Extractables and leachables: An Introduction

Tim Hulme
Smithers Rapra

THulme@smithers.com
44(0)1939 252 418
Extractables and leachables: An Introduction

Tim Hulme
Smithers Rapra

thulme@smithers.com
The Smithers Group

- Polymers, rubber, and polymer materials, product and process expertise
- Environmental sciences supporting product registrations and risk assessments
- Conformity assessments of quality and environmental management systems
- Development, analytical, and bioanalytical services for the pharmaceutical & chemical industries
- Providing knowledge for niche, emerging and high-growth industries
- Materials and product knowledge focused on the packaging, paper & print supply chain

The Smithers Group
Presentation Outline

- What are they? – extractables vs. leachables & where they come from
- Why do the testing? – safety & regulatory needs/requirements
- Factors to consider in producing solutions for testing – ensuring representative analysis vs. guidelines (PQRI, BPOG etc.),
Two Key Definitions

Extractable:

Chemical species that can be released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction under laboratory conditions including extraction solvent, technique, stoichiometry, temperature and duration. Extractables themselves, and/or substances derived from extractables, have the potential to leach into a drug product formulation under normal conditions of storage and use.

Leachable:

Chemical species that migrate from a packaging/delivery system, packaging component, or packaging material of construction into an associated drug product formulation under normal conditions of use or during accelerated drug product stability studies. Leachables are typically a subset of extractables or are derived from extractables.
Two Key Definitions

The terms extractable and leachable provide clarity in terms of:

1. The potential versus the actual impact of the product on its user.
   * Extractable = possible impact.
   * Leachable = actual impact

2. The object on which the testing is performed.
   * Extractable = test the material
   * Leachable = test the final product
Extractables & Leachables

Leachables are typically a subset of extractables.
Extractables versus Leachables testing

**EXTRACTABLE**

Test the materials

**LEACHABLE**

Test the product
Possible Sources of leachables

- Pack/Product interaction
- Label adhesive/ink migration
- Secondary Packaging
- In-process leachables
What is E&L testing for?
How to determine that a material is safe for its intended use depends on:

- Route of administration
- Material(s) of construction
- Patient population
- Daily dose
- Duration
- Toxicity classification
- Contact of materials
- Dosage form
- Aqueous with or without co-solvent?
- Small or large volume parenteral

Rubber, Plastic (coated) metal, glass?

Once, twice, more?
Areas of concern

**CONTAMINANT TOXICITY**

Is there risk of harm to the patient?

24
Cr
51.9961
Chromium

**DRUG EFFICACY**

Is there impact on drug potency?
Revised Perspective 2013

<table>
<thead>
<tr>
<th>Degree of Concern with Route</th>
<th>Likelihood of Packaging Component-Dosage Form Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Highest</th>
<th>Inhalation: Aerosols and Sprays</th>
<th>Solutions: Injection Inhalation Suspension: Injectable</th>
<th>Powders: Sterile Injectable Inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Transdermal</td>
<td>Ophthalmics Nasal</td>
<td></td>
</tr>
</tbody>
</table>

Revised table adapted from USP <1664> provided by FDA/CDER/CBER, 2013
Risk-based Approach to evaluating E&L

• Safety Considerations
  • Toxicity, immunogenicity etc.

• Efficacy considerations
  • Leachables interacting with a product
  • Loss of activity
  • Leachable may induce development of neutralising activity

• Quality considerations
  • Impact on manufacturing process, product stability etc

I. Markovic PQRI meeting Feb 2011
There are as yet **no single specific standards or guidance** for extractables and leachables testing.
E&L Regulatory and method landscape

National Regulators

Methods & Advisory Bodies

USP 1663 & 1664

## Key Documents (circa 2005)

- 1993 CDRH - Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators
- 1998 FDA - MDI/DPI Draft Guidance
- 1999 FDA - Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics
- 2002 FDA – Guidance on Inhalation solution, suspension, spray and nasal spray products
- EP 3, USP <381>, <660>, <661> (Physicochemical)
- ISO10993, USP<87>, USP<88> (Biocompatibility)
### Key Documents (circa 2007)

- 1993 CDRH - Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators
- 1998 FDA - MDI/DPI Draft Guidance
- 1999 FDA - Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics
- 2002 FDA – Guidance on Inhalation solution, suspension, spray and nasal spray products
- 2005 CHMP, CVMP - Guideline for Plastic Immediate Packaging Materials
- 2006 PQRI – Safety Thresholds & Best Practices For Extractables & Leachables in OINDP
- 2006 Health Canada/EMA Guidance – Pharmaceutical Quality of Inhalation and Nasal Products
- 21CFR 170-189; COMMISSION REGULATION (EU) No 10/2011 (Food contact)
- EP 3, USP <381>, <660>, <661> (Physicochemical)
- ISO10993, USP<87>, USP<88> (Biocompatibility)
Guidance documents available

- 2011 IPAC-RS, PQG, CQI PS 9000:2011 “Pharmaceutical packaging materials for medicinal products, with reference to Good Manufacturing Practice (GMP)"
- 2012 IPAC-RS (Wiley) Leachables and Extractables Handbook
- 2012 EU cGMPs Chapter 7, “Outsourced Activities”
- 2013 Draft USP <232> “Elemental Impurities-Limits”
- 2014 ICH Q3D “Guideline for Elemental Impurities” (Step 4)
- 2014 Draft USP <661> “Plastic Packaging Systems and Their Materials of Construction”
- 2014 Draft USP <661.1> “Plastic Materials of Construction”
- 2014 Draft USP <661.2> “Plastic Packaging Systems for Pharmaceutical Use”
4.2.1.3 Extractables / Leachables (CTD 3.2.P.2.4)
For non-compendial plastic and for rubber container closure components that are in contact with the formulation during storage (e.g., valves), a study should be conducted to determine the extractables profile. Details and justification of the study design (e.g., solvents used, temperature, storage time) and the results should be provided. It should be determined whether any of the extractables are also leachables present in the formulation at the end of the shelf life of the product or to the point equilibrium is reached, if sooner. The leachables profile should also be determined for compendial plastics and rubber container closure components. For compounds that appear as leachables, identification should be attempted and safety assessments should be conducted in accordance with adequately established safety thresholds. A cross-reference to the data presented in Module 4 (Safety) should be included. Depending on the levels and types of compounds detected, consideration should be given to including a test and limits for leachables in the drug product specification. If a correlation between extractable and leachable profiles can be established, control of leachables could be accomplished via testing and limits on extractables, either on the components or on the raw materials if a correlation has been shown between the levels in the raw materials and components. If there are no safety concerns with the type and level of leachables detected, routine monitoring of leachables would not be necessary.
PQRI recommendations OINDPs

272 Pages covering everything needed for extractables and leachables but no specifics. Provides options to follow. Has provided information on how to determine the limits of detection.

Generally accepted as the recommendation to follow has had FDA involvement in the authoring not formally accepted.

http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf
The scope of the PQRI recommendations

- It does not suggest specific test methods and acceptance criteria
- It does not suggest a comprehensive list of tests
- It does not give acceptance Criteria based on actual data for a particular system
- Test methods and acceptance criteria based on good scientific principles for each specific system
- Ensure batch to batch uniformity of packaging components
- Characterisation of extractables via “Controlled Extraction Studies”
- Correlation of extractables and leachables
- Safety qualification of extractables and leachables
- Routine control of extractables/leachables in “Critical components”
Extractables & Leachables Assessment Workflow

Select Raw Material → Risk Assessment → Risk?

Extraction Study (Material) → Leachable Study (Drug & Placebo)

Yes

Toxicological Risk Assessment

Yes

High Risk?

Yes

Establish E to L Relationship & Acceptance Criteria

Assessment Complete

No

No

No

No

Yes

Yes

Yes

No

AET = Analytical Evaluation Threshold
Applicable ICH Guidance documents

- ICHQ6B: test procedures and acceptance criteria for biotechnological/biological products 1999
- ICH Q5C: Quality of Biotechnology products stability of biotechnological/biological products 1996
- ICH Q5E: Comparability of biotechnology/biological products subject to changes in their manufacturing process 2005
- ICH Q7A: GMP of active pharmaceutical ingredients
- ICH Q8: Pharmaceutical Development 2006
- ICH Q9: Quality Risk Management 2006
- ICH Q10: Pharmaceutical Quality Systems 2008
• ICH Q3A: Chemical Impurities in new drug substances
• ICH Q3B: Impurities in new drug products
• ICH Q3C: Impurities: Residual solvents
ICH Guidance documents in between

- ICH Q3D: Metals
  - Industry groups responding to this
Leaching may take place at multiple steps of the production process:

- Upstream operations (e.g. Media preparation etc)
- Downstream operations (e.g. Concentration, buffer exchange etc)
- Packaging operations
- Intermediate storage
- Final storage

I. Markovic PQRI meeting Feb 2011
Possible sources of leachables

• In-Process/single use systems
  • Bioreactors, containers and storage bags for product intermediates, IV bags, filters, tubing, gaskets, valves, rings etc
  • Stainless steel storage tanks/bioreactors

• Primary packaging components (in direct contact with the API):
  • Vials, syringes/prefilled syringes, ampoules, bottles
  • Closures (screw caps, rubber stoppers)
  • Container liners

• Secondary packaging components
  • Cardboard containers
  • Overwraps, overseals
  • Container labels (e.g. ink, adhesives)

I. Markovic PQRI meeting Feb 2011
Biologics may deserve special consideration for the following reasons.....

• Manufacturing and stability issues
  • Protein conformation (e.g. Secondary, tertiary) is sensitive to external environment
  • Aggregation
  • Changes in glycosylation on stability

• Routine analytical testing often doesn’t detect finite changes in the protein (e.g. Protein unfolding)
• Large size and extensive surface area ensures high frequency of potential sites of interaction
• Analytical challenges in leachables testing due to masking effects/interference etc
• Proteins may be more efficient in solubilising leachables due to abundance of both hydrophobic and hydrophilic sites
• Drug dose, mode and frequency of administration

I. Markovic PQRI meeting Feb 2011
How low to go

Are percent levels, trace levels, parts per million (ppm) or billion (ppb) or lower required?

Anyone that is exposed to a species has a risk, as is seen in the following quote from Paracelsus (1493-1541), the “father” of toxicology, ‘All substances are poisons, there is none which is not a poison. The right dose differentiates a poison from a remedy’.
How low to go

• SCT: Safety Concern Threshold is defined as the threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects. The safety concern threshold (SCT) for extractables and leachables has been defined as 0.15 µg/day.

• QT: Qualification Threshold is defined as the threshold below which a given leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure activity relationship (SAR) concerns.

• AET: Analytical Evaluation Threshold is based on the SCT and is as the threshold at or above which a chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment. The AET acts as a guide for the minimum sensitivity required for the leachables method(s).

• ALARP: As Low As Reasonably Practicable. This concept is used in special cases when the safety concern threshold (SCT) is exceptionally low.
How low to go

• AAL The Analytical Action Limit (AAL) is that concentration of an analyte below which the activities of discovery and identification cannot be reliably performed.

• If the AAL can be established for a particular analytical method, the AAL can be compared to the AET and the safety risk associated with the difference between the AET and AAL can be established.
### SCT- variations

OINDPs 0.15 µg/day
OR 1.5 µg/day for PODPs or EMEA
OR ICH M7

<table>
<thead>
<tr>
<th>Duration of treatment</th>
<th>≤ 1 month</th>
<th>&gt; 1-12 months</th>
<th>&gt; 1-10 years</th>
<th>&gt; 10 years to lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily intake [µg/day]</td>
<td>120</td>
<td>20</td>
<td>10</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Which one is applicable?
Conclusions

• Background to extractables and leachables
• Issues associated with various products
• Limits of detection required
Any Questions?