Particle Pressures

IPT asked Diane Paskiet at West Pharmaceutical Services, Inc. about the process of creating parenteral drugs, the obstacles in this procedure, and how these challenges affect patients.

IPT: West Pharmaceutical Services, Inc. provide solutions and guidance on therapeutic containment and delivery. What are the primary concerns this industry is now facing?

Diane Paskiet: The landscape for containment and delivery of medicines is an evolving field with the advancement of innovative and novel therapeutics. There are four basic principles to consider for demonstrating delivery system suitability: maintain protection of the drug product, ensure the system’s functional requirements, provide assurance of component safety, and verify compatibility of the entire system. While a set of four criteria can appear to be a minor undertaking, a multitude of interrelated factors can impact the quality of the final drug product, which can cause a delay to the market. In general, the industry is challenged with understanding requirements for effectively administering advanced medicines to patients using the proper containment and delivery systems.

Could you explain the particles in parenteral drugs and why they occur in injectable biologics?

Particles will be inherent to drug products. The size of actual biologic molecules can be in the nanometres (nm) to 20+ micrometres (µm) range. Particles can arise from extrinsic sources that are foreign to the product packaging and assembly process. Extrinsic particles can come from the product manufacturing process or from material that is loose or adhered to product contact components. Intrinsic particles can occur in biologic products due to interaction with components of the delivery system. It is well-documented that silicone oil – when applied to the barrel of a pre-filled syringe – can interact to some degree with biologic products, thereby causing protein aggregation. Components of containment and delivery systems are scrutinised for particle contributions from visible (>100µm) to subvisible (1-100µm). However, each biologic product in the final system must be evaluated for particles to understand inherent and total impact. Protein aggregation can arise over time during storage, shipping, and handling of the final system. Protein stability is highly dependent on its environment, including the materials of contact, throughout the product lifecycle.

What makes this such a serious concern for drug manufacturers?

It is critical to understand sources of particulate matter in biologic products to ensure quality and manage risks as they relate to patient safety. Injectable products are required to be essentially free of visible particulates. Several product rejects or recalls in the industry have been due to particles that could potentially harm patients. When such recalls occur, if not managed properly, they may lead to shortages as well as lost revenue. There is documented evidence of drug product recalls that are related to interaction with containment and delivery systems. One such example that occurred among drug manufacturers is the numerous occurrences of glass delamination particles caused by surface erosion of glass in contact with drug products.

Patient exposure to subvisible particles is especially notable because of concerns for immunogenicity. The linkage between protein aggregation and immunogenicity has been frequently cited in scientific literature. Protein formulations can have low levels of aggregates with sizes ranging from dimers to subvisible and visible particles – it is a challenge to fully characterise and control these particles. Stresses from various environments, handling, and contact with containment and delivery systems can initiate aggregation over time. The overall quality of biologics and the potential for particles can be affected by adsorption/absorption of the product or formulation on contact surfaces, interaction or modification of the product due to leachables, or destabilisation.

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- Controlled release formulations
- Patient compliance
- Personalised medicine
resulting from loss of container integrity. Minimising drug product compatibility and safety issues associated with containment and delivery systems is an important aspect of the development process.

**How do these issues impact patients?**

Parenteral products can expose patients to various sizes of particulates, and the concerns will depend upon the type, size range, number, and source. Particles in drug products from extrinsic or foreign sources could compromise product sterility and potentially cause harm. Injecting particles could cause irritation or inflammation of surrounding tissue, damage to local tissue, or possible blood clots to occur. Subvisible particles in biologic products have been suspected to induce immunogenicity, but the clinical effect is not well-understood and is difficult to verify without conducting specific human studies. Particles and clinical impact depend on multiple factors that would consider the patient and health condition connected to the particle type, size, and number injected.

**What are the important considerations for measuring and understanding particle loads in primary components?**

Assessments include determination of particle size, count, morphology, identification, and source. Essentially, a standard particle specification for components does not exist nor does a single endpoint. Particle data is typically generated for the purpose of:

- Comparing particle loads from various components
- Monitoring components for release to a defined specification
- Qualifying suitability of containment and delivery systems
- Monitoring and investigating drug product specifications

Particle data generated on components can be reported relative to some liquid concentration (component extractions) or dry counts (filtered extracts). The drug product excipients, manufacturing process, and the complete delivery system will influence particle loads, while the measurement technology and sample preparation will influence particle data. Several methods are necessary for comprehensive assessments of particles in pharmaceutical products and should be conducted at appropriate stages of development through commercialisation. Multiple particle technologies should be considered based on the type of sample analysed, size range of interest, and property to be investigated.

**Can you detail the best practices for controlling this problem, and how can advances in technology help?**

Particle profiles are not easily correlated due to their dynamic and transient nature and various measurement technologies. The wide variety of particle types, sizes, and analysis methodologies will have limitations, and variability of results will be inevitable. Assessments are challenging because of the analysis parameters for different detection technologies and sample preparation approaches and reporting. Additionally, reference materials for particle measurements are lacking. Combined, these issues can reduce the accuracy, recovery, and reproducibility of particle measurements, especially with biologic products. Suitability of analytical methods depend on the capability of the technology, particle attributes, and properties to be assessed. Methods should consider potential interferences and consistent reporting criteria to be correlated to product quality and safety. Due to limitations of different measurement principles and samples, evaluating data trends from orthogonal methods may be more meaningful than relying on absolute numbers.

**How do you think the industry will fare against this issue in 10 years?**

As novel medicines advance, so will the requirements for containment and delivery systems. Risk management and Quality by Design viewpoints will be critical to developing and commercialising medicines in the future. In 10 years, innovative products are likely to be more available as science and risk-based approaches begin to drive decisions for efficient manufacture and delivery of pharmaceutical products.

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Diane Paskiet is Senior Director of scientific affairs at West Pharmaceutical Services, Inc. She has over 20 years’ experience in polymer analysis relating to product failures, de-formulation, and migration studies. Diane has served as a project advisor in support of qualification studies associated with packaging and delivery systems for regulatory filings. Prior to this role, she was in charge of site operations for West-Monarch Analytical Laboratories. Diane is a co-recipient of the US Pharmacopoeia award for Innovative Response to a Public Health Challenge and Expert Committee member. She serves on the Product Quality Research Institute Development Technical Committee and Chair of Parenteral and Ophthalmic Drug Product Leachables and Extractables Working Group.