# Dealing with Extractables & Leachables from a Regulatory Perspective

- Design of Extractables & Leachables Studies
- Safety Assessment of Leachables

Timothy W. Robison, Ph.D., D.A.B.T.
Division of Pulmonary, Allergy, and Rheumatology Products
Office of New Drugs/Center for Drug Evaluation and Research
U.S. FDA

**Disclaimer for Timothy W. Robison**:

The views expressed in this presentation are those of the speaker and do not necessarily reflect the views of the US FDA.

# BACKGROUND

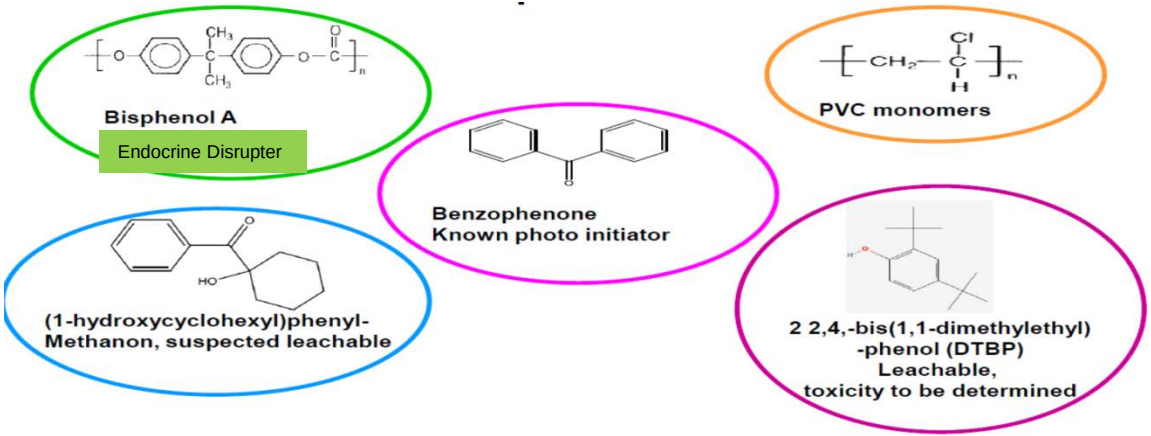
Leachables in the drug product present concerns for both patient safety and product quality

- Presence of leachables in inhalers (MDIs)
  - Sensitive, compromised patient populations
  - Paradoxical bronchospasm
  - Long-term safety for chronic use

- Presence of leachables in parenteral products
  - Direct exposure to leachables
  - Aluminum in large volume parenteral products

- Quality concerns
  - Lack of knowledge/control of source materials
  - Lack of understanding of potential risks from extractables and leachables
  - Lack of control of extractables and leachables

- Structures of Potential Leachables



**Mandate from the Federal Food, Drug, and Cosmetic Act (21 CFR 210 and 211)**:

- Requirement for adequate information related to packaging materials
  - Type and extent of information provided in an application will depend on the dosage form and route of administration

  - Information required for an injectable dosage form or a drug product for inhalation >>> for a solid oral dosage form

**Packaging components should 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**

- This consideration is especially important for those packaging components which may be in direct contact with the dosage form

- Also applicable to any component from which substances may migrate into the dosage form (e.g., secondary packaging component)

**Pre-NDA Division Boilerplate Comment**:

The NDA submission should contain information on extractables and leachables from the drug container closure system and/or drug product formulation unless specifically waived by the Division.

Solvents and conditions used in extraction studies should be justified.

Results of extraction studies should be used to assure that drug product stability samples are adequately monitored for potential leachables.

**Pre-NDA Division Boilerplate Comment (Continued)**:

A risk assessment (RA) based on results of extraction studies may be adequate to support safety during development, the RA of leachables in the drug product identified over the course of stability studies will form the basis for the final safety determination.

The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing).

**Pre-NDA Division Boilerplate Comment (Continued)**:

For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure for a chronic indication or be adequately qualified for safety.

From a genetic toxicology perspective, we will allow up to 120 mcg/day for an acute indication for most potentially genotoxic impurities.

**Pre-NDA Division Boilerplate Comment (Continued)**:
A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day. The risk assessment should be based on the levels of leachables detected in long-term stability samples.

The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission.

**This presentation will provide recommended approaches for handling the Division's comments.**

# USP 1664: Leachables

**Table 1. Modified FDA/CDER/CBER Risk-Based Approach to Consideration of Leachables[a] (*1*)**

| Examples of Packaging Concerns for Common Classes of Drug Products | | | |
|---|---|---|---|
| **Degree of Concern Associated with the Route of Administration** | **Likelihood of Packaging Component-Dosage Form Interaction** | | |
| | **High** | **Medium** | **Low** |
| Highest | Inhalation Aerosols and Sprays | Injections and Injectable Suspensions; Inhalation Solutions | Sterile Powders and Powders for Injection; Inhalation Powders |
| High | Transdermal Ointments and Patches | Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays | — |
| Low | Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions | — | Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders |

[a] 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.

- A comprehensive assessment of E & L is appropriate for a drug product such as an injection, inhalation, ophthalmic, or transdermal.

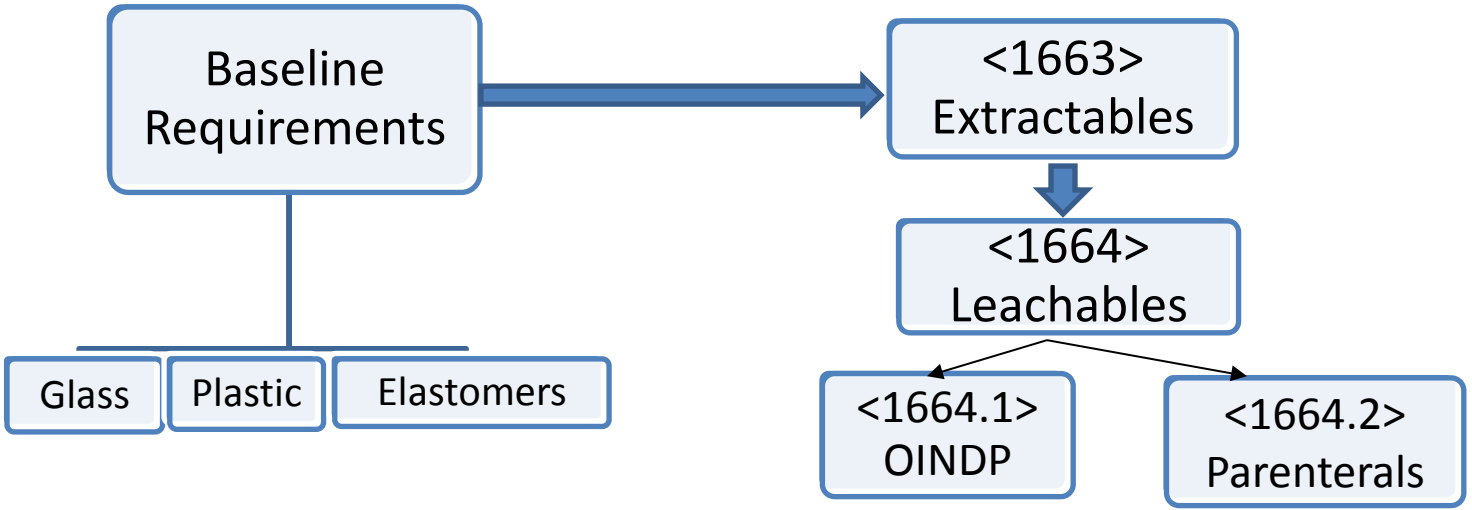
This involves two parts:

1. An extraction study on the packaging component to determine which chemical species may migrate into the dosage form (and at what concentration)

2. From long-term stability studies, leachables that have migrated from the packaging components into the dosage form should be identified and quantified.

# Criteria for Studies to Identify Extractables and Leachable

- USP 1663 for Extractables
- USP 1664 for Leachables (August 1, 2015)
  - USP 1664.1 OINDP (August 1, 2015)
  - USP 1664.2 Parenterals



**Extractables assessments conducted with critical packaging components**

Critical Components are packaging components that

- contact the drug product formulation

- contact the patient (e.g., mouthpiece of inhaler)

- affect the mechanics of the overall performance of the packaging/delivery system, including any necessary secondary packaging


14

# Controlled Extraction Studies

A Controlled Extraction Study is a laboratory investigation into the qualitative and quantitative nature of extractables profiles of critical components of a container closure system.

- Multiple Solvents, Extraction conditions, and Analytical Techniques

- The purpose of a Controlled Extraction Study is to systematically and rationally identify and quantify potential leachables (i.e., extractables, to the extent practicable, and within certain defined analytical threshold parameters)

# Recommendations for Controlled Extraction Studies

- Controlled Extraction Studies should employ vigorous extraction with multiple solvents of varying polarity.
- Controlled Extraction Studies should incorporate multiple extraction techniques.
- Controlled Extraction Studies should include careful sample preparation based on knowledge of analytical techniques to be used.
- Controlled Extraction Studies should employ multiple analytical techniques.

## Recommendations for Controlled Extraction Studies (continued)

- Controlled Extraction Studies should include a defined and systematic process for identification of individual extractables.

- Controlled Extraction Study "definitive" extraction techniques/methods should be optimized.

- During the Controlled Extraction Study process, sponsors should revisit supplier information describing component formulation.

**Ball et al., Leachables and Extractables Handbook (2012)**


17

# Outcome of controlled extraction studies

## Obtain Data for Risk Assessment

- Provide Information to Toxicologists for Preliminary Risk Assessment
- Apply Threshold Principles

## Provide Basis for Leachable Methods

- Correlate Extractable Data to Leachables Data

## Develop Routine Extractable Tests

- Test Multiple Component Lots
- Correlate to Leachables
- Establish Specification and Acceptance Criteria
- Establish Control Criteria

[Ball et al., Leachables and Extractables Handbook (2012)]

## Identification and Quantification of Leachables

- Extraction studies assist in the subsequent identification of leachables.

- From long-term stability studies, leachables that have migrated from the packaging components into the dosage form should be identified and quantified.

- Generally, most leachables identified in long-term stability studies were also identified as extractables from controlled extraction studies. However, exceptions have occurred where a leachable was identified that was not observed in controlled extraction studies.

- A toxicological evaluation of leachables should be performed.

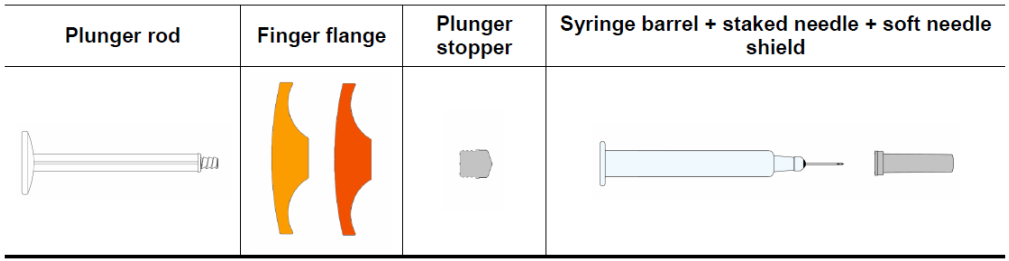
# Case Examples


20

# Example #1 Pre-Filled Syringe Container Closure System

- Drug product (DP) in aqueous solution for subcutaneous (SC) injection
- Container closure system (CCS) consists of:
  - Bulk pre-filled syringe (PFS) (syringe barrel, staked needle, soft needle shield, plunger stopper/piston)
  - Finger flange
  - Plunger rod

Primary CCS: comes in direct contact with DP




Applicant's Figure from Module 3 of BLA

# Extraction Studies: Methods

## Conditions & Analytical Techniques:

| Solvent System and Conditions | | Component Evaluated (Yes/No) | | | | | Technique Used (Yes/No) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Barrel | Piston | | Needle Shield | | LC-UV-MS | GC-MS | HS-GC-MS | ICP-MS |
| 1M Sodium Chloride | 121°C 1 Hr | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| pH 3 water | | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Placebo | | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| pH 9 water | | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 20% Ethanol | 50°C 72 Hr | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| Isopropanol | | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No |
| Hexane | Reflux 60°C 24 Hr | No* | Yes | Yes | Yes | Yes | No | Yes | No | No |

Applicant's Table from Module 3 of BLA

# Analytical Techniques

- The following analytical techniques were used for the extractable & leachable studies:
  - Inductively Coupled Plasma Mass Spectrometry (**ICP-MS**) for **metal compounds**
  - Direct injection gas chromatography mass spectrometry (**GC-MS**) for **semi-volatile organic compounds**
  - Headspace GC-MS (**HS-GC-MS**) for **volatile organic compounds**
  - Liquid chromatography coupled with UV & mass spectrometry (**LC-UV-MS**) for **non-volatile components**

# Example #2

## Extractable and Leachable Studies with 100 mL Flexible Bags for Use with IV Drug Products

### Results of Extraction Studies

| Solvent | Number of Extractables |
|---|---|
| Water pH 1.2 | 5 |
| Water pH 4.5 | 5 |
| Water pH 9.0 | 3 |
| Dichloromethane | 77 |
| Heptane | 108 |
| Hexane | 47 |
| Diluent with Heat | 5 |

| Leachable | Amount at MDD (µg/day) | | | Comments |
|---|---|---|---|---|
| | 10 months | 12 months | 18 months | Not acceptable per 21 CFR 201.325<br>For large volume parenterals (2 L/day), Level of Al ≤50 µg/day |
| Aluminum | BLD | 40 | 216 | |
| Non-volatile organic compound<br>RT = 30.6 min | 82 | 93.6 | 300 | Needs to be identified and a toxicity risk assessment performed |
| Non-volatile organic compound<br>(DCM extract)<br>RT = 35 min | 84 | 44 | 10 | Needs to be identified and a toxicity risk assessment performed |
| Non-volatile organic compound<br>(Hexane extract)<br>RT =36 min | 100 | 52 | 15 | Needs to be identified and a toxicity risk assessment performed |

## Example #3
## Extractables and Leachables Studies with a Pre-Filled Syringe

- IV Parenteral Product (Aqueous Solution)
- Current Product: Glass vial with rubber stopper
- Sponsor proposed to switch to a plastic prefilled syringe with rubber plunger
- Extraction Studies Completed
  - 13% ethanol in water, 60 minutes, 123°C
- Leachable Data at 3 and 6 months, 40°C
  - No long-term stability data

# Results of Migration Studies, Maximum Daily Exposure, and Permitted Daily Exposure (PDE) of Single Leachables

| Leachable | CAS-No. | Maximum Detected Amount (µg/L) | | Maximum Daily Exposure µg/day | Sponsor's calculated PDE values, µg/day (Questionable) |
|---|---|---|---|---|---|
| | | Extraction Study | Migration Study | | |
| Acetone | 67-64-1 | 208 | 8005 | 6864 | 70000 |
| Benzaldehyde | 100-52-7 | 164 | 103 | 88 | 35 |
| **Benzene** | 71-43-2 | 154 | 54 | 46 | 108.5 |
| Cyclohexane | 110-82-7 | ND | 35 | 30 | 54.3 |
| Cyclohexanone | 108-94-1 | 212 | ND | 182 | 30800 |
| Cyclopentanone | 120-92-3 | ND | 709 | 596 | 29400 |
| BHT | 128-37-0 | ND | 512 | 439 | 3500 |
| n-Hexane | 110-54-3 | ND | 2229 | 1911 | 4100 |
| 3-methylpentane | 96-14-0 | ND | 82 | 69 | 395000 |
| 4-methyl-2-pentanone | 108-10-1 | ND | 191 | 164 | 70000 |
| Phenol | 108-95-2 | 554 | ND | 475 | 1860 |
| Styrene | 100-42-5 | **ND** | 107 | 92 | 66500 |
| 4-tert-amylphenol | 80-46-6 | 34 | 500 | 429 | 7000 |
| tert-Butanol | 75-65-0 | 34 | 79 | 68 | 25200 |
| Toluene | 108-88-3 | ND | 96 | 82 | 12500 |

- Material Sourcing?
- Only one extraction condition used?


27

# Safety Assessment of Extractables and Leachables

**Qualification Thresholds described in the ICH Q3A and Q3B Guidances do not apply to E & L**

Given that extractables and leachables are derived from the container closure system, the thresholds described in the ICH Q3A and Q3B Guidances for qualification of impurities in the drug substance or degradation products in the drug product, respectively, are not applicable and not considered appropriate.

However, the general approaches in Q3A/Q3B for safety qualification could be useful.

- Evaluate relevant literature, identified exposure limits

- When necessary, conduct
  - general toxicology study up to 3 months
  - in vitro genetox in presence of a structural alert

- Identify Permissible Daily Exposure (PDE)

- Consider the Maximum Daily Human Exposure

## Toxicological Evaluation of E & L:

• The safety assessment of identified extractables and leachables from a container closure system is a complex process. Typically, the lists of chemical identified can be potentially large (e.g., up to 50 for leachables and much larger for extractables for an MDI).

- Compound specific approach

- Use of threshold of toxicological concern (TTC)

- Qualification in a nonclinical toxicological study with one species

**Best Practices**:

- Assessments of extractables and leachables should begin as early as reasonably possible during development

- Controlled extraction studies, using a range of conditions, conducted with packaging components to determine which chemicals may potentially leach into the drug product.

- Leachable studies should be conducted to identify and quantify chemicals that migrate from the packaging and/or CCS into the drug product. Most leachables will have previously been identified as extractables.

## **Best Practices (continued)**:

● Conduct assessments of individual leachables for structural alerts for mutagenicity (QSAR) and other potential toxic effects (e.g., irritation, sensitization).

● A toxicological evaluation is conducted on the leachable profile to assess the safety under the use conditions of the drug product.

- The approach should be based on good scientific principles that take into account the materials used in the CCS, indication, drug product formulation, route of administration, patient population (e.g., pediatric patients), and dose regimen (e.g., acute or chronic use).

**Best Practices (continued)**:

- Literature references or toxicological data should support intended duration of treatment (e.g., acute, chronic)

- A PQRI Working Group is evaluating a classification strategy for extractables and leachables in parenteral drug products. The FDA has participated as a member of the working group.


34

# Thank You


35

# Additional Examples

# Example #4 Coating Formulation used on Stopper

- Peroxide curing reagent, 1,1 bis(t-butylperoxy)3,3,5-trimethyl-cyclohexane, used in coating formulation on stopper

- Suspected agent of long-term toxicity

- Reformulated coating

- Impacted a large number (>300) of approved and investigational products

- New coating formulation
  - Each applicant was informed of the change and depending on the dosage form, needed to conduct suitability testing and stability testing of the drug with the new coating

# Example #5 New flexible plastic container for an approved parenteral nutrition product

- Sponsor proposed a new flexible plastic container for an approved parenteral nutrition product. The container was not previously accepted for use in FDA approved products.

- The primary container film was composed of a polymer mixture that included styrene copolymers.

- Styrene monomer was detected as an extractable in the proposed container, using Water for Injection as the solvent.

- Leaching studies confirmed that styrene was a leachable.

# Example #5 (continued)

- Worst case exposure estimated at ~300 µg/day, based on maximum concentration detected in drug product and the recommended dose.

- TTC for lifetime exposure = 23 µg/day for a 50 kg bodyweight (based on $TD_{50}$ for mammary tumors in rats).

- Worst case exposure is 12x the TTC.

# Example #5 (continued)

- Estimated daily exposure to styrene in general population (non-smoking)

- Infants:
  - 18.2 µg/day (from air and food) + 18.4 µg/day (from water)* = 36.6 µg/day

- Adults:
  - 55.2 µg/day (from air and food) + 295.8 µg/day (from water)* = 351 µg/day

*Estimated based on maximum styrene content in water as per EPA/FDA regulations

- ATSDR established a minimal risk level of 0.2 ppm for chronic inhalation exposure to styrene, equivalent to ~ 10 mg of absorbed styrene per day.