Parenteral Packaging Concerns for Biotech Drugs

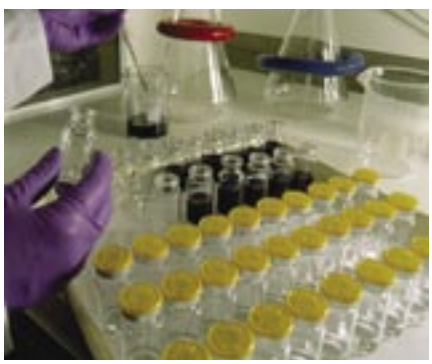
Compatibility Is Key

by Frances L. DeGrazio

Biotechnology promises treatments and even cures for many diseases previously considered intractable. Although the biotech industry began just about a quarter-century ago, since the late 1990s the number of new biopharmaceutical approvals has nearly equaled those for new small-molecule drugs.

Despite significant effort and research in delivering peptides and proteins through means such as inhalation, transdermal injection, and direct contact with mucous membranes, parenteral injection remains the principal delivery system for today's biotherapeutics. The packaging unit is typically a single-dose vial, with prefilled syringes less commonly used. The drug is provided either as a solution or more commonly a lyophilized cake that a caregiver reconstitutes and injects using a syringe. Requirements for product purity, activity, and shelf life dictate a very high standard for injectible drug packaging, particularly for highly active peptides and proteins. But with biopharmaceutical development times averaging 7–10 years and costs measured in the hundreds of millions of dollars, it is too easy for innovator companies to dismiss primary packaging as an afterthought.

Packaging represents the first line of defense for all formulated drugs. A good package protects its contents from the outside world and vice versa. At the same time the vial, stopper, and seal materials must be fully compatible with a product, whether it is lyophilized or in solution. US Food and Drug Administration (FDA) requirements in a 1999 guidance discuss understanding levels of extractables and leachables and test methods related to such contaminants (1).



Reconstitution systems and devices are often required for the transfer and administration of biotechnology drugs that are unstable in liquid form.

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Addressing evaluation of packaging systems for pharmaceutical and biopharmaceutical drug products, the guidance requires that each drug application contain enough information to demonstrate that a proposed package and its components are suitable for their intended use. All injectable products need to be evaluated for leachables that may migrate over the product shelf life during formal stability testing and beyond. In addition, the guidance also discusses evaluation of packaging components and related materials. By placing much more scrutiny on stopper processing and handling, barrier films, and leachables and extractables, FDA's container closure guidance significantly raised the bar on what is expected from biopharmaceutical drug sponsors.

Package and Product: Not Always a Perfect Match

Most modern biopharmaceuticals are proteins/peptides, which are biopolymers with unique chemical, physical, and mechanical properties. A protein or other peptide's function and activity is based on much more than its simple linear chemical structure. These molecules are sensitive to heat, light, and chemical contaminants. Minute concentrations of metals, plasticizers, and other packaging materials can deactivate or denature therapeutic proteins/peptides. The seriousness of chemical contamination is compounded by the extremely low concentrations typical of such drugs.

Whether in liquid or lyophilized form, biopharmaceuticals possess properties that make them sensitive to their packaging or delivery system. They have a tendency to adsorb onto the surface of containers and closures, which because of the small amount of drug present can essentially remove all active material from a drug formulation. In situations where the drug desorbs back into solution, it could lose potency due to that interaction. Freeze-dried proteins are no less immune from the effects of packaging. Because most lyophilized cakes are sensitive to moisture, an inadequate seal can allow water and other contaminants to enter a package and deactivate the drug inside.

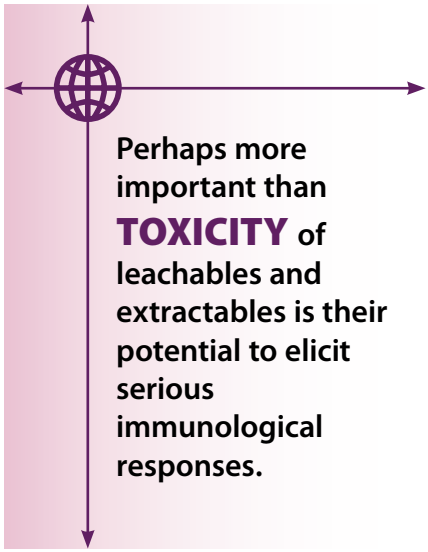
Many biopharmaceuticals are sensitive to silicone oil, a material commonly used to lubricate elastomeric stoppers during fill and finish to facilitate insertion of stoppers into vials. Silicone oil has been associated with inactivation through nucleation of proteins around oil droplets. Recently introduced fluoroelastomer coatings on stoppers provide needed lubricity in addition to an added level of chemical inertness, barrier protection, and safety. Fluoroelastomers thus serve as both a lubricant and a barrier to improve compatibility between drugs and their rubber closures.

Primary packaging should be a top priority for all drug products, even pills and tablets. Such concerns are amplified several-fold with injectible biotech products not only because of the chemical and physical unpredictability of proteins/peptides, but also because such products are injected.

Sources of Contamination

Extractables are the most common source of leachable contamination arising from a product formulation's contact with its package materials. A *leachable* is a chemical that has migrated from packaging or other components into the dosage form during stability studies or under normal conditions of use.

An *extractable* is a chemical species released from a container or component material that has the potential to contaminate a pharmaceutical product. Extractables are frequently generated by interaction between products and their packaging (e.g., glass vials and stoppers) over time, depending on solvent and temperature conditions. Extractables testing is recommended even when containers or components meet compendial suitability tests—and should be carried out as part of qualification efforts for the container and its components.



Package component fabricators test for extractables from their materials as part of their own development and qualification operations. More important, leachables tests are carried out at the point of use on the actual drug product. The goal of such testing is to determine that package materials are generally safe, compatible with a given dosage form, and present an acceptable risk of contamination for particular products.

Extractables and leachables can have a significant impact on drug products, especially highly active biopharmaceutical drug formulations, which may contain just femtograms of their active ingredient. Perhaps more important than the toxicology of such materials is their potential to elicit serious immunologic responses, even at extremely small dosages.

Mitigating the Risks of Rubber Closures

In our experience, fluorocarbon film coatings provide the best combination of protection against extractables from stopper materials while providing a high level of barrier protection for drug products, therefore minimizing leachables concern. When applied to stoppers, fluorocarbon films significantly reduce a drug's adsorption on them, which is critical for maintaining product potency and shelf life. In addition, fluorocarbon films provide extra lubricity for proper vial seating without the need for silicone oil. Fluoroelastomer films are made from highly inert materials, so they also significantly reduce the possibility of extractables migrating from rubber stoppers into biopharmaceutical product formulations.

Because the cost of specifying the wrong closure components and materials can be high, a biopharmaceutical manufacturer should devise a separate development plan for primary packaging, just as for process, molecule, and clinical development. Often this separate activity is contracted out to companies that specialize in packaging components. Some typical deliverables to expect from such a relationship include

- Better understanding of the product
- Ability to work off-site on the product and its proposed packaging
- Recommendations for components, especially for seals and stoppers
- Knowledge of the engineering and regulatory aspects of packaging appropriate for a given application
- Forewarning of potential problems
- Support for package option evaluation through engineering and laboratory services.

This function must be acquired, one way or another, by phase 1, which is usually when sponsors and regulators "get serious" about product and package working together. During phase 1, a package component expert company will begin screening for closure designs and materials. Such screening involves assessing packaging alternatives, generating preliminary data on leachables, and choosing one or several alternatives that provide the highest degree of product compatibility with the lowest level of leachables.

By phase 2—earlier if possible—sponsors need to begin developing precise, validated methods for

determining extractables and leachables. For products that make it this far, methods development becomes almost a separate phase of stability testing. When such development and validation are complete, testing can be carried out using samples stored under typical ICH conditions (2). Accelerated testing is typically done over six months at high temperatures and humidities, whereas real-time testing uses standard 25 °C and 60% relative humidity conditions over a two- to three-year storage period.

The importance of carrying out stability studies over the full testing period cannot be overstated. In our experience, some product–package combinations that show little or no degradation over the first few months have led to significant inactivity because of adsorption onto the glass vial before expiration of a two-year shelf life. Leachables that do not appear in the first several weeks may emerge later on, well within a product's specified shelf life.

Strategies for Minimizing Risk

Drug developers who do not understand the impact of packaging on their biopharmaceutical products are carrying an unnecessary level of regulatory and product-related risk. Problems often arise when a contract manufacturer tries to convince a sponsor that a particular stopper, vial, or other closure product is appropriate simply because it has been validated with the contractor's fill line. That is all well and good—even necessary. But stoppers must be validated with a given product first, and then with the filling machinery. It is far more prudent and much more cost-effective in the long term to test and validate packaging within the context of each drug product.

Submissions that lack properly generated data on product stability within proposed packaging are very likely to be held up until such data are provided. Often the information is generated, and that's the end of the problem. Occasionally, however, when rigorous testing uncovers leachables/extractables, product inactivation, or other packaging-related problems, market authorization can be held up for months. Very few biotechnology companies are willing or prepared to gamble on significant delays in their clinical programs for the sake of a minor short-cut.

Lyophilization Is a Special Case

Many biotech products are lyophilized inside their package, usually a vial, before it is stopped and sealed. Freeze-drying presents its own peculiar process and packaging requirements. As with drugs in solution, packaging can make or break the success of a final formulation for a lyophilized product, particularly its long-term stability and package compatibility. Vials that are not designed specifically for lyophilization (e.g., with convex rather than flat bottoms) will make a freeze-drying process less efficient, leading to an extended lyophilization cycle. Rubber closures can also hinder freeze-drying if they do not permit adequate venting during sublimation.

Rubber stoppers adsorb and desorb water at different rates. Under storage conditions, stoppers that have not been properly dehydrated can release water into a lyophilized product, affecting its stability over time. That can be especially problematic with biopharmaceuticals, which tend to have very small cake weights compared with traditional freeze-dried pharmaceuticals. With their weight often measured in milligrams or less, these cakes are significantly more sensitive to moisture, pH changes, and extractables that can migrate from rubber closures.

A small difference in moisture of a lyophilized cake can make the difference between an active or denatured protein. And contaminants can cause pH differences that seriously affect protein structure and activity. In our experience, the wrong rubber closure can easily shift pH in a small volume of product or a diluted lyophilized cake. Fluoroelastomer-coated stoppers eliminate the rubber closure as a source of leachables that could affect pH. Glass vials, however, can also leach ions.

Any precautions taken with solution formulations are doubly applicable to freeze-dried biopharmaceuticals. During lyophilization, all primary package components must work together without interfering with either the product or the freeze-drying process. Here are a few packaging issues to be aware of for lyophilized products:

- Closures that allow adequate sublimation rates and cleanly insert into vials without "back-out" or sticking to lyophilization chamber shelves
- Glass vials that provide adequate contact between their base and a lyophilizer shelf
- Compatibility during freeze-drying between vials and their elastomeric closures.

Examples from Experience

Globalization of the pharmaceutical supply chain presents new challenges for biomanufacturers. One big pharma manufacturing an injectible US orphan drug product in Europe had difficulty obtaining validated presterilization washing services for rubber stoppers produced by one of our European subsidiaries. To save time, this client used local washing services, which ultimately resulted in FDA rejecting its US regulatory application. Curiously, the company had experienced something similar with a different product. The approval delay cost tens of millions in lost revenues as well as considerable prestige. Even more serious, for several months US patients were denied the only effective treatment for their chronic condition. The problem eventually was resolved by shipping stoppers to our Pennsylvania facility

for washing, then reshipping them to the finishing plant in Europe.

Seemingly trivial changes in formulation can affect drug–package compatibility. One of our clients had received European approval to market a protein drug but was asked by those regulators to eliminate human serum albumin (HSA) as an additive stabilizer. The sponsor found a surfactant stabilizing agent that worked just as well with that drug as HSA. But it did not pay close attention to potential interactions between that new stabilizer and the rubber plunger in the prefilled syringes used to deliver the medication. Initial data showed acceptable leachables levels, so the product gained marketing approval—only to be recalled several months later due to serious adverse events related to leachables. The manufacturer's error was in assuming that a plain rubber stopper would provide the same level of compatibility with the new formulation as with the old one. This problem could have been prevented by careful stability and leachables testing and by using a fluoroelastomer coating for the syringe plunger. Eventually that is what the manufacturer did—but not before a debacle that cost many millions in lost sales and opportunity.

Another Kind of Risk to Manage

The high value, clinical efficacy, and price tags of biotherapeutics, coupled with their need for injectible delivery in most cases, demand a high level of attention paid to their primary packaging. Biotechnology companies entering the clinical stage need to take the same science- and risk-based approach to packaging materials that they exercise with molecule and process development. If that expertise is lacking in-house, drug developers must look outside their organizations for the know-how and experience to ensure a smooth transition from laboratory to clinic to market.

Specifying advanced coatings (e.g., fluoroelastomers) for most stoppers or plungers used with lyophilized or solution-based therapeutic proteins and peptides may seem like an extravagance. In reality, given the long development times and consequences of being wrong, these measures are actually prudent and should lower costs in the long run.

Reference

1 *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics—Chemistry, Manufacturing, and Controls Documentation.* US Food and Drug Administration, May 1999; www.fda.gov/cder/guidance/1714fnl.htm

2 Q1A (R2) *Stability Testing of New Drug Substances and Products.* International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Geneva, Switzerland, February 2003; www.ich.org/LOB/media/MEDIA419.pdf.

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