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Single-use Manufacturing: Prioritizing Particulate Control for Safer Therapy Development

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The swift adaptation of single-use technologies (SUTs) to meet the growing demands of the bioprocessing industry creates significant opportunities for faster, safer, and more streamlined drug manufacturing. Yet SUTs also require close evaluation of their design, construction, and assembly to mitigate potential quality risks related to particulate contamination, particularly for cell and gene therapies.

Particles found in drug products can pose a significant risk to patient safety. Despite this, many SUT suppliers find it challenging to adequately address particulate control in the design and development of standard or custom polymer-based processing solutions such as bags, tubing, transfer sets, and manifolds with overmolded designs used to manufacture advanced therapies. The issue lies in the fact that biologics-based therapies cannot be filtered, and therefore any particulates introduced to a therapy during manufacture or packaging cannot be removed. This can result in a range of issues for biopharmaceutical companies and manufacturers, including product recalls and, more significantly, the release of advanced therapies that could actually harm, rather than help, patients.

As particulate control continues to be a top concern for advanced therapy manufacturers, SUT suppliers must regularly assess every element of the single-use component supply chain, including:

- the raw materials they receive from suppliers;
- their own production facilities; and
- the operator training and in-house processes that support production and final transport.

As regulations continue to evolve around the complexities of developing new treatment modalities and the single-use solutions that make them possible, identifying SUT suppliers who proactively address the challenges of particulate control will be crucial to enabling greater manufacturing success for these fragile, lifesaving therapeutics.

Particulates And Their Impact

In biopharma processing, particulate contamination typically falls into three categories: inherent, intrinsic, and extrinsic. The first, inherent contamination, refers to particles innate to a drug product and which may be considered acceptable according to its target product profile. Intrinsic particulates are introduced by the manufacturing process itself and may include rubber, glass, silicone, or other materials. Extrinsic particles are those that may come from outside the process and can include hair, skin, dust, fibers, cleaning products, or other materials from personnel or the surrounding environment. While SUT suppliers cannot control the presence of inherent particles in a product, they must work to reduce intrinsic and extrinsic particles where possible, both through their own production of these SUTs and through their design.

Particulates are a critical issue because cell-based materials used in the manufacture of cell and gene therapies do not undergo a final filtration step. For these modalities, any filtration step – particularly a step designed to address particulates that may be of similar size to the relevant cells or cellular products that make up a therapy – would only serve to filter out valuable drug product. As such, ensuring that an SUT is as free as possible from particulates is critical for ensuring successful cell and gene therapy product development.

Transcending Standards for Safer SUTs

Although regulatory guidance for managing particulates in injectable drug products is available, many biopharmaceutical companies understand that their own manufacturing processes need more stringent standards. In draft industry guidance issued in December of 2021, the FDA recommended establishing "a holistic, risk-based approach to visible particulate control that incorporates product development, manufacturing controls, visual inspection techniques, particulate identification, investigation, and corrective actions designed to assess, correct, and prevent the risk of visible particulate contamination."[1]

Additionally, USP standards permit varying allowable particle counts to meet ISO standards, while other guidelines from industry groups like BPSA outline best practices for particle control. However, even today's most comprehensive standards may require ingenuity on the part of a single-use solutions supplier to devise their own standards – based on customer requirements – where less straightforward regulation exists. For example, USP 788 is directed at the inspection of sterile injectables. Even though SUTs are not classed as sterile injectables, using USP standards as guidelines for single-use manufacturing operations requires the implementation of more rigorous testing and release criteria, thus adding another level of particulate control. At this point, SUT manufacturers must evaluate their own standards to adequately reduce particulates to minimize impact on the development of new and novel treatments.

Achieving a Comprehensive Approach To Particulate Control

For SUT suppliers, addressing potential contamination should begin with the supply chain. SUT suppliers must vet raw material suppliers so they can better understand their cleaning practices for raw materials, as many of the raw materials used in SUT fabrication are made using processes that introduce significant risk for increased extraneous particulate matter. Understanding raw material suppliers' inspection processes, as well as their standards for handling and transporting materials, is the first step to establishing a workflow that can enable optimized particle control during SUT fabrication. From there, a well-codified inventory control process can help ensure that raw materials selected for processing are either clean or can be cleaned using methods that do not introduce new potential for contamination, or even damage. Adapting a "one-piece flow" production approach – where multiple operators inspect each component as it is passed down the assembly line – can help operators more tightly control their SUT assembly. This enables closer inspection when compared to the way inspection is handled through a traditional batch production process.

Ultimately, SUTs are fundamentally different than their stainless-steel counterparts and cannot undergo the same arduous chemical cleaning procedures that enable traditional stainless-steel systems to maintain ISO standards. Because of the sterility SUTs provide, they cannot be rinsed with water or inflated with air to facilitate impurity removal. Instead, they require more intensive protocols that involve vacuum systems and particulate traps. Adapting existing regulation and finding workarounds for any "noise" introduced by traditional analytical techniques are key to establishing a workflow that prioritizes particulate control at every step.

Navigating the 'Path to Zero' Particulates

As key players in enabling the design and development of these fragile, potentially lifesaving biologic drugs, SUT suppliers must align with advanced therapy manufacturers to de-risk single-use manufacturing processes and internally create more stringent requirements to maintain the safety and efficacy of new treatment innovations.

Charter Medical, an innovative single-use solutions developer and supplier for advanced therapy manufacturers, prioritizes particulate control across its product portfolio and throughout its production facility. While particulates can never fully be eliminated, Charter's "Path to Zero" initiative takes a holistic approach to particulate control via continuous improvement techniques that address best practices for gowning; monitoring environmental conditions; cleaning; inspection processes both during production and for incoming raw materials; facility assessments; operator training programs; and supplier management programs to drive down the potential for particulate contamination in its single-use solutions. This also includes conducting process and post-market surveillance of products using modified USP 788 standards.

As an additional layer, Charter replicates as closely as possible the conditions of a cell and gene therapy manufacturing facility wherever possible. For example, while Charter operates in an ISO 7 facility, many of its therapy-producing customers utilize ISO 5 cleanrooms and impose much more stringent limitations on the amount

of allowable particulates in the production space. This has led Charter to adhere to ISO 5 gowning standards as well as adopting other control measures such as introducing equipment and technologies that have proven to be critical to this important initiative.

Finally, another key component of Charter's approach to particulate control has been to establish cross-functional teams dedicated to continuously evaluating its manufacturing processes to identify areas of improvement. By seeking representation from many departments and roles within the organization, Charter is working to unite the perspectives of manufacturing, engineering, and customer-facing roles such as business development and beyond. The result is an effort that incorporates continuous improvement practices with proactive, prioritized innovation aimed at making SUTs safer for advanced therapy production.

By working with a single-use partner that proactively engages in continuous improvement initiatives such as monitoring raw materials suppliers and managing and upgrading production facilities to better control particulates, and enhancing in-house operator and production procedures, advanced therapy manufacturers can rest assured that their single-use solutions are designed and developed with the highest quality standards in mind. In doing so, these organizations can remain proactive in their goals of ensuring safer, higher-quality drug products and reducing risk to patients, enabled by SUTs tailored to patient, product, and process needs. As more advanced therapies gain commercial approval, this focus on particulate control will be increasingly critical in achieving the level of safety and reproducibility necessary to safeguard patients worldwide.

Reference

1. U.S. Food & Drug Administration. Inspection of Injectable Products for Visible Particulates. Draft Guidance for Industry. (December 2021). Retrieved July 21, 2023, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/inspection-injectable-products-visible-particulates• IVD Regulation 2017/745: Kahles, A., Goldschmid, H., Volckmar, A., ... & Stenzinger, A. (2023). Structure and content of the EU-IVDR. *Springer Nature*. Retrieved May 31, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9896441/

About The Author

Jessica Harvey is Supervisor, QC Analytics, at Charter Medical in Winston-Salem, North Carolina. Jessica manages Charter's Quality Microbiology Laboratory and the facility's technical cleaning staff. She is part of an interdisciplinary team at Charter that works to reduce cleanroom issues such as particulates. Jessica has nearly 5 years of experience in the medical device industry after 4 years of practical medical device application in the regenerative medicine and clinical settings. Jessica has a B.S. in Chemistry from Concord University in Athens, WV, and a Certificate of Medical Laboratory Science from Radford University Carilion in Roanoke, VA, formerly Jefferson College of Health Sciences.

About Charter Medical, LLC

Charter Medical, LLC has more than 30 years' experience developing and providing specialty single-use products for bioprocessing, advanced therapies, and blood management applications, delivering solutions to the biotechnology and pharmaceutical markets.

Our 16,000 square feet of cleanroom space located in Winston-Salem, NC, is ISO 13485:2016-certified and FDA-registered, with a focus on designing and supplying single-use solutions for cell growth, frozen storage, and biological fluid handling. Custom product design services are available for clients who need specialized single-use products for biomanufacturing. Our team of engineers will work with you to develop the best solution for your specific requirements.

Charter Medical is committed to providing quality products and services with an experienced staff dedicated to exceeding customer expectations from product development to delivery and implementation.

At Charter Medical, we work closely with our sister companies, Polyzen, SanaVita Medical, and Secant Group, to provide essential products and services to life science companies. Through integrated research and development activities, we are helping to bring new technologies and therapies to market. Visit www.chartermedical.com.

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