Extractables and Leachables Testing in the Pharmaceutical Industry

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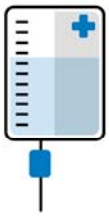
INTRODUCTION

Requirements from regulatory agencies have become increasingly rigorous, with regards to the detection, identification and quantification of extractable and leachable compounds in pharmaceuticals, drug delivery systems and biomedical devices. This increased scrutiny is the result of several well-documented incidents of contaminants leaching from containers and packaging, resulting in a potential or real risk to humans. As a result, regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA), have increased regulations on potential extractables and leachables in drug product container and closure systems.

During the 1990s, the FDA became aware that some of the elastomers used as seals in metered-dose inhalers (MDI's) used for inhalation delivery were leaching polycyclic aromatic hydrocarbons (PAHs) into the chlorofluorocarbon-based formulation[1]. These contaminants were present only in trace amounts, but this example initiated the first concerted efforts to discover additional leachable compounds in MDIs.



Diethylhexyl phthalate (DEHP) is a plasticizer widely used in the manufacture of polyvinylchloride (PVC) products. PVC products include tubing, bags and catheters used for intravenous drug delivery. It was discovered that DEHP could leach out of the IV infusion lines into Total Parenteral Nutrition (TPN) fat emulsions used to help patients gain weight[2]. The FDA issued a Public Health Notification in 2002, restricting the medical use of PVC products containing DEHP[3] after it was discovered that infants were sensitive to DEHP-triggered toxicity[4]. It has also been discovered that DEHP is an endocrine disruptor[5].

In 2010, McNeil Consumer Healthcare voluntarily recalled more than 500 lots of Tylenol, Motrin, Benadryl and Zyrtec. This was in response to consumer complaints to the FDA regarding a "musty" odor in drug products. The cause was determined to be migration of 2, 4, 6-tribromoanisole in wooden shipping pallets through external packaging and container closure system into the drug product. This recall cost the manufacturer an estimated $900 million in lost sales and an unknown amount in remediation efforts.

WHAT ARE EXTRACTABLES AND LEACHABLES?

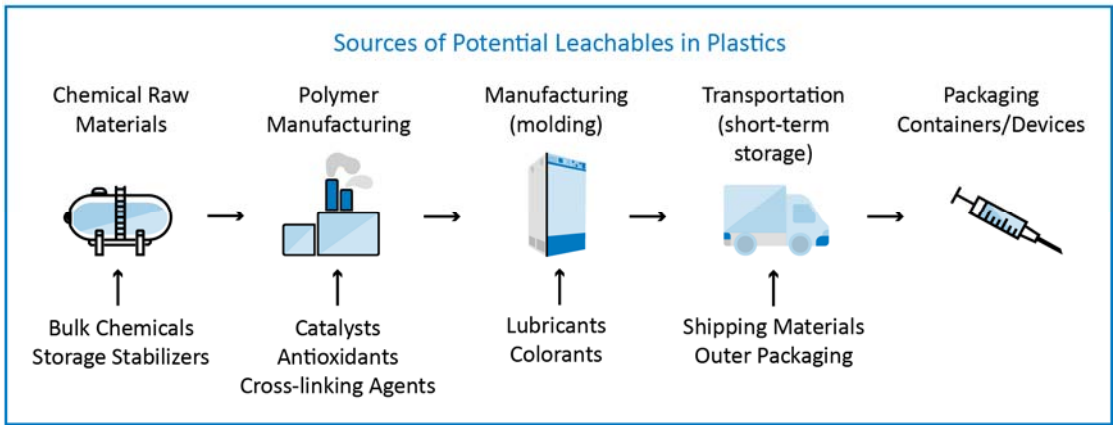
Leachables are organic or inorganic compounds that migrate into the drug product formulation from the container closure system as result of direct contact with the formulation. They are typically low-molecular weight volatile compounds that migrate through semi-permeable containers. Leachables testing is required for monitoring and controlling container closure-derived impurities in the drug product during stability and/or to qualify container closures for use. Potential sources of leachables include the container fabrication components, migrants from labeling or secondary packaging, and reaction products between the formulation and the container closure system. Leachables can present difficult analytical challenges, as they are frequently present at levels that are orders of magnitude lower than drug degradation products or related substances, well below the sensitivity of the Drug Product testing methods. Therefore, separate analytical methods are usually needed for leachable analysis on the drug product containers.

Extractables are compounds that can be extracted from a container closure system via laboratory manipulation, such as exposure to solvents or heat. Extractables are potential leachables. Extraction studies are performed for the qualification and quality control of container closure components. These studies are used to screen for the presence of toxic materials, such as DEHP or PAHs and the analytical methods are frequently used in leachables testing. The conditions of an extraction study are designed to mimic a “worst-case scenario” for the drug product. Care must be taken that extraction conditions are not overly aggressive and generate an unrealistic number of extractables that would not be leachables.

Migrants are compounds that may move from packaging components or materials into the drug product. They differ from leachables in that they accumulate in the drug product after crossing a physical barrier, such as the primary container/closure and/or secondary packaging.

In the late 1990s, regulatory agencies, particularly the FDA, began to raise concern about extractables and leachables in pharmaceutical container closure systems, providing the impetus for increased regulation in this area.

Plastics used for container closure systems are one of the primary sources of leachables. Organic or inorganic contaminants can be introduced at any point during the manufacturing process. Drug containers and modern drug delivery systems meant to protect a drug from environmental contamination are actually themselves a potential source of contamination.



REGULATORY REQUIREMENTS

The U. S. FDA Guidance document, U. S. FDA 21 CFR 211.94(a), states that: "Drug product containers and closures shall not be reactive, additive or adsorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements…Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing and processing to remove pyrogenic properties shall be written and followed for drug product containers an closures." A drug product is deemed to be adulterated if it contains "…a poisonous or deleterious substance which may render the contents injurious to health…" Unfortunately, many common inorganic and organic leachables used in pharmaceutical packaging are considered "poisonous or deleterious" at high enough concentrations, which has spurred increasing regulation of these substances.

Numerous regulatory bodies now address the appropriate evaluation of packaging components, some of which can be found in Table 1.

Regulatory Agency	Document
U.S. Food and Drug Administration	Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (1999)
International Conference on Harmonization	ICH Q6A: Test Procedures and Acceptance Criteria for New Drug Substances an d New Drug Products: Chemical Substances (1999)
	The Common Technical Document for the Registration of Pharmaceuticals for Human Use, Quality (2003)
European Medicines Agency	Guideline on Plastic Immediate Packaging Materials (2005)
Health Canada	Guidance for Industry: Pharmaceutical Quality of Inhalation and Nasal Products
United States Pharmacopeia (USP39-NF34)	<661.1> Plastic Materials of Construction
	<661.2> Plastic Packaging Systems for Pharmaceutical Use
	<1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
	<1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
	<1664.1> Orally Inhaled and Nasal Drug Products

Table 1 – Regulations surrounding extractables and leachables

The Product Quality Research Institute (PQRI), a working group recognized by the FDA, has also worked to develop guidelines for extractable/leachables analysis in inhalation products and submitted them to the FDA in 2006.[6]

Other industry groups have also established recommendations for dosage forms as the risk of dosage form interaction and patient safety relative to the route of administration varies by dosage form. An example of this would be USP <1664> which outlines safety and identification thresholds, leachable/extractable study design, method validation considerations and discusses a risk-based approach to leachable testing.

Examples of Packaging Concerns for Common Classes of Drug Products			
Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	HIGH	MEDIUM	LOW
Highest	Inhalation Aerosols and Sprays	Injects and Injectable Suspensions; Inhalation solutions	Sterile Powders and Powders for Injection; Inhalation Powders
High	Transdermal Ointments and Patches	Ophthalmic Solutions and suspensions; Nasal Aerosols and Sprays	–
Low	Topical Solutions and suspensions; Topical and Lingual Aerosols; Oral Solutions and suspensions	–	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders
(USP39 <1664>)			

Table 2 - Examples of Packaging Concerns for Common Classes of Drug Products

ANALYTICAL TECHNOLOGIES

A single analytical technique is insufficient for detection and quantification of all extractables. Multiple methods and state-of-the-art technology are required to obtain accurate and reliable results.

Analytical Technology	Potential Extractable/Leachable	Examples
GC-MS (Headspace)	Volatile organics	Adhesives Inks Processing solvents
GC-MS (Direct Inject)	Semi-volatile organics	Preservatives PAH's Plasticizers
HPLC-MS	Non-volatile organics	Large antioxidants Large oligomers
Ion HPLC	Ionic contaminants	Bromide Chloride Fluoride
ICP-MS	Toxic elements	Arsenic Chromium Lead

Table 3 – Analytical technologies for extractables and leachables analysis

It is ultimately the responsibility of the drug product manufacturer to ensure that extractables and leachables testing is performed appropriately and completely on the container closure, packaging/delivery systems and packaging components. The challenges in extractables and leachables testing should not be underestimated and should be addressed scientifically and methodically while taking all of these requirements into consideration. Every new delivery system, new raw materials supplier, new component source is a potential new source of leachables. If using a CDMO, it is important to minimize risk by partnering with a company that has experience and utilizes state-if-the-art technology.

WHY ALCAMI?

Alcami is an experienced partner for performing extractables and leachables studies. The Alcami laboratories have extensive experience supporting a wide range of dosage forms and offer a full range of key extractable and leachable studies, including:

- Extractable/Leachable method development and validation
- Controlled extraction studies under GMP and PQRI guidance
- Identification and quantification of major extractables and leachables using GC-MS, ICP-MS and HPLC-MS.
- Determination of the Analytical Evaluation Threshold (AET)
- Monitoring of leachables during drug product stability

ABOUT ALCAMI

Alcami is a world-class contract development and manufacturing organization (CDMO) headquartered in Wilmington, North Carolina. With over 1,000 employees operating at seven sites globally, Alcami provides customizable and innovative services to small and mid-size pharmaceutical and biotechnology companies by offering individualized and integrated services across multiple areas. We connect our clients with innovative solutions for API development and manufacturing, solid-state chemistry, formulation development, analytical development and testing services, clinical and commercial finished dosage form manufacturing (oral solid dose and parenteral), packaging, and stability services.

[1] Norwood, D. L. et al. Analysis of polycyclic aromatic hydrocarbons in metered dose inhaler drug formulation by isotope dilution gas chromatography/mass spectrometry. J. Pharm. Biomed. Anal. 13, 293-304 (1995).

[2] Loff S, Kabs F, Witt K, Sartoris J, Mandl B, Niessen KH, Waag KL (2000) Polyvinylchloride infusion lines expose infants to large amounts of toxic plasticizers. *J Pediatr Surg*; 35:1775-81.

[3] FDA Public Health Notification: PVC Devices Containing the Plasticizer DEHP. (2002) at [INSERT LINK].

[4] 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, 770-775 (2011).

[5] Moore RW, TA Rudy, TM Lin, K Ko, RE Peterson. 2001. Abnormalities of sexual development in male rats with in utero and lactational exposure to the antiandrogenic plasticizer di92-ethylhexyl) phthalate. Environmental Health Perspectives, 109: 229-237.

[6] Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products (2006) http://pqri.org/wp-content/uploads/2015/08/pdf/LE_Recommendations_to_FDA_09-29-06.pdf