with extensive environmental monitoring, in-process inspection activities and process validation. Each of these is put in place to both monitor and minimize the introduction of particulates to and overall particulate load in the final manufactured product. Additional steps put in place to reduce the introduction of particulates after manufacturing may include the use of a secondary pouch that is removed prior to the materials entering the cleanroom, designated items that do not leave the cleanroom, and non-shedding cleanroom gowns or other garments used by manufacturing personnel. For specific raw materials such as plastics (films used for disposable bags, etc.), deionizing devices can be put in place to aid in the removal of particulate matter of different types that may be attracted to the film surface.

However, there are some inconsistencies in the area of raw materials; while disposables, equipment and containers for pharmaceutical processes are typically manufactured under the above conditions, and may be the cause of particulates in rinse effluents, laboratory equipment and other disposables used in the manufacture of cell therapy products are not considered to be for use in parenteral product manufacturing and are not claimed to be controlled for particulates. This can also be the case for raw materials, which may be sterile filtered and therefore capable of meeting particulate standards for injectables, but are filled into containers that are not controlled for particulates and have no particulate quality claims. Materials designated for 'Research & Development (R&D) use' or 'non-Good Manufacturing practice (GMP) grade' are not manufactured under the same quality systems and controls as that of a pharmaceutical or clinical-grade material and this may result in higher particulate levels. The limited number of raw materials and disposables available for clinical and commercial applications presents another hurdle with respect to cell therapy development and subsequent manufacturing. Overcoming these hurdles cannot happen in a silo, and close collaboration is needed between cell therapy manufacturers and suppliers to control particulate levels.

During the course of cell therapy manufacturing activities, various types of particulates have been observed as contaminants in the final products. Some of these particulates have been identified by physical and spectra analysis and are listed in Table II.

In general, particulates observed during GMP production of cell therapy products have been classified using terms such as fibrous in nature, fiber-like particles, soft particles and stringy particles. On occasion these particulates have a color associated with them, providing a useful clue for identifying the source of the material. The sizes of particulates found in the final cell therapy, based on the authors' experiences, have ranged from 10 μm to 4000 μm. Most particulates larger than 600 μm have been classified as fibrous in nature (visual assessment) and are often observed by visual examination of the product held against either a white or black background in a well-lit environment, while smaller ones, in the 10–250 μm size range, typically have no shape descriptor connected with them and usually require an instrument-based detection strategy, for example microscopic examination (information based on direct experience by the authors). It is important to note that the method used to detect and characterize particulates in the final products needs to be qualified or validated with the final formulation for the product manufactured. Not all particulates will have easily identifiable sources; the accumulation of data can also help identify probable raw material associations and thus help drive an improved manufacturing of raw materials that is optimized for cell therapy applications.

Methods for detecting particulates

As discussed earlier, the living cells are the active ingredient as well as a particulate. Manufacturers need to distinguish the cells in media (which may contain serum components) from other types of particulates, and, as detailed in the previous section, in Table II it can be seen that particulates are derived from a wide variety of sources. The cells have a size of about 10–20 μm and are typically produced at a concentration of 1–100 million/mL, with efforts to push as high as 1 billion/mL; however, non-cellular particulates come with no size limitations and should be tested to a much lower detection limit than the cell concentration. That being said, an important consideration when selecting a method to use is whether the test requires isolation of the particle before analysis (example light and electron microscopy, and photothermal induced resonance (PT-IR) spectroscopy). A critical factor for manufacturers of these type products should be whether the test itself is destructive to the cells (fluorescence microscopy, microflow imaging and light obscuration). Any method of detection for particulates in the presence of cells would need to be uniquely specific and still adequately sensitive for the material being tested.

There are several publications in the literature describing methods for detecting particulates. Singh

Table III. Analytical methods for the detection of particles of various size ranges.

Analytical methods	Particle size ranges
Visual inspection	>100 μm
Light microscopy, light obscuration, flow imaging microscopy, Coulter principle, flow cytometry	1 μm to 1 mm
Dynamic light scattering, static light scattering, aggregate ultracentrifugation	1 nm to 1 μm
SDS–PAGE, SEC HPLC	<1 nm to 100 nm

SDS–PAGE, Sodium dodecyl sulphate polyacrylamide gel electrophoresis; SEC HPLC Size Exclusion Chromatography High Performance Liquid Chromatography

et al. (9) have listed a range of methods used by the pharmaceutical industry for monitoring subvisible, proteinaceous particles in the 0.1–10 μm size range, because of the potential immunogenic risk of these particulates; these are summarized in Table III. Microflow imaging and continuous-flow Coulter counting are popular methods that are relatively easy for laboratories to use for measuring fine particles (10,11). Others have used high-frequency ultrasound to detect whole blood cell aggregation (12) and more complex biochemical techniques to detect leukocyte-derived microparticles (13). A novel approach is to use real-time cell electronic sensing (RT-CES) technology, which measures the cytotoxic responses of cell lines to dust particles (14) instead of just measuring inert particulates. This technology might add a biological impact attribute (cell toxicity response) to the study of foreign particulates.

It is likely that a combination of some of these methods will be able to shed light on the presence of inert particulates in cell products. Alternatively, one could consider spiking a known level of particles in a cell product to see if the particulates are still detectable by one of these methods, with or without a separation/filtration step. A more conventional approach would be to run a 'blank' bioprocess without cells (typically done as part of process validation and training in a GMP clinical manufacturing setting), to assess what type and number of particulates are generated in the process from start to finish. These particulates can be isolated and sent out for characterization to assist in troubleshooting the system, to identify sources of particulates so that the system can be refined further to minimize the presence of particulates. Incorporation of such new tools and evaluation procedures could provide the cell therapy industry with an early glimpse of what is happening during critical cell bioprocessing steps and support rational development of new guidelines.

Clinical importance

Despite the controls of a GMP environment, the generation of particulate matter is an inevitable part of manufacturing. As stated earlier, particulates can originate from packaging materials, the manufacturing environment (facilities, equipment and personnel) and the manufacturing process (product, excipient, number of open manipulations and container closures). It is well accepted in the drug industry that the visual inspection process is inherently problematic. Standard practice is to use a black/white background to detect visible particulates, which is subjective and left to the interpretation of the screener. Despite these challenges, the detection of particulate burden in products is driven by the need to minimize the inadvertent introduction of particulate matter to patients during the administration of medications and therapeutic products, such as cellular therapy products.

Many animal studies have been conducted to determine the fate of intravenous particles of differing sizes. The smallest subvisible particles (approximately 1 μm in diameter) are often trapped in the liver, lungs and spleen. The intravenous infusion of particles larger than the internal diameter of capillaries may be clinically significant because it can increase the risk of foreign particle embolism. Larger particles generally do not migrate far from the infusion site. The most common response observed is the formation of emboli or granulomas. Several reviews in the literature describe the effect of particles in products on patients (15–17). All of the particles implicated are subvisible, with a diameter of less than *c.* 50–100 μm.

When cellular products are infused intravenously with some macro-aggregates, this is often a consequence of DNA released from lysed cells that occur during the thawing process. The concern is less that they will migrate to the lungs and cause some symptoms as a result of the embolic event, but rather that the aggregate will contribute to trapping of multiple cells that cannot be infused. A great deal of time and effort is dedicated to trying to break up these macro-aggregates into smaller aggregates that can be infused, albeit slowly and cautiously, to minimize the quantitative loss of the valued cell product. However, a product being administered intrathecally, within an Ommaya reservoir directly into the cerebral ventricles, or intra-arterially results in a greater concern regarding the aggregates, because their potential clinical impact is amplified. It is therefore necessary to identify clearly the cell therapy product and subsequent delivery method to better understand the particulate risk. Whether particulates result directly in a specific adverse

reaction in patients or impact on the overall clinical performance of the cell therapy product requires additional data to be collected and subsequently reviewed, to determine the extent of the potential problems they pose. Given the limited available data specific to cell therapy, the industry is currently reliant upon the publications and guidance described for other industries, most notably the pharmaceutical industry.

Solution

Points to consider

Because of the risks to patients as a result of an unanticipated particulate being administered with a product infusion, it is important that thoughtful, well-intended consideration be given to the approach an establishment elects to apply to its manufacturing process, in addition to how the product administration will occur. It is therefore essential to determine a control strategy for particulate contaminants in the final product early in development. The particulate data collected are critical to process characterization, which identifies which particulates are inherent to the process and which are not. A few points or questions to consider when developing a specific strategy include the following.

- What size is unacceptable? (What particulate size will be filtered out during the process or immediately before administration?)
- How will particulates inherent to the process be monitored? What will be the trigger to initiate an investigation?
- What composition, size and amount of particulate are safe?
- Will the particulates negatively impact patient health and safety?
- How will particulates that originate from the raw materials, process equipment and disposables be controlled?
- How can non-cellular particulates be differentiated from the cellular material?
- How will the product be administered to the patient?
- How is the particulate load over the course of therapy weighed (e.g. administering a total volume of less than 1 mL versus the administration of a couple of hundred mL)?
- Can a cell therapy product manufacturer be compliant with current requirements for particulates in injectables (drugs)?

Compliance with the USP standards for particulates in injections needs to be evaluated with reference to cell therapy products being developed. Some of the principles described in the requirements can be applied to cellular therapy products, but not necessarily in their entirety because many cellular therapy products are a cell suspension for parenteral administration, and not a solution. Unlike many of the parenteral drug products manufactured, filtration of these cellular products cannot be employed to remove subvisible particulates, because the size of the cells in suspension is similar or larger in size to the potential particulate contaminants. At high cell concentrations, the cell suspension will appear opaque, obscuring visual inspection. A simple specification based on analysis of subvisible particles in the product and/or subsequent visual clarity of the product, is therefore not sufficient to determine whether they are foreign particulate contaminants that may pose a risk to the safety of the patient or an indication of inadequate manufacturing quality. In addition, the opaque nature of some containers currently used may also make visual inspection of the product ineffective. Finally, the regulations described earlier are focused on commercial manufacturing environments for parenteral drug solutions. Because of these points, more work is needed to establish both testing requirements for product and/or process disposables, as well as ranges of acceptability for particulate testing.

Potential strategy

A potential strategy would be to start by using the same classification that the FDA uses to determine complex manufacturing processes from minimally manipulated processes in 21 Code of Federal Regulations (CFR) 1271 (18). Cellular therapy products that are classified as more than minimally manipulated, or whose manufacturing activities appear more analogous to parenteral drug solutions being mass produced within the pharmaceutical industry (with highly complex processing steps and multiple open manipulation and holding steps), should consider compliance with the standards and industry expectations for those types of products. Areas to consider include the following.

1. Characterization of particulates generated during the process and within the facility. Including:
    a. qualification of raw materials, disposable process equipment and final product containers (including supplier controls where applicable)
    b. assessment of the manufacturing process (via Feature Modes and Effects Analysis (FMEA)) to identify potential ingress routes and establish controls to minimize the introduction of particles

   c. performance of periodic aseptic process validations (simulate with all processing steps, personnel, equipment, consumables and containers, etc., that will be used to manufacture, with the exception of the cells)
   i. use filtered water runs to determine compliance with USP 788 (7) in final product containers
   d. collection of data to determine the 'expectable' particle burden, including visual inspections and rejection rates (if applicable)
   e. creation of training materials that include actual (or images of) particles integral to the process for each type of product

2. Visual inspection process:

   a. confirmation of the effectives of the visual inspection procedure for cell-based finished products (this can be done using a process simulation run with filtered water or equivalent material), as well as for raw materials and process equipment
   b. qualification process for the operator(s)
   c. 100% visual inspection for finished product batches where applicable
   d. establishment of a batch accept/reject rate.

3. Environmental monitoring program.
4. Filtration of solutions added during manufacturing:

   a. a 0.2-μm rated sterilizing grade for potential additives, such as serum and exogenous cytokines
   b. a 170–260-μm rated filter, as often used during bone marrow harvest and processing (19,20), could be applied as a final processing step for some cell therapy products.

5. Delivery method and filter(s) used in the preparation of the product prior to administration.

Minimally manipulated cellular therapy products, more closely resembling blood or blood product manufacturing activities, should align their product development, visual inspection and release processes with that of the blood industry. These activities would include the following.

1. Visual inspection process:

   a. an operator qualification process
   b. documented visual inspections for all finished products
   c. unit accept/reject criteria.

2. Approval of final product containers appropriate for their respective use (infusions).
3. Filtration of solutions added during manufacturing (0.2-μm rated sterilizing grade).
4. Filtration of final products (170–260-μm rated).
5. Handling of open manipulations under aseptic conditions (minimally within a qualified biosafety cabinet).
6. Screening of raw materials/disposables prior to use and lot acceptance.
7. Employing more clinical- and pharmaceutical-grade raw materials/disposables for use in product manufacturing.

Steps to optimize the process and reduce particulates

As products move through development, the data collected for particle characterization should be used to optimize particle controls and reduce the particle burden. Several steps can be taken to do both.

1. Developers and manufacturers should work closely with their suppliers to reduce the particles that originate from their materials. Often suppliers have not been approached by smaller manufacturers to make changes to their own processes, so changes to their practice are not compulsory because market forces did not encourage any modifications. As suppliers see the demand for low particulate materials rise, they will probably make the necessary changes in order to remain viable.
2. Evaluating the ingress routes and particle controls, starting in early development and after changes are made to the process, can inform the manufacturer of potential risks and mitigations that can maintain or even reduce the particulate burden.
3. Characterization of particulates during development offers information that can be used to improve the process.
4. Collection and storage of the product to be retained when possible for subsequent analysis. This will be helpful in establishing a larger database for particulate characterization and source, in addition to addressing potential product performance and patient safety issues.
5. As methods for particulate identifications improve, and as manufacturers become more aware of their utility, they can be used to characterize the particulates observed better and contribute to improvements to the process.

Conclusion

As described in this document, one set of guidelines for product particulates does not apply equally well between cell therapy, blood products and pharmaceutical products. Injectable pharmaceutical products

typically have a distinct advantage in that they can be sterile filtered prior to the final fill process, and this can remove the vast majority of particles that may be present in the solution prior to filling. Further, these clarified solutions can then have appropriate visual inspections performed on them so that there is increased confidence in a low particulate burden being present in the solution. For cell therapy products, the work needs to be done upstream, making sure that adequate controls are in place to control the level of particulate matter in the final product. The current specifications can be used to qualify lots of raw materials prior to use, but to have a particulate specification for the final product will be difficult until more work is performed using some of the methods that have been mentioned above. As cell therapies advance through clinical trials and into commercialization, it will be important for members of the cell therapy community to define what is reasonable for this industry.

A number of new techniques and applications, outlined above, have been identified where the cell therapy industry itself can generate meaningful data to guide further discussions regarding our capabilities to first measure and then control unwanted contaminating particulates in cell therapy products. Regulatory concordance with these efforts is also essential.

The field of cellular therapy is presented with some obvious challenges with respect to particulates. The unique manufacturing processes and resulting products cannot be compared directly with that of pharmaceutical drugs or blood components for transfusion, and therefore the way in which particulates, subvisible and visible, are viewed and subsequently tested represents a challenge. No specific test or method for particulates will apply to all products. As with other disciplines, guidance documents will be generated over time as more and more cell therapy products are approved. The details of the processes, testing methods used and acceptance criteria established for particulates will play a significant role in generating the guidance documents. This will ultimately allow for the manufacture and administration of safe and effective products without thwarting the advancement of the cellular therapy field.

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