Risk Assessment for Extractables and Leachables: Chemistry Perspective

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The General Issue of Suitability for Use

1. Contact between a drug product and a system (such as a container or a device) provides the opportunity for the two to interact.

2. When the drug product and the system interact, the interaction may affect the composition of the drug product and/or the system.

3. The resultant change in the composition of the drug product and/or system may adversely impact the drug product’s (or system’s) ability to perform in its desired, necessary and required manner (i.e., produce the expected clinical outcome).
The Interaction Between Solution and Material Phases

Material Phase

Additive (e.g., leaching)

Product Phase

Equilibrium Distribution?

Deductive (e.g., binding)

Contact Interface

Note: The arrows denote the direction of solute movement. The oval represents a solute molecule, which can end up in either phase at equilibrium.
Two Key Definitions

**Extractable:**

A substance that is extracted from a resin, material, part, component, system or device via a solvent under specified conditions of contact including temperature, duration, stoichiometry, extraction technique, etc.

**Leachable:**

A substance that is present in a finished drug product as a result of its contact with a packaging system under actual product use conditions.

The terms *extractable* and *leachable* provide clarity in terms of:

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

2. The object on which the testing is performed.
   * **Extractable** = test the material
   * **Leachable** = test the finished product
Packaging Components shall be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed when being treated with the drug product.

To comply with this expectation:

1. Substances leached into drug products have to be discovered, identified and quantified.
2. The propensity of the leached substances to be harmful or undesirable has to be established.

Of these activities, number 1 is an exercise in analytical chemistry and number 2 is an exercise in toxicological and chemical science.

Of these activities, #1 must be completed before #2 can be initiated. If number 1 is not accomplished, then #2 cannot happen.
The Process of Chemical Safety Assessment: Extractables

**Chemical Assessment:**

Generate the Extract + Test the Extract = Extractable Profile

**Toxicological Assessment:**

Safety Assessment

Extractables Profile

Calculated Dose

Safety Threshold
How Would You Establish that a Container or Device is Safe?

What Would You Test?

- Test the Package?
- Test the Contents?
- Test the Components?
- Test the Starting Materials?

How Would You Test?

- Chemical testing?
- Biological testing?
- Clinical testing?
The Process Of Chemical Safety Assessment:
The Chemical Assessment Triad

Material Screening and Selection
Characterize candidates and assess their worthiness for application; ingredients as probable extractables and potential leachables

Simulation Study
Worst case simulation; extractables as probable leachables

Product Assessment
Actual case; measurement of confirmed leachables
The Evolution of Leachables from Ingredients and through Extractables
The Triad Approach to Chemical Assessment

One Qualifies

Materials
1. Confirming their identity.
2. Establishing their composition (specifying their ingredients).
3. Demonstrating their biocompatibility.
4. Documenting their physiochemical properties.

Systems
1. Using qualified materials.
2. Establishing their potential to interact (extractables).
3. Demonstrating their biocompatibility.
4. Demonstrating functionality.

Packaged Products
1. Using qualified packaging.
2. Establishing the degree of interaction (leachables).
3. Demonstrating compatibility between the packaging and the dosage form.
4. Demonstrating functionality.
The Chemical Assessment Triad:  

Material Screening and Selection

Test Article:  Materials of Construction

Test Strategy:  Characterize the test article for ingredients, biocompatibility and general chemical properties.

Impact Assessment: During the development of a packaging system, potential materials of construction are characterized and screened for use based on their characteristics. Uns suited materials are rejected, suitable materials are adopted.

Value Proposition: The best means of insuring packaging suitability is to use suitable materials of construction.
The Chemical Assessment Triad:

Simulation Study

Test Article: Packaging System

Test Strategy: Test packaging system under conditions that simulate their clinical conditions of use.

Impact Assessment: Complete impact assessment of extractables as worst case leachables, including toxicology for safety. Assessment guided by use of Thresholds.

Value Proposition: Analytical methods applied to simulation studies have actual and practical limits that are lower than the limits for methods applied to leachables testing of drug products. Can identify and safety assess extractables at lower levels than leachables.
The Intent of the Simulation Study

Simulation Quality

Extractables

Leachables

Extractables

Leachables

Extractables

Leachables

Extractables

Leachables

Simulation Quality

Poor ---------------→ Good ---------------→ Excellent
The Chemical Assessment Triad:

**Product Assessment**

**Test Article:** Packaging Drug Product

**Test Strategy:** Test packaging drug product for targeted leachables (leachables which, as extractables, had the potential for adverse safety impacts).

**Impact Assessment:** Complete impact assessment of targeted leachables, including toxicity for safety. Compare levels of target leachables with levels of extractables in simulation study.

**Value Proposition:** Drug product is tested, using validated analytical methods, only for those substances which have the potential for an adverse impact. The purpose of the test is to establish concentration, not to establish identity. Confirms applicability of simulation study.
The Chemical Assessment Triad: Important Observations

Material Screening is never sufficient, in and of itself, to establish suitability for use.

The Simulation Study, in conjunction with Material Screening, may be sufficient to establish suitability for use.

Product Assessment, in conjunction with Material Screening and the Simulation Study, is always sufficient, but may not be necessary, to establish suitability for use.
Use of the Chemical Assessment Triad to Manage Safety Risk

Total Safety Risk From Packaging System

Use the Triad to take out risk!
Use of the Chemical Assessment Triad to Manage Safety Risk

Material Screening (ingredients)
Takes risk out through use of well characterized materials whose potential for safety impact can be forecasted.

Simulation Study (extractables)
Takes risk out by fully assessing extractables which are generated in such a way that they forecast leachables.

Product Assessment (leachables)
Takes risk out by fully assessing discovered and reported leachables.

Remaining Safety Risk From Packaging System

Note: ¹The remaining risk is associated with leachables that were not assessed, with the inherent uncertainty in the leachables study and the inherent uncertainty of toxicity assessment.
The Tactics of Chemical Safety Assessment: The Two Steps of Chemical Assessment

1. The Generation of the Extract.

2. The Testing of the Extract.
The Tactics of Chemical Safety Assessment: Generating the Extract, Extraction Solvent

- The ideal situation is for the extracting solvent to have the same propensity to extract substances as the dosage form, thus obtaining the same quantitative extraction profile. (ref. 1)
- The solvent used for extraction should have the same propensity to extract substances as the active substance/dosage form. (ref. 2)
- The solvents used during a controlled extraction study should have similar extracting properties to the drug product vehicle. (ref. 3)
- The overriding requirement for the simulating medium is that it has the same propensity to accumulate leached substances as the therapeutic product. (ref. 4)

The Tactics of Chemical Safety Assessment: Generating the Extract, Extraction Conditions

• The purpose of elevated temperature is to increase that rate of extraction, so that a short experimental time may simulate longer exposure time. (ref. 1)

• Extraction techniques/methods should be vigorous, but not so aggressive as to alter the qualitative and/or quantitative nature of the extractables profile. (ref. 3)

• An effective and acceptable extraction is performed under conditions that are slightly more aggressive than actual contact conditions, but not conditions that are so aggressive that the resultant extractables survey is dramatically different than that obtained if the extraction was performed with the drug product under the worst case contact conditions. (ref. 4)

• Care should be taken to avoid model solvent studies that represent extremes well beyond those appropriate for intended use. If the intended use is in a cold room ... a study conducted at 60°C may be too extreme and lead to concerns over elevated extractables levels that are unfounded in regard to intended use. (ref. 5)
The Tactics of Chemical Safety Assessment:
Testing the Extracts:
The Essential Challenge to Analytical Chemistry

1. Utilize analytical methods that are capable of producing a recognizable, unique and useful response to all extractables (or leachables).
2. Utilize information contained within the response to identify the extractables (or leachables) that are responsible for the observed responses.
3. Process the response in such a way that the concentration of the extractables (or leachables) in the tested sample can be established.

It is the case that no single analytical method exists which tests a sample and as direct output provides identities and concentrations for all detected compounds.
The Tactics of Chemical Safety Assessment: Testing the Extracts: Processes that Occur During Testing

1. **Scouting.** Obtain general chemical information that provides insight into the nature of the extractables (e.g., total amount, acid/base, aromaticity).

2. **Discovery.** The process of looking for the extractables. Search for instrumental responses. The objective is to produce responses (you can’t ID or quant what you can’t find).

3. **Identification.** Provide names (or general structures) for compounds responsible for the discovered responses.

4. **Quantification.** Provide concentration estimates for both the identified compounds and for the responses whose parent compounds were not identified.
The Tactics of Chemical Safety Assessment: Testing the Extracts: Typical Analytical Methods

<table>
<thead>
<tr>
<th>Nature</th>
<th>Purpose</th>
<th>Desirable Characteristics</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scouting</td>
<td>Establish general chemical properties</td>
<td>Bulk property methods</td>
<td>TOC, NVR, pH, UV absorbance, IR, conductivity</td>
</tr>
<tr>
<td>Discovery</td>
<td>Find the Extractables</td>
<td>Sensitive, specific, broad scope and range, “universal” response</td>
<td>GC/FID, GC/MS, LC/PDA, LC/MS, LC/ELSD, Headspace GC/FID, IC, atomic spectroscopy (scanning)</td>
</tr>
<tr>
<td>Identification</td>
<td>Identify what you find</td>
<td>Sensitive, specific, “information rich”</td>
<td>LC/MS/MS, LC/MS (accurate mass), LC/NMR, GC/MS, GC/IR, IC/MS, Headspace GC/MS, “off-line” spectroscopy coupled to preparative techniques, specialty detection methods, atomic spectroscopy (scanning).</td>
</tr>
<tr>
<td>Quantification (for profiling)</td>
<td>Measure what you identify (and estimate what you don’t)</td>
<td>Accurate, precise, specific, sensitive, “universal” response, known response function</td>
<td>GC/FID, LC/UV, LC/MS, LC/ELSD, IC, Headspace GC, atomic spectroscopy (analyte specific)</td>
</tr>
</tbody>
</table>
The Tactics of Chemical Safety Assessment: Testing the Extracts; Four Realities of Analytical Chemistry

1. For all analytical methods, there is a concentration of an analyte in a sample below which the processes of discovery, identification or quantitation cannot be reliably accomplished (absolute limit).
2. For all analytical methods there is a concentration of an analyte in a sample below which the processes of discovery, identification or quantitation can only be reliably accomplished with a great deal of diligence, care, and good technique (practical limit).
3. The absolute and practical limits depend on the complexity of the sample that is being tested and other parameters related to the conditions of use.
4. Leachables can be present in drug products at concentrations near to and even below the absolute and practical limits.
The Tactics of Chemical Safety Assessment: Testing the Extracts; How Low Do You Go?

Practical Implication: More peaks to identify at lower concentrations.
Chemical Safety Assessment: Case Study
Polyisoprene Injection Site on a Solution Bag

- Plastic Film
- Injection Site
- Port Tube
- Printing
- Sleeve Stopper
Chemical Safety Assessment: Case Study Polyisoprene Injection Site on a Solution Bag, Material Qualification

Information available about the polyisoprene injection site material:

- Compliant with USP <381>
- Compliant with USP <87>, <88>
- General composition known:
  - a. Sulfur cure system
  - b. Xanthate accelerator
  - c. Hindered phenol antioxidant
  - d. Hindered amine stabilizer
  - e. Stearic acid and zinc as activators

**Decision:** Insufficient information to make a product suitability decision, perform controlled extraction study to obtain extractables information.
# Case Study; Polyisoprene Septum on a Solution Bag, Material Qualification - Design of Controlled Extraction Study, Extraction

<table>
<thead>
<tr>
<th>Extraction Parameter</th>
<th>Value Used</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraction Solvents</td>
<td>pH 3 mixture, water, pH 9 buffer, 40/60 (v/v) Ethanol/water</td>
<td>Encompasses chemical nature of candidate products</td>
</tr>
<tr>
<td>Extraction Temperature</td>
<td>Aqueous = 121°C (autoclave), Ethanol/water = 55°C</td>
<td>Product is terminally sterilized, issues with autoclaving ethanol/water</td>
</tr>
<tr>
<td>Extraction Duration</td>
<td>Aqueous = 1 hour, Ethanol/water = 3 days</td>
<td>Represents longest product autoclave cycle; 3 days at 55°C roughly corresponds to the autoclave cycle</td>
</tr>
<tr>
<td>Amount of Material Extracted</td>
<td>38 grams</td>
<td>Exaggerated amount of material to obtain higher concentration of extractables, potentially facilitating their identification.</td>
</tr>
<tr>
<td>Extraction Volume</td>
<td>200 mL</td>
<td>Sufficient quantity to allow for the required testing.</td>
</tr>
</tbody>
</table>
### Case Study; Polyisoprene Septum on a Solution Bag, Material Qualification - Design of Controlled Extraction Study, Extract Analysis

<table>
<thead>
<tr>
<th>Function</th>
<th>Method</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scouting</strong></td>
<td>pH</td>
<td>Presence and amount of extracted acids or bases</td>
</tr>
<tr>
<td></td>
<td>UV absorbance</td>
<td>Presence and amount of organic extractables, aromatic versus aliphatic</td>
</tr>
<tr>
<td></td>
<td>Total Organic Carbon (TOC, aqueous only)</td>
<td>Total amount of organic extractables, reconciliation</td>
</tr>
<tr>
<td><strong>Discovery, Identification, Concentration Estimation</strong></td>
<td>Atomic Spectroscopy (ICP-AES)</td>
<td>Presence and amount of extracted and targeted metals and trace elements</td>
</tr>
<tr>
<td></td>
<td>GC/MS with Headspace sampling</td>
<td>Volatile organic extractables, identification and amount</td>
</tr>
<tr>
<td></td>
<td>GC/FID/MS, Solvent exchange and evaporative concentration</td>
<td>Semi-volatile organic extractables, identification and amount</td>
</tr>
<tr>
<td></td>
<td>LC/UV/MS</td>
<td>Semi- and Non-volatile organic extractables, identification and amount</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- GC = Gas chromatography
- FID = Flame Ionization Detection
- LC = Liquid Chromatography
- UV = Detection by Ultraviolet Light Absorption
- MS = Detection by Mass Spectrometry
- ICP-AES = Inductively Coupled Plasma Atomic Emission Spectroscopy
Case Study; Polyisoprene Septum on a Solution Bag, Results of Controlled Extraction Study

GC/FID Chromatograms for the Underivatized Aqueous Extract of the Test Material. The major compound present in this extract was Tinuvin 770.

<table>
<thead>
<tr>
<th>Peak</th>
<th>Tentative Compound Identity</th>
<th>≈ Conc., mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Tinuvin 770</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>2,2,6,6-tetramethylpiperidinol (Tinuvin RS)</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Tinuvin-related substance</td>
<td>0.9</td>
</tr>
<tr>
<td>8</td>
<td>Tinuvin-related substance</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>Unknown</td>
<td>0.2</td>
</tr>
<tr>
<td>9</td>
<td>Tinuvin-related substance</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>Tinuvin-related substance</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>Decane</td>
<td>0.05</td>
</tr>
<tr>
<td>7</td>
<td>Unknown</td>
<td>0.04</td>
</tr>
<tr>
<td>IS1</td>
<td>Internal Standard, Dimethylphthalate</td>
<td>0.2</td>
</tr>
<tr>
<td>IS2</td>
<td>Internal Standard, Anthracene d10</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Case Study; Polyisoprene Septum on a Solution Bag, Results of Controlled Extraction Study

GC/FID Chromatograms for the Derivatized Ethanol/Water Extract of the Test Material. The major compound present in this extract was Tinuvin 770.

<table>
<thead>
<tr>
<th>Peak</th>
<th>Tentative Compound Identity</th>
<th>≈ Conc., mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Tinuvin 770</td>
<td>&gt; 120</td>
</tr>
<tr>
<td>6</td>
<td>Hexadecanoic acid, TMS</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>Tinuvin-related</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>Stearic acid, TMS</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>2,2,6,6-tetramethylpiperidinol (Tinuvin RS), TMS</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>Irgafos 168 degradation product, TMS</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>2,6-di-t-butyl phenol, TMS</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>Unknown</td>
<td>&lt;1</td>
</tr>
<tr>
<td>T</td>
<td>Unidentified Tinuvin-related compounds</td>
<td>---</td>
</tr>
<tr>
<td>IS2</td>
<td>Internal Standard; Anthracene d10</td>
<td>2</td>
</tr>
</tbody>
</table>
Case Study; Polyisoprene Septum on a Solution Bag, Material Qualification - Controlled Extraction Study, Discussion

**Action:** Safety assess the extractables profile assuming the worst case that all the identified extractables accumulate in a contained drug product as leachables at levels comparable to those measured in the extractables study.

**Decision:** Maximum accumulation levels of Tinuvin-related extractables represents an unacceptable safety risk, perform simulated migration study to obtain extractables information under conditions of clinical use.
Case Study; Polyisoprene Septum on a Solution Bag, Material Qualification - Simulation Migration Study, Design

- Injection sites were put onto two types of bags; 100 mL single chambered bags (monobag) and 1000 mL triple chambered bags.
- Bags were filled with water.
- Filled bags were subjected to 1, 2 or 3 sterilization (autoclave) cycles.
- Autoclaved bags were stored at 40°C for 6 months to accelerate 2 years of ambient temperature storage.
- After storage, the fill solutions were tested for their levels of Tinuvin 770 and a related substance using a validated chromatographic method.
Case Study; Polyisoprene Septum on a Solution Bag, Material Qualification - Simulation Migration Study, Target Extractables

**Tinuvin 770:** Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate, CAS RN # 52829-07-9, C_{26}H_{52}N_{2}O_{4}, molecular weight = 480.72.

**Tinuvin RS:** 2,2,6,6-Tetramethyl-4-piperidinol, CAS RN #2403-88-5, C_{9}H_{19}NO, molecular weight = 157.25.
### Accumulation of Target Analytes in Filled Bags Autoclaved and after 6 Month, 40°C Storage

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Rep.</th>
<th>Concentration, ng/mL (ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Tinuvin 770</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Autoclave Cycle</td>
</tr>
<tr>
<td>Multi-Chambered Bag</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>&lt;10</td>
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<td>7</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Monobag</td>
<td>1</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>79</td>
</tr>
<tr>
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<td></td>
<td>5</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>110</td>
</tr>
<tr>
<td><strong>Mean:</strong></td>
<td></td>
<td>103</td>
</tr>
</tbody>
</table>

**Conclusion:** Actual migrating levels are significantly reduced versus worst case estimate from extraction study.