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200 Gilbert Street
Mansfield, MA 02048
P: (508) 966-1301
jordilabs.com

Characterizing Pharmaceutical Packaging Systems for Suitability

Overview

The following white paper provides an overview of the process used to determine the suitability of pharmaceutical packaging systems for their intended purpose. This applies to plastic packaging systems, glass containers, and elastomeric closures for injection.

- *Definitions*
- *The Purpose of Pharmaceutical Packaging Testing*
- *How is Pharmaceutical Packaging Testing Conducted?*
- *Characterization of the Plastic Materials of Construction*
- *Characterization of Plastic Packaging Systems*
- *Extractables, Leachables, and Toxicological Risk*
- *Glass Containers for Pharmaceutical Use*
- *Elastomeric Closure Injections*

Definitions

Packaging System

> "The sum of packaging components and materials that together contain the product and the article. This includes primary packaging components as well as secondary packaging components when such components are required to provide additional protection."[4]

Primary packaging Component

> "A packaging component that is in direct contact with or may come in direct contact with the article."[4]

Secondary packaging Component

> "A packaging component that is in direct contact with the primary packaging component and may provide additional protection for the article"[4]

Tertiary Packaging Component

> "A packaging component that is in direct contact with a secondary packaging component and may provide additional protection for the article during transportation and/or storage."[4]

USP Documents

USP <661.1> Plastic Materials of Construction
USP <661.2> Plastic Packaging Systems for Pharmaceutical Use
USP <659> Packaging and Storage Requirements
USP <660> Glass Containers Used in Pharmaceutical Packaging/Delivery Systems
USP <670> Auxiliary Packaging Components
USP <381> Elastomeric Closures for Injection
USP <87> Biological Reactivity Tests, In Vitro

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USP <88> Biological Reactivity Tests, In Vivo
USP <671> Containers – Performance Testing
USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging
USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging
USP <665> Polymeric Components and Systems used in the Manufacturingof Drug products (Draft)
USP <1665> Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products (Draft)

The Purpose Pharmaceutical Packaging Testing

In an era of exponentially increasing technological advancements, there are also exponentially increasing products to satisfy demand. The pharmaceutical industry is no stranger to this trend, as new drugs are developed and sold to the public each year. For the past five years, the US FDA has approved an average of 44.4 novels drugs yearly.[2] Each new drug comes with its associated packaging, and that does not include the much larger pool of previously approved drug products. Therefore, determining whether a drug packaging system is suitable for its intended use is of the utmost importance.

Since Jordi Labs performs frequent regulatory analyses, we have a good understanding of regulatory expectations. Thus, not only can we perform your desired testing, but we can also prescribe testing based on the current regulatory climate.

The wide variety of drug products available today correlate to a variance in packaging types. Drug packaging can be in the form of plastic blister packs, glass bottles, syringes for injection, and inhalers to name a few. For each type of packaging, the primary function of the packaging system remains the same. The packaging system for a given drug product should not interact with the product in a way that impacts the products safety, identity, strength, quality and purity.[7]

How is Pharmaceutical Package Testing Conducted?

An overview of packaging and storage requirements for pharmaceutical packaging can be found in USP <659> *Packaging and Storage Requirements*. The testing that is required is determined by the materials that are used to construct the final packaging system. Three types of packaging systems that are addressed in USP <659> and beyond are plastic, glass, and elastomeric materials used for container closure. Any plastic material used to construct a packaging system should be characterized according the requirements that are stipulated in USP <661.1> *Plastic Materials of Construction*. Thereafter, all packaging systems must adhere to the applicable requirements in USP <660> *Containers – Glass,* USP <661> *Plastic Packaging Materials and Their Materials of Construction*, USP <661.2> *Plastic Packaging Systems for Pharmaceutical Use,* and USP <670> *Auxiliary Packaging Components.* Packaging systems with elastomeric closures must also adhere to USP <381> *Elastomeric Closures for Injections.* As part of the testing for plastic packaging systems in USP <661.1>, extractables and leachables assessments are performed using USP <1663> and USP <1664> as guidelines for establishing the correct analysis conditions. Following the aforementioned testing, stability studies, and container closure integrity can be performed to ensure a products safety throughout shipment, as well as determine the shelf life of the product.

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Characterization of Plastic Materials of Construction

When considering packaging systems that contain plastic components, USP <661.1> is the natural starting point of analysis. As stated in USP <661>, plastic materials of construction must be "well characterized" in order to be suitable for use in packaging systems. A well characterized material meets all of the testing requirements in USP <661.1>. The aim of this guidance is to demonstrate that the plastic materials of construction do not interact with the drug packaging product in a way that may impact the safety and efficacy of the product. USP <661.1> specifies testing for cyclic olefins, polyethylene, polypropylene, polyethylene terephthalate, polyethylene terephthalate G, and plasticized polyvinyl chloride. For any plastics that are not specified in the guidance, their suitability for use in packaging systems must be established by using methods similar to those outlined in this chapter. A plastic material of construction is deemed to be well characterized if the following have been established:

- Identity
- Biocompatibility
- Physicochemical Properties
- Additives Characterization
- Extractable Metals

Additionally, the physicochemical, additives, and extractable metals tests use extractions of five base solutions. Materials are extracted with either water, toluene, acid, alkali, or alcohol depending on the chemistry of the material and the intended testing. For instance, extractable metals for polyethylene are determined using acid extraction.

Identity

Identity of plastic materials is confirmed through the use of Fourier Transform Infrared Spectrophotometry (FTIR) and Differential Scanning Calorimetry (DSC). Instrumental conditions, as well as acceptance criteria for each specified plastic can be found in USP <661.1>.

Biocompatibility

All plastic materials of construction must be characterized according to USP <87> *Biological Reactivity Tests, In Vitro.* For oral and topical dosage forms, meeting the requirements of USP <87> is considered satisfactory. All other dosage forms must also be characterized according to USP <88> *Biological reactivity Tests, In Vivo.*

Physicochemical Properties

To further investigate the attributes of the plastic materials of construction, the physicochemical properties of the extracts for each material must be determined. This includes Total Organic Carbon (TOC) testing, acidity and alkalinity tests (pH determination), and Ultraviolet-Visible Spectroscopy (UV-Vis) for absorbance. Conditions and acceptance criteria for each test our outlined in USP <661.1>.

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Additives Characterization

Additives in the materials of construction are targeted based upon the stated composition of the plastic material. Methodology has been provided for additives that are common in each of the specified plastics (i.e. cyclic olefins) in USP <661.1>. Materials of construction are chemically compared to the profile of USP plastic additive standards in order to investigate their additive levels. While specifics are included in the chapter, in general a suitable technique and peak area percentage are used to compare the concentration of additive in the raw materials to a standard of known concentration. Additives characterization at this stage of testing can provide an idea as to how the extractables and leachables profile of the packaging system may look in subsequent testing.

Extractable Metals

The materials of construction should be extracted and then analyzed for the specified elements. Additionally, if there are any other metals relevant to the materials of construction, then they should be tested as well. The appropriate instrumentation and methods for this testing can be found in USP <233>, and includes Inductively Coupled Plasma – Mass Spectrometry (ICP-MS).

Characterization of Plastic Packaging Systems

The next phase that must be considered when evaluating plastic drug packaging systems, is the system itself. A plastic packaging system refers to all of the packaging components that are used to contain the drug product, which includes closures. Furthermore, both primary and secondary packaging components are considered to be part of the packaging system as a whole. USP <661.2> provides testing to ensure that the drug product and the packaging do not interact in a way that compromises the drug's effectiveness and safety. Additionally, although the materials of construction will have already been characterized per USP <661.1>, the properties of the materials may change after they are incorporated into the final packaging systems. Procedures such as molding, or interactions of two different materials of construction should be considered in this stage of the analysis process. Similar to the materials of construction, the packaging system is considered chemically suited (in terms of safety) for its intended use if the following conditions are met:

- The packaging system is constructed from well-characterized materials according to USP <661.1>.
- The packaging system has established general physicochemical properties.
- The packaging system's biocompatibility has been established
- The packaging system has been established to be safe by the appropriate chemical testing, such as an extractables and leachables assessment followed by a toxicological risk assessment of the data.

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Physicochemical Properties

The procedures for the required physicochemical testing of the packaging system are very similar to those of the materials of construction. Testing includes extraction of the packaging system followed by Total Organic Carbon (TOC) testing, acidity and alkalinity tests (pH determination), and Ultraviolet-Visible Spectroscopy (UV-Vis) for absorbance. Conditions and acceptance criteria for each test our outlined in USP <661.2>. As opposed to the physicochemical testing of materials of construction, USP <661.2> include added testing. Polyethylene terephthalate and polyethylene terephthalate G packaging systems are analyzed to investigate the total terephthaloyl moieties by UV-Vis analysis. A similar analysis is also performed for the ethylene glycol in polyethylene terephthalate and polyethylene terephthalate G packaging systems.

Biocompatibility

The process required to determine biocompatibility of the pharmaceutical packaging is the same as that for the materials of construction, with the substitution of using the packaging system as the test subject.

Extractables, Leachables, and Toxicological Assessment

In order to establish the safety of a pharmaceutical packaging system for its intended use, chemical testing must be performed. Extractables and leachables studies are utilized to profile compounds that are present in the drug product and in the packaging, as well as how they may potentially interact with one another. Guidelines for extractables and leachables testing can be found in USP <1663> and USP <1664>. In the case of drug packaging systems, extractables are chemicals that can be released from a packaging system under laboratory conditions. Leachables in drug packaging systems are chemicals which migrate from a drug packaging system into the drug product under normal conditions of storage and use (or during accelerated drug product stability studies). Extractables data can be used to not only characterize packaging systems, but also to establish a worst-case probable leachables profile and facilitate subsequent leachables analysis. A toxicological risk assessment should be performed on the subsequent extractables and leachables profile of the drug packaging system, in order to demonstrate the chemical safety of the product.

Choosing an Extracting Medium and Conditions

An extraction medium for an extractables study should have a similar or greater propensity to extract compounds as the drug formulation. Therefore, solvents for extractables should have similar chemical properties when compared to the drug product. Additionally, it is recommended that multiple solvents be chosen for drug products with a high risk of dosage form interaction with the packaging (i.e. inhalable aerosols or solutions, etc.). The extraction medium for a leachables study is the drug product itself, and the conditions should be those of the simulated use of the product (shelf life), or equivalent accelerated aging studies. The extraction ratio for extractables should be based on the known chemical compounds expected to be in the leachables profile, the safety-based thresholds of those compounds, as well as the sensitivity of the instrumentation utilized. Extractions should be carried out for a sufficient amount of

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time to reach equilibrium. Alternatively, a leachables assessment may be replaced by a simulation study when such a study can be justified in place of a leachables analysis. A simulation study can simulate a worst-case leachables profile for the drug packaging system, and produces extracts in less time than a drug product leachables study.

Extractables and Leachables Chemical Characterization

Extractables and Leachables should be identified and quantified using a combination of techniques which can detect compounds of a wide variety of chemistries. For instance, Gas Chromatography Mass Spectrometry (GCMS) can be used to identify and quantify semi-volatile and volatile organic compounds. The same can be said for Gas Chromatography Flame Ionization Detection (GC FID). For identification of polar, ionizable organic compounds, Liquid Chromatography Mass Spectrometry (LCMS) can be utilized. Techniques such as ICP-MS can analyze the inorganic profile of extracts. Additionally, some drug products such as inhalers contain very volatile compounds, therefore in such circumstances it is recommended that an analytical technique such as Headspace Gas Chromatography Mass Spectrometry (HGCMS) be utilized. Quantitation of all analytes observed above the safety-based threshold should be performed using internal or surrogate standards.

Compounds observed in the extractables profile can be correlated to an expected leachables profile, and with sufficient justification, leachables can be targeted by the appropriate analytical screening technique. To wrap up the extractables and leachables analysis, a toxicological risk assessment is then performed in order to verify the chemical safety of the product.

Glass Containers for Pharmaceutical Use

When the packaging system is composed of glass, testing per USP <660> is performed. USP <660> outlines three initial tests that are used to characterize the glass. These are the glass grains test, the surface etching test, and the surface glass test. The tests characterize the glass in terms of thermal resistance and hydrolytic resistance in order to determine their suitability for use with certain drug products. Depending on the results of the tests, glass materials for packaging systems are characterized into one of three categories that dictate the drug product that a specific glass is suitable for.

Elastomeric Closures for Injection

Elastomeric closures for injection are tested if they are intended for long term storage of drug products, as outlined in USP <659>. Testing of elastomeric closures is based upon the type of closure coating that is potentially applied to the product. In USP <381>, testing for each type of elastomeric closure can be broken down into three main categories:

- Biocompatibility
- Physicochemical Testing
- Functionality Testing

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Biocompatibility

Biocompatibility is performed on the elastomeric closures per USP <87> and USP <88>, the same as for previous packaging components.

Physicochemical Testing

Elastomeric closures for injection are subject to multiple physicochemical tests. The tests specified in USP <381> are acidity and alkalinity (pH), heavy metals analysis, color and turbidity determination, extractable zinc determination, absorbance with UV-Vis, a test for reducing substances, and volatile sulfides determination.

Functionality Testing

An important aspect of analyzing elastomeric closures for their suitability for use in drug packaging is their physical properties. These tests include fragmentation, self-sealing capacity, and penetrability.

Conclusion

Due to the varied nature of pharmaceutical prescription and over the counter drugs, drug packaging has many forms. Thus, testing a packaging system for its suitability of intended use is a process that requires a strategy that is appropriately catered to the drug product. While testing materials of construction or various components of the packaging system may be straightforward, analyzing the entire drug packaging system can be challenging. Extractables and leachables studies are dependent on the chemistry of the drug product, and new pharmaceuticals are being developed every year. At Jordi Labs, we can work with you to verify the chemical safety of your drug packaging system. Let us help you get your product approved and add to the field of medicine in a positive way!

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