Leachables & Extractables

BioScreen Bulletin: # 2011-03

Introduction

Drug packaging is meant to store the drug product at appropriate condition and allow delivery of that drug to the consumer. The package is meant to protect the drug from the environmental (sun light, moisture, etc.), microbial contamination and act as a tamper proof container. Drug packaging should not allow harmful chemicals into the drug that have negative effects such as toxic, genotoxic, carcinogenic or effect the efficacy of the drug. Chemicals or components that may leach into the drug from the drug packaging include plasticizers, heavy metals, phthalates, nitrosamines, etc.

Definition

Extractable: Compounds that can migrate (removed) from the sample (container) into the drug product under aggressive laboratory conditions. These may be elevated temperature, prolonged contact time, or aggressive solvent systems.

Leachable: Compounds that migrate from the sample (container, label, outer packaging or outer label) into the drug product under normal conditions of storage.

Which Regulations Govern This Subject?

The following regulations are applicable for protecting drugs and biologics from adulteration.

- Food, Drug and Cosmetic Act section 501(a)(3): A drug is deemed to be adulterated if its container is composed in whole or part of any poisonous or deleterious substance which may render the contents injurious to health.
- Good Manufacturing Practices 21CFR211.94(a): Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.
- Biologics 21 CFR600.11(h) (h) Containers and closures. All final containers and closures shall be made of material that will not hasten the deterioration of the product or otherwise render it less suitable for the intended use. All final containers and closures shall be clean and free of surface solids, leachable contaminants and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. After filling, sealing shall be performed in a manner that will maintain the integrity of the product during the dating period. In addition, final containers and closures for products intended for use by injection shall be sterile and free from pyrogens. Except as otherwise provided in the regulations of this subchapter, final containers for products intended for use by injection shall be colorless and sufficiently transparent to permit visual examination of the contents under normal light.
- Food and Drug Administration: Guidance for Industry Container Closure for Systems for Packaging Human Drugs and Biologics, May 1999

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Which Procedures are Available for Testing of Containers and Closures?

The United States Pharmacopeia (USP) and European Pharmacopoeia (EP) contain monographs which specified the tests to be performed on various container/closure types.

- USP <661> Containers –Plastics
  - Polyethylene Containers
  - High-Density Polyethylene
  - Low-Density Polyethylene
  - Polyprolylene Containers
  - All Other Plastics
- USP <671> Containers-Performance Testing
  - Multiple-Unit Containers for Capsules and Tablets
  - Single Unit Containers for Capsules and Tablets
  - Multiple-Unit Containers and Unit-Dose Containers for Liquids
- USP <381> Elastomeric Closures for Injections
- USP <87> Biological Reactivity Tests, In Vitro (cytotoxicity tests)
- EP 3.2.2 Plastic Containers and Closures for Pharmaceutical Use
- Dye Ingression Studies
- Microbial Ingression Studies
- Custom Studies for leachable and extractables using LC-MS-MS, GC-MS-MS and ICP.

What does BioScreen Offer?

BioScreen can perform USP testing for <661> Containers-Plastics which may include the following tests:

- Sample Extraction in Water, Alcohol and Hexane
- Heavy Metals USP <231>
- Nonvolatile residues extracted in water
- Nonvolatile residue extracted in alcohol
- Nonvolatile residue extracted in hexane
- Buffering capacity
- Residue on ignition
- Colorant extraction
- Total terephthaloyl moieties extracted in alcohol
- Total terephthaloyl moieties extracted in heptane
- Ethylene glycol extracted in water
- Multiple Internal Reflectance - BioScreen has a Horizontal Attenuated Total Reflectance (HATR)-FTIR with a KRS-5 internal reflection plate to compare resins to known standards for polymer ID tests.
- Thermal analysis (not offered by BioScreen)

BioScreen can perform USP testing for <671> Containers – Performance Testing, for Moisture Permeation. BioScreen will require the client to submit containers that are filled with DI water or glass beads with closures attached prior to testing.

BioScreen offers the <381> elastomeric Closures for Injections monograph which include the following tests.

- Biological Reactivity Tests, In Vitro <87>
- Preparation of Solution S

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- Appearance of Solution (Turbidity/Opalescence and Color)
- Determination of color
- Acidity or Alkalinity
- Absorbance
- Reducing Substances
- Heavy Metals <231>
- Extractable Zinc
- Ammonium
- Volatile Sulfides
- Self-Sealing Capacity

BioScreen can test per EP 3.2.2, Plastic Containers and Closures for Pharmaceutical Use.

In addition to performing USP <87>, <381>, <661>, <671> and EP 3.2.2, BioScreen offers analytical instrumental methods for detecting trace level compounds that may not be observed with the above gravimetric and colorimetric tests.

Organic Analysis by GC, GC/MS, HPLC, LC/MS/MS

For resins, such as low density polyethylene (LDPE), BioScreen can perform extractable or leachable tests using polar or non-polar solvent mixtures, drug vehicle or other solvents. The extracted solutions are then analyzed using GC-FID for evaluation of residual solvents and volatile components, and by HPLC-UV for evaluation of plastic additives, anti-oxidants, photo-initiators (such as benzophenone), and other unknown analytes. Known standards of example compounds are injected for reference. Trace level compounds can be detected by GC-MS or LC-MS-MS analysis.

For identification of impurities found up in the chromatograms, BioScreen can use GC-MS and LC-MS to compare the fragmentation patterns of the impurities against a library for tentative identification. For positive identification of key impurities, standards of the tentatively identified compounds can be ordered and be used to spike the samples. Quantitation of the impurities can then be done after method development and method validation per ICH guidelines.

Elemental analysis by ICP, GFAA:

BioScreen also has ICP-OES and AA for quantitation of low levels of transition metals or metalloids in the extract solutions, particularly if the product specification requirements fall below the limits tested in USP <231>.

Container Closure Integrity

BioScreen can also test Container Closure Integrity by dye immersion using visual or spectroscopic confirmation.

BioScreen can also test for microbial ingress.

What Information is Needed to Provide a Quotation for Your Project?

Do you wish to follow USP or EP guidelines or both?
What type of container/closure material is used?
What is the drug product?
What type of solvents should be used?
What types of impurities are of interest?

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