EXTRACTABLES AND LEACHABLES TIMELINE

American Pharmaceutical Review™

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USP

1965:

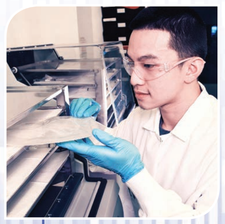
USP publishes a new section of the compendium: Biological Tests – Plastics Containers, the precursor to the current USP <661>.

Late 1990s:

Recall of Eprex due to interaction between polysorbate 80 in formulation and uncoated rubber stopper. Polysorbate 80 leached a compound from an uncoated rubber stopper that bound to protein causing an increase in cases of pure red cell aplasia.

Late 1990s:

First single-use bioreactor (WAVE) is used to manufacture a biopharmaceutical. The advent of single-use systems in biopharmaceutical production introduces a new area of concern in terms of leachables.



1999:

FDA's CDER and CBER publish Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics.

1999:

Code of Federal Regulations (CFR) Title 21, Part 211.65 is published stating that equipment used in the manotacture of drugs "shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product."

2001:

Product Quality Research Institute (PQRI) workgroup forms with the goal of introducing guidance for the industry on assessing Extractables and Leachables from Orally Inhaled and Nasal Drug Products.

2004:

Eurofins Lancaster Laboratories performs its first extractables study.

2005:

International Organization for Standardization (ISO) publishes ISO 10993-18 Biological Evaluation of Medical Devices – Part 18: Chemical Characterization of Materials. Part 18 details how to test the extracts, generated per ISO10993-12, for extractable compounds.

2005:

EMEA's CHMP and CVMP publish Guideline on Plastic Immediate Packaging Materials.

2006:

PQRI publishes Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products.

2006:

Eurofins Lancaster Laboratories begins compiling its proprietary database of extractable compounds, the Eurofins Extractables Index.

2007-2008:

Bio-Process Systems Alliance (BPSA) publishes its two-part Recommendation for Extractables and Leachables Testing.

2009:

Recall of Tylenol Arthritis Pain Caplets due to odor. Source of odor is identified as 2,4,6-tribromoanisole, which is a breakdown product of a chemical used to treat wooden pallets. The compound migrated through the secondary and primary packaging and into the product.

BPSA

2010:

BPSA publishes Recommendations for Testing and Evaluation of Extractables from Single-Use Process Equipment.

2011:

Eurofins Lancaster Laboratories purchases its first accurate mass time-of-flight (TOF) LC/MS for use in extractables studies.

BPOG

2014:

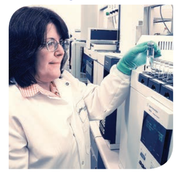
The BioPhorum Operations Group (BPOG) publishes the Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing in a push to shift the burden of extractables testing from end users to single-use system suppliers.

2015:

Eurofins Lancaster Laboratories purchases its first accurate mass quadrupole time-of-flight (QTOF) LC/MS, to better support structural elucidation of extractable compounds.

2015:

USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems and USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems become effective. These USP chapters are the first to specifically address extractables and leachables.



2016:

A major revision to USP <661> Plastics, with subsection <661.2> Plastic Packaging Systems for Pharmaceutical Use, becomes effective. USP <661.2> is the first non-guidance chapter to address extractables and leachables testing by calling for a chemical safety assessment for plastic packaging systems.

2017:

BPOG publishes the Best Practices Guide for Evaluating Leachables Risk from Polymeric Single-Use Systems Used in Biopharmaceutical Manufacturing.

USP

2017:

USP revises <661.1> and <661.2> to make them applicable to all marketed products (i.e., removes the "grandfathering clause") but delays implementation until 2020, allowing industry time to prepare for the change by reverting back to the previous version of <661>.

2017:

USP publishes draft chapter <665> Polymeric Components and Systems Used in the Manufacturing of Pharmaceutical and Biopharmaceutical Drug Products.

2017:

Eurofins Lancaster Laboratories currently has a team of >50 scientists dedicated to performing extractables and leachables studies on container closure systems, single-use systems, and devices. The Eurofins Extractables Index now contains >1,500 compounds.