

Extractables and leachables: Regulatory requirements for vaccine and biologic products

Key Words

Extractables, leachables, polycyclic aromatic hydrocarbons, plastics, container-closure systems, pharmaceutical manufacturing.

Extractables are chemical species that migrate from packaging or container materials into the contents when exposed to certain solvents under exaggerated temperature and time conditions. Leachables are chemical species that make their way into the product under normal application conditions. Extractables and leachables are important factors to consider as they have the potential to interact with a drug at multiple stages during development and production, which could impact efficacy, safety and quality. There is generally an overlap such that the leachables involved may be classified as a subset of the extractables. However, if the leachable interacts with the drug product or packaging materials, new components can be present (Figure 1).

Based on the problems these factors can cause, their presence must be evaluated in those components which come into contact with the product during formulation, intermediate storage and final packaging for any sign of extractables or leachables¹. This not only enables a greater understanding of how to manage extractables and leachables during development, but also assists with ensuring they fall within regulatory requirements for container closure systems (CCS) and packaging materials.

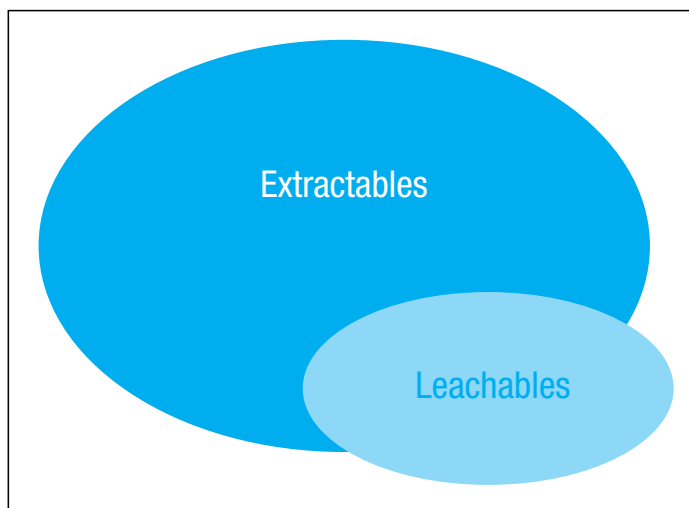


Figure 1. The U.S. Food and Drug Administration (FDA) defines extractables as compounds that can be extracted from the CCS when in the presence of a solvent, and leachables as compounds that leach into the drug product formulation from the container closure as a result of direct contact with the formulation.

Manufacturers of drugs and biologic products are responsible for conducting any and all assessments for the detection of extractables and leachables in a finished product. For example, the European Medicines Agency (EMA) guidelines require packing material data from extraction studies, interaction studies (which include sorption and migration studies) as well as toxicological information and documentation². However, often time and/or internal resources to conduct extensive chemical testing may be limited.

Some vendors of manufacturing and packaging components, including Thermo Fisher Scientific, provide customers with extractables data. This information is used for preliminary screening and will require further studies to assess the risk to a particular product and/or process.

Thermo Fisher Scientific offers extractables and leachables studies, including off-the-shelf forced extraction studies (extractables), custom product/container studies (leachables), specific compendia testing (for European, Japanese, Chinese and US Pharmacopeia) as well as other custom testing. Worth noting is that non-cGMP studies, such as our forced extraction studies, should not be submitted to regulatory bodies, nor interpreted to indicate the absolute levels of extractables. Non-cGMP studies and data provided are to be used as guidelines only. Custom studies and testing can be requested to follow cGMP guidelines. Such services help customers to save time and resources.

Lessons from the past

Prior to the implementation of more stringent regulations regarding extractables and leachables in pharmaceutical packaging or containers, there were several incidents in which potentially harmful leachables were identified in certain products.

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are a large group of organic compounds formed during the incomplete combustion of organic materials. During the 1990s, the U.S. Food and Drug Administration (FDA) became aware of reports concerning PAH contamination within chlorofluorocarbon (CFC)-filled metered-dose inhalers (MDIs), inadvertently introduced by some of the elastomers used as seals in MDI drug products³. Although the PAHs were only present in trace amounts, these findings promoted the first concerted efforts to look for additional leachables in MDIs.

Worth noting is that non-cGMP studies, such as our forced extraction studies, and therefore should not be submitted to regulatory bodies, nor interpreted to indicate the absolute levels of extractables. Non-cGMP studies and data provided are to be used as guidelines only. Custom studies and testing can be requested to follow cGMP guidelines.

Vanillin

Another case study example of interest is Vanillin, a phenolic aldehyde used in the food industry. Vanillin has been detected in inhalation solutions contained within primary low-density polyethylene (LDPE) containers and was found to be capable of migrating through the LDPE wall into the product from the outer cardboard packaging⁴. An aluminum foil overwrap was later introduced to prevent this. However, those inhalation solutions that had already been packaged without this new overwrap had to be tested for any extraneous contaminants, introducing significant time delays and increasing the costs of production. Worth noting is that non-cGMP studies, such as our forced extraction studies, and therefore should not be submitted to regulatory bodies, nor interpreted to indicate the absolute levels of extractables. Non-cGMP studies and data provided are to be used as guidelines only. Custom studies and testing can be requested to follow cGMP guidelines.

Diethylhexyl phthalate

Diethylhexyl phthalate (DEHP) is used around the world as a plasticizer in a range of polyvinyl chloride (PVC) products, including several medical devices such as intravenous tubing, bags and catheters. DEHP has been found in the total parenteral nutrition (TPN) fat emulsions used to help patients gain weight, as it can migrate from the PVC infusion lines into the emulsion and enter the body of the patient. This is especially worrying, as infants are known to be particularly sensitive to DEHP-triggered toxicity⁵. Based on these risks, in 2002 the FDA released a notification suggesting that alternatives to DEHP-containing devices must be used in “male neonates, pregnant women who are carrying male fetuses, and peripubertal males”⁶.

These are just a few examples of the potential risks that extractables and leachables present. Implementation of regulatory guidance has clearly been a necessity and detailed testing of all components involved in the construction of end products is now required. However, testing for extractables and leachables can still be a challenging process and requires a significant level of expertise.



A move towards single-use components

In light of the growing level of attention afforded to the packaging components involved throughout the pharmaceutical manufacturing process, the trend has been towards the implementation of disposable, single-use components. In the pharmaceutical industry, such single-use devices and components have contributed to reduced contamination rates, enhanced production efficiency and throughput, and a reduction in overall manufacturing operation and maintenance costs⁷.

Single-use devices can provide labor and material cost savings, as well as reduce the manufacturing footprint, in the case of storage containers. Manufacturers of single-use components and equipment may provide assistance with the qualification and validation of these products, e.g. cleanliness, durability and sterility, helping to reduce required time and financial constraints.



Since single-use devices are disposed of after use, the risk of batch cross-contamination is essentially eliminated. However, concerns regarding contaminants leaching out of single-use components may be holding back widespread adoption. Companies are thus working hard to provide customers with relevant data on these single-use products to guide product selection.

We offer ISO and GMP compliant manufacturing practices that help to ensure the integrity, compatibility, and stability of the critical products you choose to store. We also offer off-the-shelf extractables studies to proactively provide the information customers need to make informed decisions.

Detecting extractables and leachables – using the right tests

Extractable and leachable studies identify several key components:

- Semi-volatile organic compounds
- Non-volatile organic compounds
- Volatile organic compounds
- Metals.

Extractables studies are typically carried out under exaggerated conditions with more than one solvent in order to create a 'worst case scenario' using common laboratory solvents. This data is meant to provide information to help customers determine what further studies are needed to mitigate risks associated with the final product.

A typical extractions study may include:

1. Extraction
 - a. Using suitable solvents (e.g. water, ethanol and hexane) selected based on the material in question.
 - b. Extraction following exaggerated conditions such as boiling to reflux or soxhlet sonication.
2. Analytical techniques to detect the extractables and leachables, e.g. gas chromatography-mass spectrometry (GC/MS), liquid chromatography mass spectrometry (GC/MS), inductively coupled plasma-mass spectrometry (ICP/MS), headspace GC/MS.
3. Quantification of these compounds, in which a qualified toxicologist calculates the analytical evaluation threshold (AET), above which an extractable or leachable needs to be reported for toxicological assessment.

The results of toxicology and other tests or procedures can be compared against industry standards to assess the impact on patients. For example, the Extractables and Leachables Safety Information Exchange (ELSIE) was formed in 2007 and provides a database of safety information on various extractable and leachables, as well as standardized protocols for generating controlled extractables data⁸.

Incorporating leachables testing into your risk analysis procedure early can prevent delays in product launch. However, planning these studies requires some foreknowledge of the types of extractables typically encountered. To that end there are a number of Extractables studies already available from Thermo Fisher Scientific to help get you started:

- Thermo Scientific™ Nalgene™ PETG Bottles (container/closure system)
- Thermo Scientific™ Nalgene™ PC Biotainer™ Bottles (container/closure system)
- Thermo Scientific Nalgene PP Carboys (container/closure system)
- Thermo Scientific Nalgene PET Bottles (container/closure system)
- Thermo Scientific Nalgene PETG Biotainer Bottles (container/closure system)
- Thermo Scientific Nalgene Sterile HDPE Carboy (container/closure system)
- Thermo Scientific™ Nunc™ Cell Factory™ System
- Thermo Scientific™ Nunc™ EasyFill™ Cell Factory™ System.



A valuable partnership from your container supplier

The choice of a container and manufacturer can play a vital role in enabling commercialization of a finished product. A stable and reliable manufacturing partner can ensure the consistency and stability of extractable and leachable testing you perform. Key data from controlled testing and simulation studies should be readily available from your container supplier to help you assess what further studies you might need to perform. Ultimately, having the data readily available helps you to go to market faster.

Conclusions

Including extractables and leachables from packaging components in an overall assessment of product risk is important in ensuring patient safety. A partnership with a trusted supplier that also provides extractables and leachables testing alleviates some burden from the pharmaceutical manufacturer. This can speed up the commercialization of a product and reduce financial overheads, while enabling products to conform to all designated regulations.

Biographies/References

1. Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics. Food and Drug Administration (FDA). at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070553.pdf>
2. Guideline on plastic immediate packaging materials. European Medicines Agency (EMA). at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003448.pdf
3. Norwood, D. L. *et al.* Analysis of polycyclic aromatic hydrocarbons in metered dose inhaler drug formulations by isotope dilution gas chromatography/mass spectrometry. *J. Pharm. Biomed. Anal.* 13, 293–304 (1995).
4. Schroeder, A. Leachables and Extractables in OINDP : An FDA Perspective. (2005). at http://www.pqri.org/workshops/leach_ext/imagespdfs/presentations/AlanSchroederDay1.pdf
5. Bagel, S. *et al.* Influence of lipid type on bis (2-ethylhexyl)phthalate (DEHP) leaching from infusion line sets in parenteral nutrition. *JPEN. J. Parenter. Enteral Nutr.* 35, 770–5 (2011).
6. FDA Public Health Notification: PVC Devices Containing the Plasticizer DEHP. (2002). at <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062182.htm>
7. Trotter, M. Adoption of Single-use Disposable Technology in Biopharma Industries – Manufacturing, Economic and Regulatory Issues to Consider. (2012). at <http://www.americanpharmaceuticalreview.com/Featured-Articles/39300-Adoption-of-Single-use-Disposable-Technology-in-Biopharma-Industries-Manufacturing-Economic-and-Regulatory-Issues-to-Consider/>
8. The Extractables and Leachables Safety Information Exchange (ELSIE). at <http://www.elsiedata.org/>

© 2015 Thermo Fisher Scientific Inc. All rights reserved. All trademarks are the property of Thermo Fisher Scientific Inc. and its subsidiaries.

www.thermoscientific.com/intermediatestorage

ANZ: Australia: 1300 735 292, New Zealand: 0800 933 966

Asia: China Toll-free: 800-810-5118 or 400-650-5118; India: +91 22 6716 2200, India Toll-free: 1 800 22 8374; Japan: +81 3 5826 1616; Other Asian countries: 65 68729717

Europe: Austria: +43 1 801 40 0; Belgium: +32 53 73 42 41; Denmark: +45 4631 2000; France: +33 2 2803 2180; Germany: +49 6184 90 6940, Germany Toll-free: 08001-536 376; Italy: +39 02 02 95059 or 434-254-375; Netherlands: +31 76 571 4440; Nordic/Baltic/CIS countries: +358 10 329 2200; Russia: +7 (812) 703 42 15; Spain/Portugal: +34 93 223 09 18; Switzerland: +41 44 454 12 12; UK/Ireland: +44 870 609 9203

North America: USA/Canada +1 585 586 8800; USA Toll-free: 800 625 4327

South America: USA sales support: +1 585 586 8800

Countries not listed: +49 6184 90 6940 or +33 2 2803 2180

Thermo
SCIENTIFIC

A Thermo Fisher Scientific Brand