

Prioritizing product integrity: Innovative liquid handling solutions for bulk drug substance management

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Liquid handling plays a critical role in biopharmaceutical manufacturing. Ensuring that bulk drug substances are stored, handled, transported, and treated properly is of paramount importance to guarantee their integrity and safety. This is true throughout the pharmaceutical pipeline, but becomes even more pressing as drug products reach the manufacturing stages.

The further bulk drug substances progress along a manufacturing workflow, the more valuable they become—and the more damaging it would be to lose them.

Manufacturers need containment technologies that enable them to optimize and streamline their bulk drug substance management workflows.

Such technologies must eliminate the risk of contamination and conform to stringent cleanliness standards to facilitate compliance and, crucially, protect the integrity of the product. Innovative technologies—both single-use and rigid—bring flexibility and efficiency for biopharmaceutical manufacturers of all sizes, increasing their ability to develop new therapies and fast-tracking the process of bringing a new drug to market.

Keep your product contaminant-free

Small foreign particulates or substances lingering within containment technologies can compromise a drug substance and threaten batch failure. Bulk drug substances must be protected from leaks, contamination, and potential batch loss, so that they can be safely and confidently used as active ingredients or finished drug dosage forms.

It comes as no surprise that ensuring the safety of bulk drug substances is a key aim of the U.S. Food and Drug Administration (FDA) [1], making verifiable product integrity an issue of increasing priority. Product safety and integrity must be maintained throughout all liquid handling processes, and across every single piece of equipment used. This applies to bags, bottles, vials, and other containment technologies used to store a sample, as well as the fluid transfer assemblies, tubing, ports, and various connectors used to link technologies together during drug manufacturing.

Different applications require varying levels of cleanliness and validation. Sterility tiers are often defined by particulate and endotoxin levels, with an industry-standard sterility assurance level (SAL) of 10^{-6} (1 in 10^6 chance of a unit being nonsterile) for both the interior and exterior of containment technologies. However, potentially subvisible particulate contamination is also of concern, especially in the production of parenteral infusions or injectables. To this end, USP <788> ensures that containment technologies meet strict guidelines for allowable levels of subvisible particulate matter, and defines risk mitigation strategies for extrinsic and intrinsic contamination. By selecting containment technologies that are USP <788> compliant, manufacturers can maintain appropriate quality and cleanliness levels throughout production, and reduce the risk of process or batch noncompliance.

Intrinsic contamination is a crucial consideration in terms of the risk that containment technologies may pose in terms of extractables and leachables. Requirements for extractables and leachables are well-defined by regulatory agencies for setups of all types. For single-use technologies,

the BioPhorum Operations Group (BPOG) has published a standardized testing protocol for extractables, covering sample preparation, extraction conditions, data recording, and results reporting. This protocol represents the combined opinion of the pharmaceutical industry and supply chain, and guides workstreams towards valid, standardized extractables and leachables testing [2,3].

Manufacturers of containment technologies must demonstrate that their equipment and processes are compliant, and all materials used to produce the final products, from plastic films and ports to end treatments and tubing, must adhere to best practice guidelines. To this end, advanced containment technologies, both single-use and rigid, are supporting bulk drug substance management throughout the manufacturing process, helping to streamline workflows, maximize output—and protect valuable product.

Advanced solutions for every workstream

Both single-use and rigid technologies are seeing ongoing innovation. Vendors are offering increasingly clean and compliant technologies, emphasizing the importance of reliability, quality, and consistency in liquid handling solutions—and helping to ensure that market standards for sterility and product integrity remain high.

Advanced rigid and single-use technologies for liquid handling demonstrate compliance, and help manufacturers to easily and efficiently do the same. They are produced via stringent and validated production and packaging processes that further minimize the risk of drug substance contamination, using verified materials of known consistency. This consistency enables a better understanding of material safety, interactions, and suitability, reducing validation time and further guaranteeing process and product compliance.

Additionally, the latest, most sophisticated containment technologies do not require sizable new infrastructure and can be integrated with existing equipment in a flexible, straightforward way. As a result, they bring a minimized footprint, creating new opportunities for manufacturers of all sizes. Containment technologies are available in configurations ranging from benchtop to production scale, providing flexible, scalable solutions that work across all stages of therapeutic drug and vaccine production.

This scalability reduces the labor costs and capital investment involved in implementing a verified, reliable liquid handling process to ensure product integrity—and, therefore, alleviates risk earlier on in the product manufacturing cycle (due to lower initial investment).

Single-use technologies: clean, closed, and compliant

Single-use technologies offer closed, self-contained systems that are designed to mitigate contamination risk, reduce the chances of leakage, enhance quality control, and support the production of safe, compliant drugs. A significant benefit of single-use technologies arises due to these systems needing no cleaning: as the name suggests, they are only used once. As a result, they vastly reduce system downtime, in turn allowing manufacturers to establish an uninterrupted workflow and boost their productivity. With single-use technologies, production downtime can be reduced from around two weeks to just a single day. The time needed for system setup and maintenance is also reduced, optimizing processes and improving cost and resource efficiencies.

Such technologies are available in two- and three-dimensional forms in a variety of sizes, with two-dimensional solutions typically being flatter pillow-style bioprocessing containers and three-dimensional solutions being larger, more complex boxes, drums, tanks, bottles, and bins.

Throughout the drug manufacturing process, single-use technologies are kept closed and connected via appropriate fluid transfer assemblies, eliminating open-air exposure and ensuring that outside contaminants are kept out.

Despite the connotations of “single-use”, these technologies are actually environmentally friendly, and offer a verified, efficient way forward for manufacturers aiming to improve the sustainability of their workflows. By eliminating the need for cleaning- and sterilization-in-place procedures, single-use technologies require less water and fewer chemicals for their use and maintenance, lowering their carbon footprint. Manufacturers of single-use technologies are also working to reduce the amount of corrugated cardboard material used to package their products. This lowers the amount of raw material needed for production, the waste generated at the point of use, and the fuel and emissions associated with distributing packaging material, helping biopharmaceutical manufacturers to meet and maintain their sustainability objectives.

Rigid containment solutions: configurable and certified particulate-free

Rigid technologies offer a variety of options to suit different applications. Each part of the drug manufacturing process is highly complex and specialized, and there is no one-size-fits-all choice for liquid handling. As such, biopharmaceutical manufacturers must make informed decisions for maximum return on investment.

Latest innovations have seen the introduction of novel plastic technologies that can be selected according to the “level of clean” needed to suit a particular application, allowing manufacturers to feel confident in their choice while staying conscious of strict budget constraints.

Advanced plastic technologies comply with USP <788> to minimize the risk of particulate contamination, and range from nonsterile options up to those with a SAL of 10^{-6} on both the inside and outside, particulate limits of less than 33% of those allowable under USP <788>, and endotoxin levels of below 0.25 EU/mL.

These highest levels of sterility are necessary for bulk drug substance management; suitable plastic technologies for this purpose include triple-layer sterile barrier packaging and double-walled cartons, produced within Class 5 (100) cleanrooms using appropriate aseptic controls (including Class 4 (10) operator attire).

Such technologies undergo strict washing procedures to ensure minimal contribution of particulate load to the final product, and to protect batch quality while maintaining productivity.

While rigid technologies require cleaning, many containment technology manufacturers are taking on this burden, offering cGMP-compliant washing, packaging, sterilization, silanization, depyrogenation, and low total organic carbon services for plastic technologies up to 50 L in size. These are performed in ISO 9001 registered facilities, in Class 4 packaging areas and Class 5 cleanrooms. In this way, manufacturers are seeking to alleviate contamination concerns both upstream (via advanced packaging solutions) and downstream (via cleaning and custom processing services) in bulk drug substance workstreams.

Towards safe, efficient bulk drug substance management

Bulk drug substances must be certified safe before therapeutic biologics and vaccines can be developed and released to the market. It is, therefore, of the utmost importance that biopharmaceutical manufacturers reduce the risk of product contamination and streamline their bulk drug substance management workflows.

To do this, they are increasingly turning to innovative rigid and single-use technologies, which offer safe, configurable, scalable, “plug and play” containment solutions for liquid handling. Such technologies lower the risk of losing product as a result of contamination, utilizing closed

or highly sterile configurations to minimize the chances of airborne or residual impurities finding their way into containment technologies and causing a batch to fail. They also meet or exceed vital extractables and leachables requirements, biodegradable particulate organic carbon (BPOC) guidelines, and USP <788> standards for particulate levels, minimizing any contamination risk posed by the containment technologies themselves.

Overall, innovative containment technologies help production managers, process engineers, and quality control managers to safeguard precious product, increase output, demonstrate compliance, reduce costs, and swiftly and efficiently bring safe drugs to the market.

References

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