Overview

- Established 40,000 sq. ft. state-of-the-art laboratory in 1997
- Market leader in Geochemical and trace metal analysis
- Global Foot Print
  - Serving clients across 5 continents
- Member of WAITRO (World Association of Industrial and Technological Research Organizations)
- ISO 9001: 2015 Certified
- ISO/IEC 17025: 2005 Accredited
- OHSA 18001 Certified in 2013
- Recognized Lab for Ph.D. program by Tumkur University, Karnataka
First commercial Laboratory in India to start ICP-MS analysis in 1997

First Third Party Lab to provide Fire Assay Test facilities in India

Participating Laboratory in Certification of Inorganic Reference Standards

Strategic tie-ups with International/National Labs for Advanced Material Analysis i.e. Glow Discharge Mass spectrometry

Contract Research
Our Core Values

Integrity

Quality

Compliance

Service Excellence

Customer Satisfaction

"A customer is the most important visitor on our premises. He is not dependent on us. We are dependent on him. He is not an interruption of our work. He is the purpose of it. He is not an outsider of our business. He is part of it. We are not doing him a favour by serving him. He is doing us a favour by giving us the opportunity to do so."

- Mahatma Gandhi in a speech in South Africa in 1890
Global Footprint in 2018
Serving customers in 20 countries and 5 continents

Shiva Analytics
(A Cotecna Group Company)

North America
United States of America (8 Locations)
Canada

South America
Brazil
Columbia

Europe
Luxembourg

Asia Pacific
Japan
Indonesia
Singapore
Malaysia
Thailand
China

Africa & Middle East
Tanzania
Zambia
Congo
Nigeria
Oman
Botswana
Pharmaceuticals
Accreditations/Certifications

- ISO 9001: 2015
- Facility audited by USFDA in 2007 & 2016
- Department of AYUSH
- Karnataka Drug Control Department
- OHSMS 18001: 2007
cGMP & 21 CFR Part 11 Compliant Lab

- Facility is Registered and Site Self Identified with USFDA

- Data Management through Agilent Open Lab ECM Software
  - 100% data generated during analysis are Audit Trailable
  - Real-time auto backup of data on the server

- Caliber LIMS 3.2.1 version roll out is in progress

- Dedicated cGMP area with access controls

- HPLCs, GCs, LCMSMS, GCMSMS, FTIR, UV, ICPMS, ICP-OES, AAS and Stability Chambers are compliant and connected with ECM to Server
GMP compliant Analytical R&D services

- Analytical Method development and validations
- Extractable and Leachable Studies
- Impurity identification and quantification
- Dissolution Studies
- Method development and validation for Heavy metals by ICP MS / ICP OES / AAS
- Stability studies as per ICH
Core Competencies

GMP compliant QC testing services

- Raw materials
- Excipients
- APIs
- Bulk drugs
- Finished products
- Gases – Nitrogen & Compressed air
- Medical Devices
- Cosmetics
- Ayurvedic products
- Residual Ethylene Oxide
- Residual solvents and pesticides
- Aflatoxins / Ochratoxins
Extractable & Leachable Studies
**Definitions**

**Extractables**: Extractables are organic and inorganic chemical entities that are released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction and into an extraction solvent under laboratory conditions.

**Leachables**: Leachables are foreign organic and inorganic chemical entities that are present in a packaged drug product because they have leached into the packaged drug product from a packaging/delivery system, packaging component, or packaging material of construction under normal conditions of storage and use or during accelerated drug product stability studies.
Different Types of Packaging Components

Primary Packaging Component – Packaging component in direct contact or may become in direct contact with the main drug product. e.g. Ampoules, vials, syringes etc.
Secondary Packaging Component – Packaging component in direct contact with the primary packaging component. e.g. Cartons, Boxes, etc.
**Different Types of Packaging Components**

**Tertiary Packaging Component** – Packaging Component in direct contact with a secondary packaging component and may provide additional protection to the product during transportation and/or storage. e.g. shipping carton
Ancillary Packaging Component – Packaging component which may come into contact with a tertiary packaging component during distribution, storage, and transportation of a packaged product. e.g. shrink wrap
Is E/L Study Limited to Packaging Materials only?

- E/L study is not just for packaging components.
- Recently FDA has raised concerns about the extractables from processing components used during manufacturing of drug products.
- During manufacturing processes, the drug product exists as a solution and thus has the potential for leachables and extractables from materials in contact.
- Components possibly to contact drug product are:
  - Tank - Stainless steel, Glass-lined tanks
  - Tubings - Tygon; Silicone; Cflex; Cflex Ultra; Pharmed; PFA (teflon); Silicone Pharma 50; Stainless steel
  - Diaphragms - Red TL silicone; clear TL silicone
  - Filters - PVDF; PES; Nylon66
  - Filler - Stainless steel, ceramic
Why perform an E/L study?

- The short answer is because you must.

- The FDA, EMA, MHRA and Health Canada and other pharmaceutical regulatory authorities require that all NDA and BLA (Biologics licence application) submissions include E&L data.

- While general guidance on the standards and approaches for E&L testing have been provided by the FDA, EMEA and USP, these guidance do not provide prescriptive procedures.
Extraction studies can be designed to answer questions such as:

- What are the chemical additives in a particular packaging component or material of construction?
- What are the maximum accumulations of chemical additives from a particular packaging component into the dosage form?
- What are the likely contents of an end-of-shelf-life drug product leachables profile?
All questions can be addressed by a set of parameters like

- Extraction time
- Extraction temperature
- Extraction technique
- Sample surface area to extracting solvent volume ratio
How to design an E&L Study?

An E&L investigation is **not 1 single** study, it is at least divided in **4 subsequent major steps**:

**Step 1)** Critical assessment of the packaging system and the properties of the pharmaceutical formulation plus an evaluation of the guidelines.

**Step 2)** Extractables Study is a set of forced lab experiments to extract as much as possible out of the packaging material (but not to destroy the material). In this case the chemists & polymer chemist’s “creativity” is necessary to design reasonable experiments.

**Step 3)** Leachable check study - The data evaluation of the extractable study, including a tox.-assessment. Selection of critical leachables.

**Step 4)** Leachables Study is finally performed as part of the stability study for the drug product after appropriate method optimisation & validation for the selected leachables.
E/L Study Flow

Gather Information

Determine AET

Start with controlled extraction studies

Identify for any leachables above AET

Start with leachable check study

Develop extractable method and analyze on GC-MS, LC-MS/MS, ICP-MS and IC (Validate if necessary)

If found above AET, develop & validate method for leachable study

Leachable study using stability samples

Leachable toxicological evaluation
Critical Parameters – SCT, AET & QT

- Safety Concern Threshold (SCT) is the threshold below which a leachable has a dose so low that it presents negligible safety concerns from carcinogenic and non-carcinogenic toxic effects.

- Analytical Evaluation Threshold (AET) is the threshold at or above which a leachable should be characterized and reported for toxicological assessment.

- Qualification Threshold (QT) is the threshold below which a given noncarcinogenic leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure-activity-relationship (SAR) concerns.
### Safety Thresholds

- **QT and SCT by Therapeutic Area**

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>OINDP (PQRI-OINDP)</th>
<th>Injectables / PDP (PQRI-PODP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCT</td>
<td>0.15 µg/day</td>
<td>1.5 µg/day</td>
</tr>
<tr>
<td>QT</td>
<td>5 µg/day total daily intake for an individual organic leachable</td>
<td></td>
</tr>
</tbody>
</table>
Conversion of SCT into AET

For liquid dosage forms

\[
AET \left( \frac{\mu g}{\text{container}} \right) = \left( \frac{0.15 \mu g/\text{day}}{\text{doses/day}} \right) \times \left( \frac{\text{labeled doses}}{\text{container}} \right)
\]

For solid dosage forms

\[
AET \left( \frac{\mu g}{\text{mL}} \right) = \frac{\mu g}{\text{container}} \div \frac{\text{mL}}{\text{container}}
\]

\[
AET \left( \frac{\mu g}{g} \right) = \frac{\mu g}{\text{container}} \div \frac{g}{\text{container}}
\]
## Possible Extracting Media as per USP

<table>
<thead>
<tr>
<th>Packaging Component</th>
<th>Possible Extraction Media</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI valve elastomer seal (MDI) formulation contains 1,1,1,2-tetrafluoroethane and ethanol</td>
<td>Nonaqueous solvents (e.g. Dichloromethane Isopropanol Hexane)</td>
</tr>
<tr>
<td>Dry powder inhaler mouthpiece</td>
<td>Water (unbuffered) Isopropanol</td>
</tr>
<tr>
<td>Small-volume parenteral vial rubber (aqueous formulation buffered at pH 6.5)</td>
<td>Water (pH 5.2) Water (pH 9.5) Isopropanol:Water (50:50)</td>
</tr>
<tr>
<td>Large-volume parenteral plastic bag (aqueous formulation buffered at pH 7.2)</td>
<td>Water (pH 5.2) Water (pH 9.5) Isopropanol:Water (50:50)</td>
</tr>
</tbody>
</table>
## Mechanism of Extraction—Different Extraction Techniques

<table>
<thead>
<tr>
<th>Sl.</th>
<th>Extraction Techniques</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Maceration (Solvent Soaking) (most preferred)</td>
<td>Fill the packaging system units with extraction solvent and incubate at relevant temperatures</td>
</tr>
<tr>
<td>2.</td>
<td>Reflux</td>
<td>The test article is immersed in boiling solvent for a period of time</td>
</tr>
<tr>
<td>3.</td>
<td>Soxhlet</td>
<td>The test article is placed in the “thimble” of a Soxhlet extraction apparatus that is slowly filled with redistilled solvent from a boiling flask/condenser system</td>
</tr>
<tr>
<td>4.</td>
<td>Sealed Vessel</td>
<td>The test article and extracting solvent are sealed inside a container capable of withstanding elevated temperatures and pressures, placed into a laboratory autoclave and heated with steam for a period of time</td>
</tr>
<tr>
<td>5.</td>
<td>Sonication</td>
<td>The test article and extracting solvent are placed into a glass container and partly immersed in water inside an ultrasonic bath</td>
</tr>
</tbody>
</table>
Extraction Procedure at Shiva Analyticals

- Instrument used: REMI orbital shaking incubator
- 21 CFR part 11 compliant software
- Simulation study done at elevated temperatures with shaking for fixed time
- Most preferred technique as it generates extracts close to real time leachable samples without destruction of packaging material
Sample Preparation

After incubation, extraction by Liquid-Liquid extraction with suitable solvent like DCM, n-hexane, etc.

Extraction to be done at acidic, neutral and basic pH values

Appropriate workup for GC-MS and LC-MS/MS analysis

For GC-MS, with and without derivatization sample analysis to be done

For LC-MS analysis, after extraction, reconstitution with suitable solvent for injection

For ICP MS, sample preparation to be done by acid digestion
E/L Analytical Methods

Different analytical techniques used in E/L study

- **GC**
  - GC-MS (Direct Injection) for SVOCs
  - GC HS MS for VOCs

- **LC-MS/MS**
  - For semi-volatile & non-volatile compounds

- **ICP-MS**
  - For Elemental Analysis

- **IC**
  - For cations & anions
List of Instruments available at Shiva Analyticals

<table>
<thead>
<tr>
<th>Sl.</th>
<th>Name of Instrument</th>
<th>Make/Manufacturer</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LC-MS/MS</td>
<td>Waters</td>
<td>TQS Micro</td>
</tr>
<tr>
<td>2</td>
<td>GC-HSS/MS</td>
<td>Agilent Technologies</td>
<td>7697A</td>
</tr>
<tr>
<td>3</td>
<td>ICP-MS</td>
<td>Agilent Technologies</td>
<td>7700</td>
</tr>
<tr>
<td>4</td>
<td>Ion Chromatography</td>
<td>Thermo Scientific/Dionex</td>
<td>ICS5000+DC</td>
</tr>
<tr>
<td>5</td>
<td>Microwave Digester</td>
<td>Anton Paar</td>
<td>Multiwave Pro</td>
</tr>
<tr>
<td>6</td>
<td>Microwave Digester</td>
<td>Milestone SRL</td>
<td>Ethos Up</td>
</tr>
<tr>
<td>7</td>
<td>Orbital Shaking Incubator</td>
<td>REMI</td>
<td>CIS-24</td>
</tr>
</tbody>
</table>
Flow of an E&L Study

Step 1) Sample receipt and storage at required storage conditions

Step 2) Initiation of Extractable Study as per protocol and report all the unknown compounds observed.

Step 3) Leachable check study (As per protocol) - The data evaluation of the extractable study, including a tox.- assessment. Selection of critical leachables.

Step 4) The Leachables Study is finally performed as part of the stability study for the drug product after appropriate method optimisation & validation for the selected leachables. (If at all any compounds are found above AET level)
## Risk-Based Approach to Consideration of Leachables

### Examples of Packaging Concerns for Common Classes of Drug Products

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

While this table provides a convenient overview of the general level of regulatory concern with various dosage forms regarding leachables, it should not be inferred that “low-risk” dosage forms (e.g., oral tablets) by that definition carry no risk for leachables issues.
Relevant USP Chapters for E/L Study

- Glass Containers – 1660, 660
- Elastomers Components – 1381, 381, 1382, 382
- Plastics Materials – 1661, 66
- Polymer Manufacturing Components – 1665, 665
- L&E – 1663, 1664, 87, 88, 1031
E/L Questionnaire

E/L Questionnaire
Contact us

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