

Evaluating Pharmaceutical Container Closure Systems

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The use of qualitative and quantitative methods can help packaging professionals determine the presence of extractables and leachables.

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The United States Pharmacopeia (USP) and FDA have been and continue to be the driving force behind the safety evaluation of materials and container closure systems in the United States. An important step in such evaluations is characterizing the materials and the chemicals that can migrate or extract from container closure system components to the drug product. Figure 1 shows the various types of chemicals that can migrate from polymeric materials¹. Such basic information is critical to understanding the biological safety and suitability of a container. A number of tests can be used to establish initial qualification of the container closure system, and a quality control plan can help ensure compatibility and safety.

Background

Establishing the safety of container closure systems is of key importance to the medical and pharmaceutical industries. It is no less important than the contents themselves. FDA's guidance document, *Container Closures System for Packaging Human Drugs and Biologics*, makes this point clear². This document, which stands as the latest reference evaluating drug product packaging materials, is the primary governing standard. Understanding the principles presented is imperative, and implementing them is an essential part of establishing product safety. This paper defines what the document requires and what qualitative and quantitative tests can be used to satisfy the requirements with an emphasis on leachable and extractable chemicals to satisfy compatibility and safety.

Evaluations

FDA's guidance document requires the evaluation of four attributes to establish suitability: protection, compatibility, safety, and performance/ drug delivery². The document also provides a structured approach to ranking packaging concerns according to the route of drug administration and likelihood of packaging component-dosage form interaction. A container closure system acceptable for one drug product cannot be assumed to be appropriate for another. Each product should have sufficient information to establish that a container and its components are right for their intended use. For example, the type or extent of information provided for an injectable drug product is expected to have more detail than that provided for the container closure system of a solid oral-dose form. Table I ranks the concerns of containers according to the route of administration².

To establish suitability, all four attributes must be evaluated and be shown to pose no concern to the drug product or to product performance. Suitability refers to the tests used for the initial qualification of the container closure system with regard to its intended use. The guidance defines what tests must be done to evaluate each of the attributes of suitability.

While the tests and methods described in Table II allow one to provide data that the container closure system is suitable for its intended use, an application must also describe the quality control (QC) measures that will be used to ensure consistency in the packaging components. Principle considerations for the QC measures are physical characteristics and the chemical composition. By choosing two or three of the tests done in the initial suitability study, a QC program can be established that will ensure the consistency of the container closure system.

Protection

A container intended to provide protection from light or offered as a light-resistant container must meet the requirements of the USP <661> Light Transmission test³. The procedure requires the use of a spectrophotometer, with the required sensitivity and accuracy, adapted for measuring the amount of light transmitted by the plastic material used for the container.

The ability of a container closure system to protect against moisture can be ascertained by performing the USP <661> Water Vapor Permeation test³. The USP sets limits to the amount of moisture that can penetrate based upon size and composition of the plastic components (HDPE, LDPE, or PET).

Evaluating the integrity of the container can be done in several ways. A couple of the most common tests are dye penetration and microbial ingress^{4, 5}. Container closure systems stored in a dye solution and exposed to pressure and vacuum cycles are examined for dye leakage into the container. The microbial ingress is similar in fashion, but determines the microbial contamination of the contents when soaked in a media contaminated with bacteria. Other quantitative tests that can be run are vacuum/pressure decay, helium mass spectrometry, and gas detection.

Compatibility

Figure 1. Polymeric biomaterials are composed of mixtures of chemicals, some of which are bound to the polymer backbone or into the material matrix, while others are free to migrate into the surrounding environment. The identities and abundance of these chemicals determine a material's suitability. [Click to enlarge.](#)

Table I. The probability of interaction between dosage form and container closure system and the degree of concern. [Click to enlarge.](#)

Components compatible with a dosage form will not interact sufficiently to change the quality of the drug or the component. A leachability study designed to evaluate the amount and/or nature of any chemical migrating from the plastic material to the drug product should be implemented. The study should evaluate substances that migrate into the drug product vehicle for the length of shelf-life claim. The drug product should be evaluated at regular intervals, such as at one, three, or six months or at one or two years, until the length of the shelf-life claim has been met.

Analytical techniques such as liquid chromatography/mass spectrometry (LC/MS) to evaluate nonvolatile organics, gas chromatography/mass spectrometry (GC/MS) to evaluate semivolatile organics, and inductively coupled plasma (ICP) spectroscopy to detect and quantitate inorganic elements should be a part of this study.

Coupling MS to LC and GC methods provides a definitive and effective tool for identifying unknown impurities and degradation products. Information on substances identified from extractable chemical evaluation (see below) can be used to help prepare standards specific for the plastic container being studied during leachability studies⁶. Methods validation for detection of leachable chemicals in drug product vehicle and dosage forms must be based on industry practices and International Conference for Harmonization (ICH) Guidelines.

This systematic approach allows the chemist to design, set up, and calibrate methods that target substances previously identified in extractables tests, making the procedure specific for the container materials being evaluated. This will allow the results to be correlated with the extractables profiles of the container closure components determined under the various control extraction study conditions.

Other changes such as pH shifts, precipitates, and discoloration, which may cause degradation of drug product, should be evaluated. Changes in the physical characteristics of the container, such as brittleness, should be evaluated using thermal analysis and hardness testing⁷. An infrared (IR) scan of each plastic component should also be included. An IR scan can fingerprint the materials and also provide proof of identity, which will later become part of quality control.

Safety

All packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed during drug treatment. Determining the safety of a packaging component is not a simple process, and a standardized approach has not been established. However, an extraction study should be one of the first considerations. Isolation is accomplished through sample preparation, followed by incubation in solvents at well-defined and well-controlled times and temperatures. Sample preparation is an area in which an experienced chemist's knowledge of chemical procedures is indispensable.

Prior to performing any of the chemical tests described here, it is important to have precise information on the synthesis of the polymer itself. This includes descriptions of the monomers used in the polymerization, the solvents used in the synthesis, and the special additives that have been added during material production. For containers used to package drugs ranked with a high degree of concern, such as inhalation aerosols and injectables, this type of information is imperative. Knowledge of degradation products that may be released into the drug product is also important.

Table II. Properties of suitability concerns and interactions. [Click to enlarge.](#)

Some potential extractable chemicals from packaging materials are water soluble, while others are soluble only in nonpolar environments. For materials contacting drug products, extraction in both polar and nonpolar environments is relevant. The USP includes physicochemical tests for plastics based on water extracts; while water, alcohol, and hexane extracts are required for polyethylene containers under controlled temperature and time parameters (70°C for 24 hours for water and alcohol and 50°C for 24 hours for hexane). These tests are particularly useful in defining materials as rich or poor in extractable chemicals³. The tests categorize material extracts in general terms, such as nonvolatile residue (total extractables), residue on ignition, buffering capacity, heavy-metals content, and turbidity.

The USP physicochemical tests for extractables should be a part of all suitability programs, regardless of the criticality of the drug dosage form. USP Elastomeric Closures for Injections should also be a part of the extractables study to establish safety⁸. These USP tests, which have evolved over many years, are relevant, sensitive, rapid, and inexpensive. They help establish material safety.

Like compatibility, the evaluation of safety will also require analytical methods and instrumentation to identify and quantitate extracted chemicals. Gas/liquid and high-performance liquid chromatography (GLC and HPLC, respectively) are powerful analytical tools that can separate and quantitate volatile and nonvolatile chemicals; however, they provide little structural information⁸. Coupling GLC to MS creates an instrument much more powerful than the sum of the two individual instruments⁹. MS is a powerful tool because it can provide valuable structural information with a high degree of specificity and is considered by many scientists as the technique that obtains the most defensible data¹⁰. The mass spectrum or fragmentation pattern acquired for each molecule makes it an excellent and effective tool for identifying unknown impurities or degradation products^{11, 12}.

The goal is to obtain sufficient information to be able to identify potential toxic hazards arising from the chemical components of the packaging materials. Toxicological risk assessors typically evaluate this information. The chemists provide the necessary qualitative and quantitative data (extraction profile) that the risk assessors use to determine container safety. The toxicological approach should take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen. The flow of information between the analytical chemists and the toxicologists is what establishes the process of characterization as an integral part of container safety and compatibility.

Biological reactivity is the second part of safety testing and is designed to test extractable chemicals for toxicological properties. FDA's guidance document suggests that the USP biological reactivity tests can determine the safe level of exposure via the label-specified route of administration.

Performance

The fourth attribute of suitability of the container closure system, performance and drug delivery, refers to its ability to function in the manner for which it was designed. There are two major considerations when evaluating performance. The first consideration is functionality that may be to improve

patient compliance, minimize waste, or improve ease of use. The second consideration is drug delivery, which is the ability of the packaging system to deliver the right amount or rate. Packaging systems that address this consideration are prefilled syringes, transdermal patches, dropper or spray bottles, and metered-dose inhalers.

Quality Control

After demonstrating container closure system suitability, it is necessary to define quality control measures that will be used to ensure consistency in the packaging components. The guidance suggests considering consistency in physical and chemical composition². Using a few simple tests, the quality of components and ultimately the container closure system can be monitored.

Dimensional criteria such as shape, volume, wall thickness, and design tolerances should be defined and monitored. Physical considerations such as water vapor transmission to evaluate seal integrity, thermal analysis such as DSC to monitor melting point and glass transitions of plastics, and IR scanning to prove identity should be a part of an ongoing quality-control monitoring program. Chemical composition should also be evaluated by performing the simple but informative USP physicochemical tests using water, drug product vehicle, and alcohol extractions of plastic components. Specifications should be set for nonvolatile residue (total extractables) during the initial suitability tests and then used to monitor the level of polar and nonpolar extractables as part of a quality-control plan.

All materials used in medical and pharmaceutical packaging require some degree of characterization testing to establish suitability. Suitability through materials characterization forms the basis for understanding the composition of materials and their potential to have an adverse biological effect when the container or closure is put into use. Characterization also serves to ensure standardization of materials from one lot to the next, and it can be used to establish a quality-control plan. While this paper emphasizes extractable and leachable chemicals, all aspects of suitability are important.

Suitability testing should be able to establish the following criteria:

- 1/2 Materials of construction of container and closure components are safe for their intended use.
- 1/2 Container components are compatible with the dosage form.
- 1/2 The container and closure system adequately protects the dosage form.
- 1/2 The entire system functions in the manner in which it is intended.

Fulfilling these criteria will minimize risk and allow for a successful product release in an appropriate manner.

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