NAMSA

Extractables / Leachables

Both the FDA and ISO mandate that:

- Containers and closures for human use be analyzed for extractable compounds.
- There is no toxic interaction between the drug product and the container.

*Devices that will be used with a specific drug or in contact with other solutions may also be tested using the same procedure as a container.

Extractables

- Chemical compounds that migrate from any product-contact material (including elastomeric, plastic, glass, stainless steel or coating components) when exposed to a solvent
- Determined by exposing components or systems to conditions that are more severe than normally found in a real-use situation, typically using a variety of solvents at high temperatures
- Goal of an extractable study is to identify as many compounds as possible that have the potential to become leachables

Extractables Profile Process - Understanding your device

- What processes it will undergo?
- Which components will have direct contact?
- Which components will have indirect contact?
- Has the supplier provided compendial testing?
- What sterilization processes will be used?

A full extractables profile involves:

- Extracting the materials in multiple solvents (as deemed appropriate by the intended use)
- Length of contact
- Route of administration of the device

*In most cases, 2-3 solvents with polar, non-polar and mixed polarity will be sufficient to determine an extractables profile. In the case of some higher risk devices, such a silicone breast implants, a 4th solvent may be recommended.

Following extraction, a variety of analytical techniques are used to identify those additives that have migrated from the device. Some of these techniques include:

- Fourier Transform Infrared Spectroscopy (FTIR)
- Inductively Coupled Plasma (ICP) Spectroscopy
- Gas Chromatography/Mass Spectroscopy (GC/MS)
- High Performance Liquid Chromatography/ Mass Spectroscopy (HPLC/MS)
- High Performance Liquid Chromatography Ion Chromatography (HPLC/IC)
- High Performance Liquid Chromatography Gel permeation Chromatography (HPLC/GPC)

Leachables

- Chemical compounds, typically a subset of extractables, that migrate into a drug formulation, solution or bodily fluids from any product contact material (including elastomeric, plastic, glass, stainless steel or coating components) as a result of direct contact under normal process conditions or accelerated storage conditions
- Likely to be found in the final drug product or to be released into the body

Once the extractables are identified, a risk assessment should be performed to determine which identified compounds pose a potential risk and should be taken forward to a leachable study. Once these compounds are identified, a method development and validation should be performed to ICH guidelines. This ensures interferences from the drug matrix solution or other medium that will be exposed to the device/container can be dealt with and appropriate detection and quantitation limits can be established.

Leachables Study

Following the validation, the leachables study is carried out. This is often in conjunction with shelf life studies and at each pull point (varying by shelf life and storage conditions.) The number of samples may be based on the acceptable quality limit (AQL) in accordance with ISO 2859-1 or ISO 1886 or statistical process control (SPC). Generally, the regulatory agencies will want a minimum of 3 lots tested. The test article should be stored both upright and inverted during aging (where appropriate.) The solution is evaluated to determine if the extractables did in fact become leachables. It may then be necessary to perform a risk assessment as a final step to make sure all identified leachables are within safety margins.

References:

Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, FDA May 1999

ISO 10993 Biological Evaluation of Medical Devices, Part 18: Chemical characterization of materials.

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