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Considerations for Packaging and Delivery Systems for Biopharmaceutical Products

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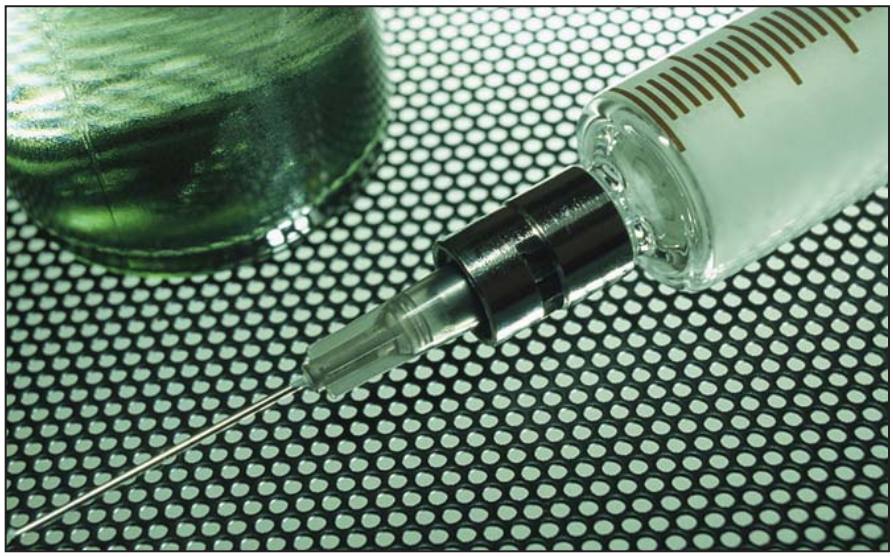

The development and commercialization of biopharmaceutical products is paving the way for significant growth in the pharmaceutical industry. Virtual and small biotech companies are researching and developing new biotechnology-based products that help large pharmaceutical companies backfill their pipelines.

Many of these products have been in development for years and are finally reaching the point of commercialization. Because of the nature of many of these substances, they are sensitive to their environment, their packaging and their delivery systems. Therefore, it is critical that developers recognize their drug's particular sensitivities, and evaluate packaging and delivery systems that can help mitigate problems related to it. Biotechnology pipelines are currently dominated by therapeutic proteins and monoclonal antibodies—drugs that will be delivered by injection. Accordingly, the focus of this article is on systems that deliver injectable drugs.

The requirements of biopharmaceutical products are unique, and there is a general market trend toward the use of prefillable syringe systems which help to facilitate administration in home healthcare situations. These trends are expected to drive the use of new delivery systems that can address both drug stability and clinical and field application issues.

Because most of these drug products are injectable, the initial storage system is a glass vial that is typically sealed with an elastomeric closure. This traditional packaging assures "proof of concept" for starting biotech development.

When evaluating any primary container closure system, four basic interactions between the drug and its container closure system can occur. These are: 1) permeation, 2) leaching, 3) absorption, and 4) adsorption.

Glass has been used as a primary container because of its high chemical and temperature resistance, low cost, and low moisture and gas transmission rates. However, glass can flake into solution, leading to higher particle loads. Glass can also impact the drug product's pH, and the inorganic extractables from the glass that cause this shift are potential leachables. Additionally, the drug may interact with both the glass and the uncoated elastomeric closure used to seal the vial.

Elastomeric closures are used to seal glass vials because they compensate for imperfections in the glass and variation in glass tolerances. They also have superb functional properties for fragmentation (coring) and resealability, and are compatible with steam sterilization and irradiation.

However, organic and inorganic extractables can migrate from the closure to the drug product itself. In addition, the use of silicone oil as a processing lubricant for the closures is common. This silicone oil may lead to higher particle levels and can initiate protein aggregation with sensitive biopharmaceuticals. The use of elastomeric closures with an inert fluoropolymer film lamination can minimize container closure interaction in two ways. First, the film reduces the potential for extractables to leach. Second, depending upon the closure chosen, a virtually silicone-oil-free stopper can be used. These factors improve compatibility and lessen the potential for problems.

Cyclic polyolefin-based plastic vials and prefillable syringe systems provide an alternative material for sensitive biopharmaceutical products, and products where breakage and glass particulates could be an issue. Daikyo Crystal Zenith cyclic polyolefin-based delivery systems have many advantages. The syringe barrels are produced in high-quality, clean manufacturing environments, are very low in extractables,

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Photos provided by the University of Kansas

Silicone Oil-Free Daikyo Crystal Zenith®

Siliconized Glass

and lend themselves to design flexibility and tight tolerances. In the case of the Daikyo Crystal Zenith RU (ready-to-use) prefillable syringe system, the unique combination of a piston with Flurotec® barrier film and a cyclic polyolefin syringe barrel provides a system that does not require silicone oil for lubricity. This mitigates many of the risks associated with silicone and other potential extractables.

Protein Aggregation and Absorption

Studies have documented that certain proteins are sensitive to silicone oil.[1] There are other mechanisms and reactions that can occur which also impact aggregation. Manufacturers have added nonionic surfactants to their drug solution to overcome aggregation. The use of surfactants can lead to other issues, such as the formation of residual peroxides.[2] They also have the potential for pulling extractables from the packaging components, leading to a greater degree of leachable interactions.

Aggregate levels in therapeutic proteins should be characterized and monitored throughout the drug product life cycle.[3] It is recommended that these levels be minimized whenever possible through drug product formulation, container closure system selection, or storage parameters.

In a recently published poster at the 2007 Colorado Protein Stability Conference, Esfandiary *et al.* at the University of Kansas compared the effect of prefillable syringe surfaces on silicone-sensitive biomolecules, demonstrating the effectiveness of silicone oil-free Daikyo Crystal Zenith syringes in reducing the extent of protein aggregation when compared to siliconized glass syringes.

The photos above are from a study comparing a Daikyo Crystal Zenith 1 mL syringe to a 1 mL glass syringe system following air shipment of a biomolecule at refrigeration. Daikyo's Crystal Zenith syringe system demonstrated a significant reduction in the formation of insoluble protein aggregates seen in siliconized glass syringes.

Protein aggregation and adsorption is a complex process that can be impacted by many factors such as the physical condition of the container surface and the unique structural aspect of the protein itself. To minimize protein adsorption loss, pretreated glass vials or excipients that reduce surface interactions are viable. However, the use of alternative plastic packaging materials such as cyclic polyolefins has also been found effective in minimizing drug adsorption.

Conclusion

Protein aggregates have been suspected as the cause of immunogenicity in many therapeutic proteins. Repetitive administration of a specific drug can increase the risk of a response in the patient—an industry-wide concern. This example of biopharmaceutical product sensitivity shows how the primary container closure system may impact the drug, and also has the potential to impact the patient if the optimal delivery system is not chosen.

Developers of a biopharmaceutical product should evaluate the container closure and delivery system early in the process to minimize any potential problems occurring during clinical trials. They should augment their development team with the expertise available from a resource knowledgeable in drug administration systems. Their resource must also be capable of presenting options for selecting components that are appropriate for a biopharmaceutical product and its clinical application.

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