**Extractables and leachables**

Pharmaceutical and Consumer Healthcare companies are under increasing regulatory pressure to perform extractable and leachable (E&L) testing to investigate potential impurities and toxicological concern resulting from interactions between their product and any contact materials.

E&L studies are essential to understand the safety and quality of a product during development, and to provide data for product registration. Designing and implementing a suitable programme can save significant time and cost in development and potentially avoid pitfalls, which may increase time to market.

Product life cycle assessments are also crucial when assessing changes to any contact materials of an established process or product, in order to assess the potential for any new impurities.

**Extractables:**
Chemical compounds that migrate from any product-contact material (including elastomeric, plastic, glass, stainless steel, or coating components) when exposed to an appropriate solvent under exaggerated conditions of time and temperature.

**Leachables:**
Chemical compounds that migrate into a drug formulation from any product-contact material as a result of direct contact under normal process conditions or accelerated storage conditions.
Extractable and simulated leachable assessments:

- Standard or bespoke protocols
- Accelerated extractions of components following contact with control solvents to provide information on potential leachable compounds
- Accelerated extractions of components following contact with product formulation to provide information on potential leachable compounds (simulated leachable)
- Screening methodology for the assessment of volatile, semi-volatile, non-volatile and inorganic compounds
- Further structural elucidation capabilities for unknown components (high resolution accurate mass-spectrometry (HRAM-MS) and nuclear magnetic resonance (NMR))
- All work is carried out according to FDA, EMA and PQRI guidance

Leachable assessments:

- Assessment of actual leachable compounds in the product following stability storage
- Screening and compound specific validated methodologies
- Storage of samples and leachable assessment in parallel with stability testing as part of a larger CMC package

Change of packaging and product/packaging interaction assessments:

For Consumer Healthcare products LGC has designed bespoke fit for purpose protocols to assess a change in contact material, to provide you with confidence that your product is safe within its new packaging material. Using expert knowledge in the field of E&L, LGC will work with you to minimise the risk associated with change in components.

<table>
<thead>
<tr>
<th>Degree of Concern Associated with the Route of Administration</th>
<th>Likelihood of Packaging Component – Dosage Form Interaction</th>
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</thead>
<tbody>
<tr>
<td>Highest</td>
<td>High: Inhalation Aerosols and Sprays; Medium: Injections and Injectable Suspensions; Inhalation Solutions; Low: Sterile Powders and Powders for Injection; Inhalation Powders</td>
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<tr>
<td></td>
<td>High: Transdermal Ointments and Patches; Medium: Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays</td>
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<tr>
<td></td>
<td>Low: Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions; Oral Tablets and Oral (Hard and Soft Gelatine) Capsules; Topical Powders; Oral Powders</td>
</tr>
</tbody>
</table>

Table 1: Examples of regulatory concerns for common classes of drug products
Overview of a typical extractables and leachables programme

The key stages involved in an extractables and leachables programme are shown in the diagram below:
Applications

- Screening studies to aid single use manufacturing component, container closure system component, transfer system component or medical device component selection
- E&L studies for regulatory submission
- Managing forced or elective changes in single use manufacturing components, container closure system components, transfer system components or medical device components
- Method development, validation and technology transfer of analytical methods for product testing and quality control

Techniques

- Solvent extraction including ultrasonication, microwave, ASE (Automated Solvent Extraction), Soxhlet and Soxetect
- Headspace GC-MS (Volatile Organic Compounds)
- GC-MS and GC-FID (Semi-Volatile Organic Compounds)
- HPLCDAD- MS/MS (Non-Volatile Organic Compounds)
- ICP-MS (Inorganic Compounds)
- Gel Permeation Chromatography (GPC)
- FT-IR, GC-ToF-MS, HRAM-MS and NMR (structural elucidation and unknown ID)

Toxicological Risk Assessment

The data generated by LGC’s E&L studies can be used for toxicological assessment of any specific compounds as part of a human health risk assessment package. We partner with one of Europe’s leading chemical hazard and toxicology risk consultants to provide this service to our customers.

Our expertise

LGC has a wealth of experience in assessing extractables and leachables for a wide range of products, including:

- Pharmaceuticals and Biopharmaceuticals
  - Container closure systems (plastic/glass bottles, stoppers, blow seal vials, labels etc.)
  - Pre-filled syringes
  - Transfer systems (tubing, iv bags, connectors etc.)
  - Single use systems / process contact materials (tubing, gaskets, filters, bags, o-rings etc.)
  - Parenteral, ophthalmic, dermal, topical, orally inhaled and nasal drug products, metered dose inhalers
- Consumer Healthcare
  - Container closure systems (plastic/glass bottles, stoppers, laminated tubing, labels etc.)
  - Creams, ointments, toothpaste, shampoo
- Medical Devices
  - Whole or component parts according to ISO-10993 (biocompatibility)
- Animal Healthcare
  - Container closure systems (plastic/glass bottles, stoppers, blow seal vials, labels etc.)
  - Tags, implants
- Electronic Nicotine Delivery Systems (ENDS)
  - Device components
  - E-liquid container closure systems

With an array of modern technologies, knowledge of regulatory issues and complimentary CMC analytical capabilities, this makes LGC your ideal partner for E&L studies.

For further information on how LGC can assist with extractables and leachables, please contact us:

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Aerial photo of LGC’s Fordham, UK site

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