Analysis of Extractables & Leachables in Pharmaceutical Products

Regulatory & Analytical Aspects

Dr. Andreas Tei
Global Pharma Segment Manager
Agilent Technologies
Outline

Section #1

• Introduction
• Defining extractables and leachables
• Guidelines
• Effects on biologic drug products
• The four essential steps of a study

Section #2

• Application Example: analysis of elemental E&Ls by ICP-MS
• Application Example: analysis of volatile E&Ls by GC-MS
• Application Example: analysis of non volatile E&Ls by LC-MS
• Appendix / References
Drug containers and modern drug delivery systems meant to protect a drug from environmental contamination but they are actually themselves a source of contamination.
Plastic Materials: Source of Contamination

Sources of extractables are plastic and elastomeric components (monomers, polymeric initiators, plasticizers, etc.) ink and adhesives (label) and degradation products (processing, storage, sterilization).

Cindy Zweiben, Pfizer, Inc., Characterization of Extractables and Leachable in Parenteral Drug Products
Compounds Identified as Extractables/Leachables

- Vulcanizing Agents
- Azo Dyes
- Antioxidants
- Phthalates
- Silicone Oils
- Monomers, Dimers, Oligomers
- Nitrosamines
- Lubricants, Slip Agents, Fatty Acids and Esters
- PAHs

Wide variety of Chemical Classes, Polarity, Molecular Weights, Properties

Toxic Elements (Hg, Cd, Pb, As, Cr, W, Tl, Os, Ba)
Various Analytical Technologies Required

Agilent delivers the most comprehensive analytical solutions portfolio

Objective: To detect a wide class of known and unknown organic/inorganic compounds that maybe present in container closure systems at levels links to risk assessment threshold levels
Defining Extractables, Leachables, Migrants

**Extractable**
Chemical compounds that can be extracted out of packaging component
- Analyze packaging component at
  - **High-temperatures**: to obtain the worst case leachable profile
  - **Solvent extraction**: polar and non-polar solvent to mimic similar properties as drug product

**Leachable**
- Chemical compounds from packaging component that leach into the drug product
- Analyze drug product at
  - Normal conditions
  - Simulate extended storage conditions

**Migrants**
- Crossed the primary packaging material barrier from secondary and tertiary packaging, accumulating in the drug product

Leachables are often a subset of extractables

New Leachables may be identified which have been not observed as extractables
FDA Regulation For Container Closure Systems (CCS)

U.S. FDA 21 CFR 211.94(a) statement (April 2015)

“(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.

…(d) 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 and closures.”

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.94
Why Worry about Extractables/Leachables?

2014: FDA Drug Recalls Surges over 836 in 2014!

2014: FDA data shows the last two years have seen almost as many recalls (2,061) as the previous nine years combined (2,217)—and that's only counting the first seven months of 2014. Ref: raps.org August 2014

August 2015: FDA warns against use of Becton-Dickinson (BD) 3 ml and 5 ml Syringes: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm458955.htm

<p>| Sodium Valproate Zentiva 500mg Gastro-resistant Tablets, PL 17780/0454, Zentiva Livery |
|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Batch Number</th>
<th>Expiry date</th>
<th>Pack Size</th>
<th>First Distributed</th>
</tr>
</thead>
<tbody>
<tr>
<td>J601</td>
<td>Aug 2016</td>
<td>1 x 100</td>
<td>01 Oct 2014</td>
</tr>
</tbody>
</table>

We have been made aware of an unusual odour associated with the above batches of Epilim / Sodium Valproate Gastro-resistant tablets. The odour has variously been described as ‘fishy’, ‘sweaty armpits’ and ‘cannabis’. An investigation by Sanofi has identified the root cause as the aluminium foil used in the packaging of affected batches. No impact on the quality or efficacy of the tablets has been detected. Sanofi has now ceased using this foil supplier.

https://assets.digital.cabinet-office.gov.uk/media/55191d6fe5274a142e000069/EL__15_A_02.pdf
USP Chapters dealing with E&L

- USP <661.1> Materials
  - USP <661.2> Packaging
  - USP <1663> Extractables
  - USP <1664> Leachables
  - USP <1665> Toxicological Assessment
- USP <661.4> Devices
- USP <661.3> Manufacturing Systems

Ref: Denise R. Jenke, Daniel L. Norwood, and Desmond G G Hunt
Guidelines Delivered By Pharma Industry Expert Working Groups

PQRI (Product Quality Research Institute) is a working group established to develop regulatory guidance for Extractable/Leachable analysis, which is also recognized by the FDA.
PQRI guidance for OINDP
(Orally inhaled and nasal drug products)

PQRI issued guidance for OINDP:
“Safety thresholds and best practices for extractables and leachables in orally inhaled and nasal drug products (OINDP) also Applicable to parenteral and injectable products (PODP)

PQRI established safety thresholds for leachables:
• Safety Concern Threshold (SCT) ≤ 0.15 µg/day patient exposure which species represent no risk
• Qualification Threshold (QT) ≤ 5 µg/day patient exposure which a leachable is not considered for safety qualification. Lower threshold applies to PAH’s, nitrosamines, and 2-mercaptobenzothiazole
• Estimated Analytical Evaluation Threshold (AET) (µg/g) = (SCT x total labeled doses) / (Doses per day x mass of component)

“Best practices” include controlled extraction studies and leachables studies.
Inorganic Impurities

New USP general chapters <232> and <233> for elemental impurities

- Reagents, Ligands, Catalysts
- Manufacturing Aids
- Inks and Dyes

**USP<232>** defines the analyte limits, while **USP<233>** defines sample preparation options including closed vessel microwave digestion, and recommends the use of modern instrumentation, such as multi-element ICP-MS and ICP-OES techniques. Analytical equipment qualification under USP<233> is based on performance testing, and includes requirements to demonstrate accuracy, repeatability, and the unequivocal identification of analytes.
Special Concerns About E&L Effects on Biologics

Even contaminations at trace levels with reactive E&L impurities can be deleterious for protein based drugs and will cause severe harm for the patient’s health (immunogenic reaction)

E&L compound as Impurity

Contact materials are: plastics/elastomers, glass and stainless steel surfaces
Sources of E&Ls as contaminants in biological drugs

- Plastics / Elastomers
  - Crosslinking agents, volatile organic E&Ls
- Glass surfaces
  - Al^{3+}, Fe^{3+/2+}, Ca^{2+}, Ba^{2+}, Mn^{2+}, Zn^{2+}
- Stainless steel surfaces
  - W^{6+/4+}, Fe^{3+/2+}, Cr^{3+/2+}, Ni^{2+}

- Sterile filtration processes are often a source of contamination
- Sterilization processes (steam autoclaving / gamma radiation) of drug containers will affect the concentration of leachables within the drug product
- Complexing agents (EDTA) facilitate migration of metal ions
E&Ls may affect protein drug products by:

- Aggregation
- Increase in particulates*
- Oxidation
- Unfolding
- Formation of clipped variants
- Formation of Protein Adducts
- Post translational events during fermentation (glycosylation)
- Altered protein translation

* See also new USP monograph <787> PARTICULATE MATTER IN THERAPEUTIC INJECTIONS

Ref: Ingrid Markovic, CBER Presentation USP/PQRI E/L Workshop April 2014
Critical Quality Attributes & Testing Methods for mAbs

Aggregate Analysis of Monoclonal Antibody

Column: Agilent AdvanceBio SEC 300Å, 2.7 μm, 7.8 x 300 mm (p/n PL1190-5301)
Flow rate: 1 mL/min
Mobile phase: 150 mM phosphate buffer, pH 7.0
Wavelength: 220 nm
Temperature: ambient
Injection volume: 5 μL
Sample: IgG

Disulfide Shuffling
SEC
Aggregation
HILIC
Disulfide Shuffling
RP
Pyro-Glutamate
IEC
IEC
IEC
IEC
Deamidation /Oxidation
Fragmentation (Hinge)
Truncation (Lys 0, 1, 2)

Glycosylation (G0, G1, G2)

mAU
45
40
35
30
25
20
15
10
5
0
2 4 6 8 10 12 min

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Key Principles of an E&L Study

1. Evaluating The Interactions Between Packaging Material And The Pharmaceutical Formulation And The Resulting Risks

2. Extractable Study: Applying Different Extraction Procedures And Different Analytical Technologies

3. Toxicological Assessment: Defining Threshold Levels For The Extracted Compounds

4. Leachable Study: Detection, Identification and Quantitation Of Leachables Within The Formulation
## Step 1: Evaluating Interactions And Risks

<table>
<thead>
<tr>
<th>Degree of concern associated with Route of Administration</th>
<th>Likelihood of interaction between packaging component and dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td><strong>Highest</strong></td>
<td>Inhalation aerosols and solution</td>
</tr>
<tr>
<td></td>
<td>Injections and injectable suspensions</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>Ophthalmic solutions and suspensions</td>
</tr>
<tr>
<td></td>
<td>Nasal aerosols and sprays</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Topical solutions and suspensions</td>
</tr>
<tr>
<td></td>
<td>Topical and lingual aerosols</td>
</tr>
<tr>
<td></td>
<td>Oral solutions and suspensions</td>
</tr>
</tbody>
</table>

Adapted from Guidance for Industry: Container Closure Systems for Packaging Human Drug and Biologics, US Department of Health and Human Services, Food and Drug Administration, Rockville, MD, May 1999

- What contributes to the high-risk in pharmaceutical packaging?
  - Prefilled syringe containing an injectable drug suspension
  - Interacts with multiple components in the packaging material (plastic barrel, rubber plunger, metal needle) with direct delivery to the bloodstream
Step 2: Extraction Procedures

Parenteral and Ophthalmic Drug Products (PODP)

Vigorous conditions
No sample dissolving solvents
No material deformation
Temp: Hot extraction techniques

Solvents should cover a wide range of polarity
Solvents should mimic drug product formulation

<table>
<thead>
<tr>
<th></th>
<th>Thermal</th>
<th>N-Hexane</th>
<th>Isopropanol</th>
<th>Isopropanol/Water</th>
<th>Aqueous pH 2.5</th>
<th>Aqueous pH 9.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headspace</td>
<td>X</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Reflux</td>
<td>---</td>
<td>X</td>
<td>X</td>
<td>PC/PVC only</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Soxhlet</td>
<td>---</td>
<td>X</td>
<td>X</td>
<td></td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Sealed Vessel</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>55°C for 3d</td>
<td>121°C for 1hr</td>
<td>121°C for 1hr</td>
</tr>
<tr>
<td>Sonication</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td>---</td>
<td>X</td>
</tr>
</tbody>
</table>

Autoclave conditions: (121°C for 1hr)

Detection of additives in LDPE (Example)

<table>
<thead>
<tr>
<th>Known Additives</th>
<th>Sonication pH 2.5</th>
<th>Sonication pH 9.5</th>
<th>Sealed Vessel IPA/Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irganox 1010</td>
<td>---</td>
<td>---</td>
<td>X</td>
</tr>
<tr>
<td>BHT</td>
<td>---</td>
<td>---</td>
<td>X</td>
</tr>
<tr>
<td>Erucamide</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Sonication successfully detects erucamide, but no other anticipated additives
Solvents with different polarity provide better understanding of the material

PQRI: Threshold and Best Practices for Parenteral and Ophthalmic Drug Product (PODP)
Step 2: Threshold Levels and Actions

<table>
<thead>
<tr>
<th>Extractable Level in Component</th>
<th>Assignment Category*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 100 µg/g</td>
<td>Structure Confirmed</td>
</tr>
<tr>
<td>20 – 100 µg/g</td>
<td>Confident</td>
</tr>
<tr>
<td>&lt; 20 µg/g</td>
<td>Tentative</td>
</tr>
</tbody>
</table>

*Assignment category:
Structure confirmed: identification categories A, B (or C), and D (or E) (see Table 2) are positive.
Confident: sufficient data to preclude all but the most closely related structures.
Tentative: data is consistent with a class of molecule only.

<table>
<thead>
<tr>
<th>Identification Category</th>
<th>Typical Identification Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Mass spectrometric fragmentation behavior</td>
</tr>
<tr>
<td>B</td>
<td>Confirmation of molecular weight</td>
</tr>
<tr>
<td>C</td>
<td>Confirmation of elemental composition</td>
</tr>
<tr>
<td>D</td>
<td>Mass spectrum matches automated library or literature spectrum</td>
</tr>
<tr>
<td>E</td>
<td>Mass spectrum and chromatographic retention index match authentic specimen</td>
</tr>
</tbody>
</table>

Ref: ITFG/IPAC-RS Collaboration Response to FDA MDI Guidance on 2001
Step 3: Toxicological Assessment & Thresholds (PQRI guidelines for OINDP)

- Based on Toxicological Thresholds of Concern (TTC) levels from to Kroes et al. (2004)

- **Safety Concern Threshold:** (SCT) 0.15 μg per day, which is defined as the threshold below which an individual leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects.

- **Qualification Threshold:** (QT) 5 μg per day: Threshold below which a given leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure-activity relationship (SAR) concerns.

- **Analytical Evaluation Threshold:** (AET) is determined by consideration of the SCT and the specific drug product delivery configuration (number of doses in a Drug Product vs single dose)

AET: How much sensitivity is required?

- 0.05 µg of a genotoxic contaminant was extracted from a drug container
  - Weight ophtalmic solution container = 1 g

\[
AET = \frac{0.05 \mu g/\text{container}}{1 g \text{ material/\text{container}}} = 0.05 \mu g/\text{g container material}
\]

- Safety Concern Threshold (SCT) for the contaminant = 0.15 µg/d
- Applied Dose = 3 opthalmic solution containers/day
- Content = 3 mL/container

Analytical requirements to detect leachables within the formulation

Leachables: \(AET = \frac{0.15 \mu g/\text{day}}{3 \text{ doses/day}} \times 1 \frac{\text{dose}}{\text{container}} = 0.05 \mu g/\text{container}\)

\[
AET = \frac{0.05 \mu g/\text{day}}{3 \text{ ml/\text{container}}} = 0.017 \mu g/\text{mL}
\]
Step #4 Leachables Study:

- Detection of leachables within the formulation
  - Different techniques of sample prep are required
    - Extraction procedures to reduce the matrix content
      - Liquid/Liquid extraction
      - SPE
      - Extraction of solids with different solvents
      - Headspace analysis
  - Recovery studies are required for quantitative analysis

Threshold levels for leachables in drug products

- Reported above 1 ppm (corresponding to 1µg/mL sample solution)
- Identified tentatively above 10 ppm
- Structure confirmation at 20 ppm

Section #2

- Application Examples: analysis of elemental E&Ls by ICP-MS
- Application Examples: analysis of volatile E&Ls by GC-MS
- Application Examples: analysis of non volatile E&Ls by LC-MS
- Appendix / References
Analytical Workflows: Sample Preparation

**Extraction**
- **Aqueous Extract PH 2.5**
  - Sealed Vessel 121°C
  - Sonication

- **Aqueous Extract PH 9.5**
  - Sealed Vessel 121°C
  - Sonication

- **IPA/Water 50/50**
  - Reflux 3 hours
  - Sealed Vessel 55°C / 3d

- **IPA Extract**
  - Reflux 3 hours
  - Sonication 24 hrs

- **N-Hexane Extract**
  - Reflux 3 hours

**Extract Processing**
- **Back-Extraction Methylene Chloride (2x)**

- **Combine, dry and concentrate extracts**

- **TMS derivatization**

- **Inject underivatized**

**Instrumental**
- **Elemental Analysis**
  - Mainly by ICP-MS

- **GC/MS GC/FID**
  - Semi-Volatiles

- **LC/MS LC/UV**
  - Non-Volatiles

**Thermal Analysis**
- (Headspace GC) Volatiles

**Concentrate**
- **Injection Solutions**

**Add Surrogate Process Standard**

**Add Injection Standard Irganox**
Analysis of Inorganic Extractables & Leachables by ICP - MS

Agilent 7800 / 7900 Series ICP-MS

Proposed new ICH and USP methods for elemental impurities: The application of ICP-MS and ICP-OES for pharmaceutical analysis

White paper

Authors
Amir Liba, Ed McCurdy and Ross Ashdown
Agilent Technologies

Abstract
The United States Pharmacopeia Convention (USP), in parallel with the International Conference on Harmonization (ICH), is developing new methods for inorganic impurities in pharmaceuticals and their ingredients. The current USP method, "<231> "heavy metals limit test", is acknowledged to be inadequate and is due to be replaced with new General Chapters USP<<232> " Limits" and <232> "Procedures" in December 2015. The new methods will address the limitations of the current method, extending the list of analytes, reducing maximum permitted exposure limits and taking account of the route of exposure. The new methods will also introduce the use of closed vessel sample digestion and modern instrumental techniques to ensure the accurate recovery and determination of individual analyte concentrations. This White Paper discusses the development of the new USP General Chapters and the ICH Guideline for Elemental Impurities (Q3D) and how Agilent’s 7800 ICP-MS and 5100 ICP-OES address the requirements of the proposed new methods.

Agilent Technologies

pub 5990-9382EN, 2014
Published Application Notes

Determination of Chromium in Gelatin Capsules using an Agilent 7700x ICP-MS

Application note
Pharmaceutical

Authors
Miao Jing, Yongping Ni, Yanghang Wang and Zhiyu Zhang
Agilent Technologies, China

Introduction
Many medications that are administered orally are enclosed within capsules. Frequently both hard-shelled and soft-shelled capsules are made from edible animal protein (gelatin) which is prepared from various animal by-products such as bone and skin. The Pharmacopeia of the People’s Republic of China (2010 version) sets a clear standard for the grade of gelatin that can be used for drug capsule production and requires that pharmaceutical companies only purchase capsules from manufacturers that are licensed [1]. There have been recent reports that some companies in eastern China have been making and selling capsules made from cheaper industrial gelatin prepared from discarded leather [2]. Chromium, which is a known carcinogen and can be toxic if ingested in large quantities, is used in the leather tanning process. Consequently, 20 to 50 times more Cr is typically found in the leather-derived gelatin than in pharmaceutical edible grade gelatin. As a result, there is a need for a routine, highly sensitive method to

Validating the Agilent 7700x ICP-MS for the determination of elemental impurities in pharmaceutical ingredients according to draft USP general chapters <232>/ <233>

Application note
Pharmaceutical

Authors
Sameer Hussain
Exxon
USA
Amir Liba and Ed McCarty
Agilent Technologies
USA

Abstract
The United States Pharmacopeia (USP) is developing new General Chapters relating to the determination of elemental impurities in pharmaceutical products and ingredients. USP<232> defines the analyte limits, while USP<233> defines sample preparation options including closed vessel microwave digestion, and recommends the use of modern instrumentation, such as multi-element ICP-MS and ICP-OES techniques. Analytical equipment qualification under USP<232> is based on performance testing, and includes requirements to demonstrate accuracy, repeatability, and the unequivocal identification of analytes. In this paper we present data to illustrate the successful validation of the Agilent 7700x ICP-MS for the measurement of elemental impurities in gelatine capsule samples, according to USP<232>/ <233>.

pub 5991-1531EN, 2012

pub 5990-9365EN, 2015
Analysis of Volatile & Semi-Volatile E&Ls by GC-MS

5977B with 7890B GC

7697A Headspace Sampler

7200 Q-TOF
Investigations of Pharmaceutical Products by

- Headspace-GC-MS
- MMI – GC-MS (Multi Mode Injection)

The following pharmaceutical products have been analyzed:

- Intravenous (IV) Bag Set & PVC Tubings
- Transdermal Patch
- Liquid Drug Product
- Pressurized Metered-Dose Inhalers (pMDI)
Analysis of Extractable/Leachable Compounds From Plastic Intravenous Bag Sets Using GC/MSD Systems

Application Note
Pharmaceutical

Abstract
Two Agilent 5977A Series GC/MSD Systems were used for the analysis of extractable and leachable compounds from plastic IV bag sets. Two types of IV bags were investigated: 150 mL dextrose bag (apricot) and 1-L sodium chloride bag (teal). Potentially toxic additives, such as phthalate plasticizers, were shown to have migrated from the IV bag to its infusion solution using the complementary of headspace sampling and liquid injection technique. High-temperature analysis was accomplished using the 7890A GC and a 5973A MSD. Solvent extracts were analyzed using the 5975A MSD. Single ion monitoring (SIM) was used to confirm compound migration.

Introduction
Particular interest has been given to extraction techniques in container closure systems (CCS) used for the pharmaceutical industry. Regulators have become increasingly aware of the need to understand whether chemical species can be extracted from the primary packaging material (package with direct contact to the drug product), as well as whether the extracted species (from the package) will appear as leachable species in the drug product. Extractables analysis involves extracting compounds from the packaging material using elevated temperatures and solvents related to the packaging composition. Leachables analysis involves identifying compounds in the drug formulation that may have leached from the primary packaging material.

The major source of extractables and leachables are additives that provide physical and protective properties to packaging material, such as flexibility, rigidity, stability, and barrier. Extractables include plastic and elastomeric components, pigments and adhesives from coating, and degradation products during processing, storage, and sterilization. Leachables are usually a subset of extractables, however new compounds can form from the interaction between drugs and packaging material.

Analysis of Extractable/Leachable Compounds from Transdermal Patches Using GC/MSD Systems

Application Note
Pharmaceutical

Abstract
A 10-cm2 adhesive patch and film release liner were used to investigate extractable and leachable compounds in transdermal drug delivery systems using two Agilent 5977A Series GC/MSD Systems. Extractable and adhesive additives were identified in acetone, dichloromethane, and hexane extracts using the large volume inject technique. Pharmaceutical ingredients were also identified using high-temperature headspace and liquid injection techniques.

Analysis of Extractable/Leachable Compounds from Generic Liquid Drug Formulations Using GC/MSD Systems

Application Note
Pharmaceutical

Abstract
Pharmaceutical liquid formulations are commonly stored in plastic containers at high risk categories. A pharmaceutical suspension was used as a model for investigating compound migration from packaging material. Two Agilent 5977A Series GC/MSD Systems were used. Fatty acid plasticizers were identified using the 7890A Headspace Sampler and a 5973A GC with a 5977A MSD. Phthalate plasticizers were found using the 5975A MSD with a 5977A MSD. Single ion monitoring (SIM) confirmed the identification of these plasticizers.

Please read the full story……
Differential Analysis in Screening Assays for an E&L Study Using an Agilent 7200 GC/Q-TOF System Combined with Data Mining Software
Why TOF Technology?
The Relationship of Mass Accuracy to the Number of Possible Molecular Formulas by Mass

![Graph showing the relationship between mass accuracy and possible formulas.](image)

- **TOF – Mass accuracy**

Legend:
- 176
- 386
- 882
- 1347
- 1672
- 5687

Possible formulas

Mass Accuracy (amu)
Analytical Workflow

Acquisition

Agilent 7200A GC/QTOF System

Library search

Agilent Unknowns Analysis Software

Compare data

Agilent Mass Profiler Professional Software

Confirmation/Expansion

- Accurate Mass Chemical Ionization Acquisition
- PCDL

Semi-quantification

MassHunter Quantitative Analysis software
TIC chromatograms in EI mode

Unheated Formulation Leachable Sample

Heated Formulation Leachable Sample

Container Extract Extractable Sample
Library search by MassHunter Unknown Analysis Software

Benzene, 1,3-bis(1,1-dimethylethyl)- confirmed by EI NIST 14.0

Di-Isobutylbenzene is potentially used for polymeric packaging
Comparing Datasets to Detect Compounds
Mass Profiler Professional Software

- Traditional blank subtraction could delete an extractable compound by mistake as it might be also present in the solvent, but in lower concentration
- A fold change analysis between the extractable and a blank sample helps to increase the confidence in results
Results: Compounds Found in Different Samples

- Benzene, 1,3-bis(1,1-dimethylethyl), and other compounds were also found in the non-heated leachable sample. The origin of these compounds are most likely from the container closure system.

<table>
<thead>
<tr>
<th>Retention Time</th>
<th>Extractable and leachable compounds</th>
<th>Fold Change in extractable</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.75</td>
<td>Octane, 3,5-dimethyl</td>
<td>UP</td>
</tr>
<tr>
<td>15.16</td>
<td>Benzene, 1,3-bis(1,1-dimethylethyl)</td>
<td>UP</td>
</tr>
<tr>
<td>15.75</td>
<td>Dodecane, 4,6-dimethyl</td>
<td>UP</td>
</tr>
<tr>
<td>16.19</td>
<td>Tridecane</td>
<td>UP</td>
</tr>
<tr>
<td>16.20</td>
<td>Nonadecane</td>
<td>UP</td>
</tr>
<tr>
<td>16.87</td>
<td>Cyclohexasiloxane, dodecamethyl</td>
<td>UP</td>
</tr>
<tr>
<td>19.92</td>
<td>Sulfurous acid, pentyl undecyl ester</td>
<td>UP</td>
</tr>
<tr>
<td>20.53</td>
<td>Cycloheptasiloxane, tetradecamethyl</td>
<td>UP</td>
</tr>
</tbody>
</table>
Ambiguity of Results

NIST Library match of diethyl phthalate

Many other compounds also can give the same spectra with matching factor >80
# Eliminating Ambiguity by Chemical Ionization (CI)

<table>
<thead>
<tr>
<th>Extractables</th>
<th>Mass</th>
<th>Formula</th>
<th>PPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>.alpha.-Cubebene</td>
<td>204.188</td>
<td>C15 H24</td>
<td>3.52</td>
</tr>
<tr>
<td>1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester</td>
<td>278.152</td>
<td>C16 H22 O4</td>
<td>4.18</td>
</tr>
<tr>
<td>1-Decanol, 2-hexyl-</td>
<td>242.261</td>
<td>C16 H34 O</td>
<td>3.67</td>
</tr>
<tr>
<td>2-Methyltetraicosane</td>
<td>352.407</td>
<td>C25 H52</td>
<td>-0.6</td>
</tr>
<tr>
<td>9H-Fluorene, 9-methylene-</td>
<td>178.078</td>
<td>C14 H10</td>
<td>4.8</td>
</tr>
<tr>
<td>Benzene, (1-butylheptyl)-</td>
<td>232.219</td>
<td>C17 H28</td>
<td>3.59</td>
</tr>
<tr>
<td>Benzene, (1-butylhexyl)-</td>
<td>218.203</td>
<td>C16 H26</td>
<td>0.07</td>
</tr>
<tr>
<td>Benzene, (1-butyloctyl)-</td>
<td>246.235</td>
<td>C18 H30</td>
<td>4.56</td>
</tr>
<tr>
<td>Benzene, 1,2,4-trimethyl-</td>
<td>120.094</td>
<td>C9 H12</td>
<td>3.53</td>
</tr>
<tr>
<td>Benzene, 1,3-bis(1,1-dimethylethyl)-</td>
<td>190.172</td>
<td>C14 H22</td>
<td>1.44</td>
</tr>
<tr>
<td>Benzene, 1,3-dimethyl-</td>
<td>106.078</td>
<td>C8 H10</td>
<td>0.09</td>
</tr>
<tr>
<td>Benzene, 1-ethyl-3,5-dimethyl-</td>
<td>134.11</td>
<td>C10 H14</td>
<td>3.55</td>
</tr>
<tr>
<td>Benzophenone</td>
<td>182.073</td>
<td>C13 H10 O</td>
<td>3.71</td>
</tr>
<tr>
<td>Cyclopentasiloxane, decamethyl-</td>
<td>370.094</td>
<td>C10 H30 O5 Si5</td>
<td>2.85</td>
</tr>
<tr>
<td><strong>Diethyl Phthalate</strong></td>
<td>222.089</td>
<td>C12 H14 O4</td>
<td>0.82</td>
</tr>
<tr>
<td>Dodecane, 4,6-dimethyl-A</td>
<td>198.235</td>
<td>C14 H30</td>
<td>4.14</td>
</tr>
<tr>
<td>Hexadecanal, 2-methyl-</td>
<td>254.261</td>
<td>C17 H34 O</td>
<td>6.11</td>
</tr>
<tr>
<td>Naphthalene, 1,6,7-trimethyl-</td>
<td>170.11</td>
<td>C13 H14</td>
<td>5.91</td>
</tr>
<tr>
<td>Naphthalene, 2-methyl-</td>
<td>142.078</td>
<td>C11 H10</td>
<td>2.03</td>
</tr>
<tr>
<td>(E)-Hex-3-enyl (E)-2-methylbut-2-enoate</td>
<td>182.131</td>
<td>C11 H18 O2</td>
<td>4.99</td>
</tr>
</tbody>
</table>

## Diethyl Phthalate (RT 22.4 min)

![Diethyl Phthalate Mass Spectrum](image)

- M/z 223.0963: (C12H14O4)+
- M/z 251.1288: (C12H14O4+C6H5)+
Eliminating Ambiguity by Collision Induced Dissociation
Fragments & accurate mass for unambiguous compound confirmation

Diethyl phthalate

\[ \text{m/z 223.0937} \]

\( (C_{12}H_{14}O_4)+H^+ \)

\[ \text{m/z 167.0278} \]

\( (C_8H_6O_4)+H^+ \)

\[ \text{m/z 149.0239} \]

\( (C_8H_4O_3)+H^+ \)

CI MS/MS spectra can be stored in PCDL software to built a custom library.

Compliance Road Show E/L May 2015
Creation of libraries from CI-MS/MS data

Database creation

Adding the spectra

Library creation
Semi-quantitative Determination of Impurities

Quantification threshold: 5 ug/day
Structure confirmed tentatively: 1 ppm
Structure elucidation: 20 ppm
Semi quantitation: 0.1 ppm to 100 ppm

The concentration of Benzene, 1,3-bis(1,1-dimethylethyl)- is ~ 0.4 ppm. Based on the daily dosage the consumption (of 9 mL solution/d) is below the quantitation threshold of 5 µg/day.
Analysis of Non-Volatile E&Ls by LC-MS
To be published soon...........

Detection and Identification of non volatile E&Ls in an ophthalmic solution by LC-QTOF-MS and MassHunter MassProfiler data mining software

1290 Infinity II UHPLC+ 6500 Series QTOF System
Extractable/Leachable LC-QTOF Workflow

**Samples**
- Standards
- Extracts Drug Containers
- Extracts Drug Product

**Chromatography**
**Columns:** C18/C8/C3
**Organic Mobile Phase:** ACN, MeOH, ACN/IPA, MeOH/IPA
**Varied Buffers:** None, 0.1% Formic Acid, 2mM & 4mM NH₄Acetate

**Ionization Sources**
Jet Stream (ESI), APCI, Multimode

**MS-Instrument**
6530 / 6545 / 6550

**Mass Hunter Data Analysis**
Comparing C3, C8, C18 Separations Using Same Buffers
Base Peak Chromatograms

Results: C3 Column Optimum for Higher Mass Extractables
Create orthogonality by using multiple chemistries
Ionization Modes: APCI vs Jet Stream ESI
Examples: Irganox and Irgacure Mixture

Red = APCI
Blue = Jet Stream
A list of plasticizers has been compiled after literature investigation. The listed compounds have been selected according to their polarity.

<table>
<thead>
<tr>
<th>#</th>
<th>Analyte</th>
<th>CAS</th>
<th>Empirical Formula</th>
<th>Monoisotopic Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ethyl paraben</td>
<td>120-47-8</td>
<td>C₉H₁₆O₃</td>
<td>166.063</td>
</tr>
<tr>
<td>2</td>
<td>Irgacure 184</td>
<td>947-19-3</td>
<td>C₁₃H₁₆O₂</td>
<td>204.115</td>
</tr>
<tr>
<td>3</td>
<td>Irgacure 651</td>
<td>24650-2-8</td>
<td>C₁₆H₁₆O₃</td>
<td>256.1099</td>
</tr>
<tr>
<td>4</td>
<td>Dipropyl phthalate</td>
<td>131-16-8</td>
<td>C₁₄H₁₈O₄</td>
<td>250.1205</td>
</tr>
<tr>
<td>5</td>
<td>4-n-Octyl phenol</td>
<td>1806-26-4</td>
<td>C₁₄H₂₂O</td>
<td>206.1671</td>
</tr>
<tr>
<td>6</td>
<td>Diethyl hexyl phthalate</td>
<td>117-81-7</td>
<td>C₂₄H₃₈O₄</td>
<td>390.277</td>
</tr>
<tr>
<td>7</td>
<td>Irganox 1010</td>
<td>6683-19-8</td>
<td>C₇₃H₁₀₈O₁₂</td>
<td>1176.7841</td>
</tr>
<tr>
<td>8</td>
<td>Irganox 1076</td>
<td>2028-79-3</td>
<td>C₃₅H₆₂O₃</td>
<td>530.4699</td>
</tr>
<tr>
<td>9</td>
<td>Iragafos 168</td>
<td>31570-04-4</td>
<td>C₄₂H₆₃O₃P</td>
<td>646.4515</td>
</tr>
</tbody>
</table>
Can I Detect All My Compounds?

Applying Positive & Negative ES Ionization Mode and UV Absorption

System suitability mix (at 50 ppb level)

UV absorption

ESI pos; TIC & EIC

ESI neg; TIC & EIC

Ophthalmic bottle extract

Overlay of positive & negative TIC

Data acquisition in MS/MS mode
MassHunter Software Tools
Why intelligent data mining software matters....

Data mining is an essential step of the analytical workflow and as important as a successful chromatographic separation and detection of organic compounds.
Mass Profiler Software has been used to identify compounds by PCDL comparison. Unknown compounds have been identified by Molecular Structure Correlator Software.
Mass Profiler Software supports the statistical comparison of data sets. After applying a cut off filter of >3,000 and a >4-fold change (abundance by height) and abundance, **66 compounds** (positive and negative ionization modes) have been displayed for the bottle extract.
Molecular Structure Correlator (MSC) Workflow

MS/MS spectra in CEF file

Structures from PCD/L or ChemSpider, PubChem, etc

Confirmation of structure based on LC or GC MS/MS data—higher confidence identifications!
## Results: List of identified compounds by PCDL

<table>
<thead>
<tr>
<th>Extractables identified by database</th>
<th>Leachables identified by database</th>
</tr>
</thead>
<tbody>
<tr>
<td>diethylene glycol dibenzoate</td>
<td>Diisononyl phthalate</td>
</tr>
<tr>
<td>tridecyl alcohol</td>
<td>Dioctyl phthalate</td>
</tr>
<tr>
<td>sodium ricinoleate</td>
<td>Phthalic anhydride</td>
</tr>
<tr>
<td>irganox 5057</td>
<td>Methyl-2-benzoylbenzoate</td>
</tr>
<tr>
<td>ethyl(2,4,6-trimethylbenzoyl)-phenylphosphinate</td>
<td>Irgacure 907</td>
</tr>
<tr>
<td>isocyano cyclohexane</td>
<td>Hexyl Amine</td>
</tr>
<tr>
<td>degradant of irganox</td>
<td>Ionox 100</td>
</tr>
<tr>
<td>hexadecanoic palmitic acid</td>
<td>Erucamide</td>
</tr>
<tr>
<td>Dioctyl Adipate</td>
<td>Glycerol dilaurate</td>
</tr>
<tr>
<td>Methyl-2-benzoylbenzoate</td>
<td>Diisodecyl Phthalate</td>
</tr>
<tr>
<td>Irgacure 907</td>
<td>Myristyl dimethylamine oxide</td>
</tr>
<tr>
<td>Erucamide</td>
<td>Acetic acid, propyl ester</td>
</tr>
<tr>
<td>Diisononyl phthalate</td>
<td></td>
</tr>
<tr>
<td>Dioctyl phthalate</td>
<td></td>
</tr>
<tr>
<td>Phthalic anhydride</td>
<td></td>
</tr>
<tr>
<td>Hexyl Amine</td>
<td></td>
</tr>
<tr>
<td>Ionox 100</td>
<td></td>
</tr>
<tr>
<td>Glycerol dilaurate</td>
<td></td>
</tr>
<tr>
<td>Diisodecyl Phthalate</td>
<td></td>
</tr>
</tbody>
</table>

Compliance Road Show E/L May 2015
Semi-quantitative compound determination

Required sensitivity for compound quantification

Quantitation of DEHP $C_{24}H_{38}O_4$
1 pg/µL to 50 ng/µL by Jet Stream ESI

UV Detection of BHT (Butylated Hydroxy Toluene) at 220 nm limit around 50 ppb
## Results: Semi-Quantification of identified E&Ls

<table>
<thead>
<tr>
<th>Leachables</th>
<th>ppm ±30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sansocizer DINP</td>
<td>1.41 ±0.43</td>
</tr>
<tr>
<td>N-DOP</td>
<td>2.48 ± 0.74</td>
</tr>
<tr>
<td>Phthalic anhydride</td>
<td>0.14 ± 0.04</td>
</tr>
<tr>
<td>Methyl-2-benzoylbenzoate</td>
<td>0.11 ± 0.03</td>
</tr>
<tr>
<td>Irgacure 907</td>
<td>0.02 ± 0.005</td>
</tr>
<tr>
<td>Hexyl Amine</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>Ionox 100</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>Eruacamde</td>
<td>1.68 ± 0.50</td>
</tr>
<tr>
<td>Glycerol dilaurate</td>
<td>0.08 ± 0.02</td>
</tr>
<tr>
<td>1,2-Benzenedicarboxylic acid, 1,2-bis(8-methylnonyl)ester</td>
<td>0.16 ± 0.05</td>
</tr>
<tr>
<td>Myristyl dimethylamine oxide</td>
<td>0.0009 ± 0.0003</td>
</tr>
<tr>
<td>Acetic acid, propyl ester</td>
<td>0.10 ± 0.03</td>
</tr>
</tbody>
</table>
## Acknowledgements

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
</tr>
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<tbody>
<tr>
<td>David Weil</td>
<td>Senior Applications Scientist</td>
</tr>
<tr>
<td>Syed Salman Lateef</td>
<td>Pharma Application Scientist</td>
</tr>
<tr>
<td>Diana Wong</td>
<td>GC/MS Applications Scientist</td>
</tr>
<tr>
<td>Roger Firor</td>
<td>Senior GC/MS Applications Scientist</td>
</tr>
<tr>
<td>Anthony Macherone</td>
<td>Senior GC/MS Applications Scientist</td>
</tr>
<tr>
<td>Amir Liba</td>
<td>US SPSD AE Manager</td>
</tr>
</tbody>
</table>
Appendix

- Posters published in 2015
- References
Posters for ASMS 2015 on E/L

Extractable/Leachable Compound Analysis in Pharmaceutical Packaging Using GC/MSD System
Diana Wang, Jessica Westland, and Roger Freni; Agilent Technologies, 2550 Centerville Road, Wilmington, DE 19803, USA

**Background**

Extractables are chemical compounds that can be unintentionally released from packaging material into the drug product and could, if present in high-enough concentrations, cause changes in the drug product. Leachables are chemical compounds from the raw materials that come into contact with the drug product due to leaching under processing and storage conditions. Compliance regulations require the control of extractables and leachables to ensure the safety and integrity of the drug product.

**Experimental**

Two GC/MSD Systems were utilized. Headspace Sampling GC/MS, GC/MS, and Headspace/Packed Column GC/MS were used. Extractables and leachables were identified using GC/MS, GC/MS, and Headspace/Packed Column GC/MS.

**References**


**Conclusions**

The identification and quantitation of extractables and leachables in pharmaceutical packaging is crucial for ensuring the safety and efficacy of the drug product. The use of GC/MSD Systems allows for the comprehensive analysis of extractables and leachables, providing valuable information for compliance with regulatory requirements.

**Transdermal Patches**

Transdermal drug delivery is a technology used to incorporate the active drug directly into the transdermal system through the skin. Patches are utilized because they allow for controlled drug delivery in a period of time. In this study, extractables were identified in a transdermal system using GC/MSD Systems.

**Analytical Technologies**

The determination of analytical technologies is required to detect all extractables. Our investigation focused on developing a GC/MSD System for the analysis of extractables in pharmaceutical packaging.

IV Bag Systems

IV bags create an average of 33% E/L in a short period. E/L is a primary target parameter that the potential to impact various materials when formulated. The objective of this study is to develop a method for the determination of E/L in IV bags. In this study, extractables and leachables were analyzed using an Agilent 6890/ MS System.

**Results and Conclusion**

In this study, extractables were identified in IV bags using GC/MSD System. The identification of extractables in IV bags was found to be a critical step in ensuring the safety and efficacy of drug products.
Introduction

The analysis of polymers and their materials using mass spectrometry has been around since the early 1960s using early methods such as Mass Spectrometry (MS) mass spectrometers. The advent of LC-MS/MS systems with very rapid infusion rates of liquid chromatography has advanced the field over the past 30 years. The combination of these two technologies is particularly useful for the investigation of complex samples containing multiple charged species, and allows mass data to be collected on a much time scale than that possible with early LC-MS systems. The first method for determining LC-MS/MS infusion rates was developed by Dr. Peter D. Walker of Agilent Technologies and is still in use today.

Experimental Conditions

For example, infusion rates are defined as the rate at which the sample is infused into the mass spectrometer and are typically measured in liters per minute (L/min). The infusion rate is typically set to be lower than the flow rate of the mobile phase to prevent sample loss. In addition, the mobile phase should be thoroughly mixed before injection to ensure consistent sample introduction. Mobile phase should be filtered to remove any particulate matter that could clog the infusion needle and affect the accuracy of the measurements.

Structure/Confirmation Examples

For example, infusion rates are defined as the rate at which the sample is infused into the mass spectrometer and are typically measured in liters per minute (L/min). The infusion rate is typically set to be lower than the flow rate of the mobile phase to prevent sample loss. In addition, the mobile phase should be thoroughly mixed before injection to ensure consistent sample introduction. Mobile phase should be filtered to remove any particulate matter that could clog the infusion needle and affect the accuracy of the measurements.

Polymer Trend Lines

A major objective in mass spectrometry of polymer and polymer materials is determining the mass of molecules and adducts that are formed during the polymerization process. These molecules and adducts can be identified and quantified by mass spectrometry, which is a powerful tool for characterizing polymers and their components. The mass spectra of polymers and adducts can be analyzed using various techniques, such as MALDI-MS, ESI-MS, and APCI-MS.

Data Analysis 4D Feature Finding

Manual comparison of mass spectrometric data is time-consuming and not practical for large datasets. By comparison, data are analyzed using feature finding algorithms, which can identify and quantify features in the data. These algorithms can be used to identify and quantify features in the data, such as peaks and shoulders, which are typically associated with different classes of molecules.

Graphical Display Drift Data

Ion mobility data can be displayed using the Mass Profiler program. The program displays the mobility vs. time for each ion. The mobility data can be displayed as a function of drift time, and the drift time vs. time for each ion. The mobility data can be displayed as a function of drift time, and the drift time vs. time for each ion. The mobility data can be displayed as a function of drift time, and the drift time vs. time for each ion.

Conclusions

Ion mobility in combination with high-resolution accurate mass and accurate feature using ESI-MS separation and data analysis provides a powerful tool for identification of polymers and their components. The combination of high-resolution accurate mass and accurate feature analysis provides a powerful tool for the identification of polymers and their components.
A Sensitive Quadrupole Time of Flight Mass Spectrometric Method for Detection and Accurate Identification of Extractables and Leachables

S. Kalakoti, S. Dash, S. Khare
Agilent Technologies India Pvt. Ltd., Bangalore, India
Agilent Technologies Inc., Santa Clara, USA

Introduction

Drug substances and products can be contaminated by chemical impurities from primary and secondary packaging materials. Due to the potential impact of these impurities on patient health, the ICH Q3D has issued guidance to the industry on container closure systems for packaging human drug product and to adopt improved containment technologies.

Experimental

Methodology

Sample solutions were prepared by combining 18 different samples in a solvent mixture containing methanol, acetonitrile, and water at a ratio of 1:1:1. The sample solutions were then filtered through a 0.2μm filter and analyzed using the Agilent LS-MS/MS system. The chromatograms were then compared to the database to identify any potential contaminants.

Results and Discussion

Analysis of Results

A selected ion monitoring (SIM) method was used to identify and quantify the impurities present in the samples. The chromatograms were compared to the database to identify any potential contaminants.

Conclusion

The developed method was able to identify and quantify the impurities present in the samples. The results were in agreement with the database, and the method was found to be accurate and reliable.
Orthogonal Analysis for Extractables and Leachables Using Accurate Mass LC/Q-TOF and GC/Q-TOF Systems

Lester Taylor1, Jared Salzman2, Andrew Tye2

Introduction

Drug containers or drug delivery systems, when produced in an environmentally controlled environment, may themselves become sources of contamination. Impurities released from the drug container or storage system and leached from the drug formulation through degradation or reaction under environmental conditions may be a concern for the pharmaceutical industry. Therefore, the drug formulation can be considered an additional source of potential contamination for commercial manufacturing processes. In the case of parenteral products, these impurities may be harmful to the patient or eventually lead to contamination of the drug product. Impurities released from the drug container can be a risk for the pharmaceutical industry.

The LC/MS/MS analysis of extractables and leachables was performed using a 1200 Series LC with a 6460 Triple Quadrupole MS. The results were compared to published data to determine the leachables.

Experimental

Sample preparation for LC/MS: Samples were prepared by placing the sample in a vial and sonicating the sample in methanol for 20 minutes. The sample was then centrifuged at 12,000 rpm for 10 minutes to remove any particles. The supernatant was then transferred to a new vial and evaporated to dryness under a nitrogen stream. The sample was then reconstituted in 100% methanol.

Results and Discussion

Table 1: Orthogonal Analysis for Extractables and Leachables

<table>
<thead>
<tr>
<th>Component</th>
<th>LC/Q-TOF</th>
<th>GC/Q-TOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1</td>
<td>0.01 ppm</td>
<td>0.02 ppm</td>
</tr>
<tr>
<td>X2</td>
<td>0.03 ppm</td>
<td>0.04 ppm</td>
</tr>
</tbody>
</table>

Table 2: Orthogonal Analysis for Extractables and Leachables

<table>
<thead>
<tr>
<th>Component</th>
<th>LC/Q-TOF</th>
<th>GC/Q-TOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y1</td>
<td>0.01 ppm</td>
<td>0.02 ppm</td>
</tr>
<tr>
<td>Y2</td>
<td>0.03 ppm</td>
<td>0.04 ppm</td>
</tr>
</tbody>
</table>

Table 3: Orthogonal Analysis for Extractables and Leachables

<table>
<thead>
<tr>
<th>Component</th>
<th>LC/Q-TOF</th>
<th>GC/Q-TOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z1</td>
<td>0.01 ppm</td>
<td>0.02 ppm</td>
</tr>
<tr>
<td>Z2</td>
<td>0.03 ppm</td>
<td>0.04 ppm</td>
</tr>
</tbody>
</table>

Conclusions

This study shows that orthogonal techniques such as LC/Q-TOF and GC/Q-TOF can be used to identify and quantify impurities in drug products. The results were compared to published data to determine the leachables.

Contact: Lester Taylor | Agilent Technologies | www.agilent.com | Phone: 1-800-227-9770
Abbreviations

AET = Analytical Evaluation Threshold
SCT = Safety Concern Threshold
TDI = Total Daily Intake
TTC = Threshold of Toxicological Concern
DP = Drug Product
OINDP = Orally Inhaled and Nasal Drug Product
MDI = Metered Dose Inhaler
QT = Qualification Threshold
SAR = Structure-Activity-Relationship
References


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• Analysis of Extractables/Leachable Compounds From Generic Liquid Drug Formulations Using GC/MSD Systems, D. Wong, R. Firor, Agilent Application Note 5991-5632EN
• Validating the Agilent 7700x/7800 ICP-MS for the determination of elemental impurities in pharmaceutical ingredients according to draft USP general chapters <232>/<233>, S. Hussain, A.Liba, E. McCurdy, Agilent Application Note 5990-9365EN
• Determination of Chromium in Gelatin Capsules using an Agilent 7700x ICP-MS, Agilent Application Note 5991-1531EN

• Proposed new ICH and USP methods for elemental impurities: The application of ICP-MS and ICP-OES for pharmaceutical analysis Agilent Application Note 5990-9382EN