Designing Disposable Single Use Filling Lines for Minimizing Losses and Maximizing Yield

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APPLICATION NOTE

In recent years, with the advent of disposable single use systems, the final fill and finish process in manufacture of sterile injectables has seen a rapid transformation. Single use filling lines have helped aseptic process owners reduce turnaround times by quickly and efficiently switching from product to product without worrying about cleaning validation, cross contamination, or improper connections that may compromise sterility.

However, the process owners are concerned about extractables and leachables, due to interaction between the drug product and polymeric single use systems, and rejections due to particulate matter, variable fill, or adsorption.

Another major concern, especially with high value drug product is losses during filling.

These challenges can be overcome through careful selection of materials of construction (MOC), efficient design, and monitoring and control of particulate matter during manufacture of these complex single use systems.

Careful Selection of Materials

Disposable single use filling assemblies are used in the last process step i.e. fill and finish. The materials should be of broader chemical compatibility with low extractables, biosafe, nitrosamines free and animal origin free, to ensure product integrity and patient safety.

Extractables and Leachables

As per BioPhorum Operations Group (BPOG) Best Practices Guide for Evaluating Leachables Risk from Polymeric Single-Use Systems Used in Biopharmaceutical Manufacturing, disposable filling lines, used with final fill and finish process pose the highest risk of leachables in the drug product.

Careful selection of single use components with smaller extractable footprint minimizes the risk of leachables with unacceptable levels, i.e. more than Permitted Daily Exposure (PDE) limits. This otherwise can force redesign of the entire single use disposable filling line resulting in higher costs and loss of valuable time to market.

At MDI, with state-of-the-art analytical labs we provide Extractable profiling of all single use components that helps identify potential leachables. Toxicological assessment of the various extractable compounds helps establish target leachable compounds for leachable studies.

Additionally, all MDI single use components are validated for following

- Nitrosamine free as per EMA/189634/2019
- Animal origin free (TSE/BSE free) as per EMEA/410/01 Rev. 03
- USP <87> Biological Reactivity Tests, in-vitro for Cytotoxicity
- USP <88> Biological Reactivity Tests, in-vivo for Class VI Plastics

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Adsorption of Drug Components

Certain drug formulations, especially those containing proteins, peptides, or low concentration actives, may adhere to the internal surfaces of disposable components such as tubing, or bags. This adsorption can lead to product loss and potency reduction, particularly in low volume or high value batches. It is imperative to evaluate component compatibility during development and consider surface modifications or material changes to minimize product interaction.

MDI through in house clean room manufacture of a wide range of single use components such as films, injection molded components (sterile connectors, disconnector, fittings, etc.), tubing and bottles, offers multiple options in different materials of construction. We also offer validation services to establish adsorption of key drug components and help establish flush volumes to ensure compliance with label claim percentage.

Efficient Design

Efficient design of disposable filling assemblies for high value specialty pharmaceuticals and biopharmaceuticals goes a long way in streamlining operations, protecting product integrity, and ensuring patient safety. By adopting a smart, risk-based approach to component selection, flow path optimization, and sterility assurance, manufacturers can significantly improve productivity and compliance while reducing cost and complexity. Some of the key design requirements for disposable filling line are:

Consistent and Accurate Fill Volumes

Achieving consistent and accurate fill volumes is challenging in disposable systems due to factors like tubing elasticity, inconsistent inner diameter (ID), pump type, and fluid viscosity. Changes in flow path geometry (e.g. from small ID to large ID tubing) can cause pulsed flow, back pressure, or air entrapment, which directly impact dosing precision. This variability can lead to under filling, overfilling, or regulatory non-compliance, especially in automated fill-finish operations. To address these issues and enhance accuracy, the assemblies can be designed using consistent ID tubing where possible.

MDI AcuFlo™ accurate pump PCS Tubing and Acufil™ disposable SS filling needles ensure accurate and consistent filling performance. These are designed to minimize fill volume variability and exceed compliance to USP <1151> and validated.

AcuFlo™ accurate pump PCS tubing are low friction optimal stiffness tubing to support optimal filling. AcuFlo™ resists collapse and deformation under fluid pressure, maintaining consistent ID and smooth flow paths even through bends, thereby maximizing filing efficiency.

Minimal Filling Losses

Despite design optimizations, residual hold-up in tubing, bags, filters, and connectors may still lead to measurable product loss, particularly in small-batch or high value biologics. MDI AseptiBag™ HV, with negligible hold up volumes, are specially designed for minimizing losses of high value drug substances and drug products in final fill operations.

MDI works closely with the process owners to understand their filling processes and requirements in terms of working environment, batch size and fill volumes, temperature and pressure conditions, transfer lengths, sampling needs, etc. to offer:

Modular and Customized Design

- Pre-assembled, ready-to-use systems that help reduce setup time and human error.
- Modular components such as filters, bags, filling needles, and manifolds for tailored configurationsfor different fill-finish operations.
- Customization to ensure compatibility with various drug formulations and container types.

Optimized Flow Path Design

- Minimal dead legs and smooth, continuous flow paths to reduce product hold-up, shear stress, and air-bubble formation.
- Proper tubing diameter selection to ensure consistent flow rates and accurate filling.

Technical and Regulatory Support

In addition to design optimization, MDI provides comprehensive technical support throughout prototype trials, installation, and operational use. This also includes complete documentation to aid regulatory product fillings and expert guidance to ensure compliance with performance standards.

Monitoring and Control of Particulate Matter

Particulate contamination is a significant concern in aseptic and injectable drug manufacturing. These single use disposable filling lines typically involve polymer-based components such as bags, tubing, connectors, filters and filling needles made from material like silicone, polycarbonate, polysulfone and thermoplastic elastomer (TPE). Particles may arise from component degradation, mechanical abrasion during handling or pumping, or environmental contamination during assembly. Particulate matter not only risks product rejection but also poses serious safety issues such as embolism or immunogenic reactions in patients. Certified cleanroom facilities, appropriate material selection, and particulate testing are critical to mitigate the risk.

At MDI, all single use systems including disposable filling lines are manufactured in ISO Class 7 clean rooms adhering to current Good Manufacturing Practices. However, to ensure considerable mitigation of risk of particulate matter, specially designed processes ensure that the fluid contact surface of AseptiBag™ HV (largest surface area single use system component in a disposable filling line) from film manufacturing to bag manufacturing is never exposed to the environment.

Additionally, all filling line tubing are flushed with 0.2µm filtered air to remove any visible particles that may have been generated during tube cutting.

Case Study

A large CDMO manufacturing high value speciality pharmaceuticals in different formats such as vials, pre filled syringe (PFS) and cartridges for pen injection systems, was facing high rejections due to variable fill in the final containers during fill and finish operations.

Rejections due to variable fill

MDI technical support team worked closely with the process owners to establish various reasons for variable fill and was able to optimize filling line tubing in terms of tube length, internal diameter and tube hardness to reduce rejections due to variable fill from a high 4-5% to < 0.5%.

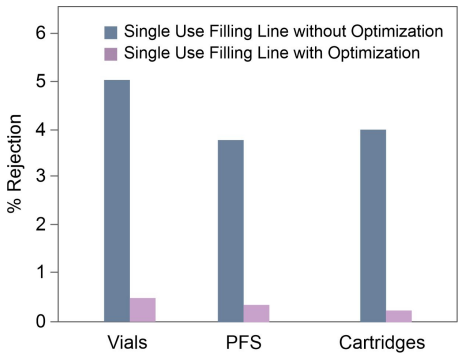

Fig. 1 Comparison graph between single use filling line with and without optimization