Current FDA Perspective on Leachable Impurities in Parenteral and Ophthalmic Drug products

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Definitions

• **Extractables**
  – Compounds that can be extracted from the container closure system when in the presence of a solvent

• **Leachables**
  – Compounds that leach into the drug product formulation from the container closure as a result of direct contact with the formulation
Extractables Testing - Purpose

• For qualification of CCS components
• Used to screen for and monitor presence of toxic materials (e.g., nitrosamines, PNA)
• Used in the development of analytical methods for leachable testing
• Used for quality control for acceptance of CCS components
Leachables Testing - Purpose

• Monitor and control CCS-derived impurities in the DP during stability and/or as part of container qualification studies
  – Immediate container fabrication components
  – Migratory materials from labeling, secondary packaging
  – Reaction products between formulation and CCS
Drug products of concern, E/L

- Ophthalmic drug products
- Parenteral drug products
- Inhalation drug products
- **THIS PRESENTATION FOCUSES ON OPHTHALMIC AND PARENTERAL PRODUCTS**
FDA practice regarding E/L

- Risk-based approach for parenteral and ophthalmic drug products regarding E/L studies

- Compendial references
  - USP <661>, <1151>, <601>

- Take into account patient population, route of administration, and potential for interaction between formulation & CCS
<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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<tbody>
<tr>
<td>Highest</td>
<td>High: Inhalation Aerosols and Solutions; Injections and Injectable Suspensions&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>High</td>
<td>High: Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays</td>
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<tr>
<td>Low</td>
<td>Low: Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions</td>
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Leachables

- Outer carton
  - Sterilization agent
  - Preservatives
  - Sealant
  - Ink

- Container closure:
  - Plasticizer
  - Lubricant
  - Pigment
  - Stabilizer
  - Antioxidant
  - Binding agent

- Labeling:
  - Ink
  - Adhesive
  - Varnish

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Ophthalmic Products

- Commonly manufactured as solution or suspension
- Container has to be squeezable to allow delivery to eye (drops)
- Stored in LDPE bottle and tip
- LDPE containers are squeezable but are also permeable to volatile compounds
Parenteral Products

• Commonly manufactured as solution or suspension
• Filled into bottles, vials, syringes
  – Glass or plastic
• Filled into flexible plastic containers
  – PVC, polyolefin, polyester, etc.
Leachables in Ophthalmic and Parenteral Products

- Can originate from primary container closure
- Can migrate through semi-permeable containers
- Can originate from resins (including additives and base polymers), adhesives, inks, and secondary packaging
Leachables

- Chemicals present in flexible plastic films and tubing
- Printing inks (labeling stamped directly on containers)
- Adhesive from labels
- Overwrapping (flexible containers)
- Elastomeric closures (rigid vials)
- Components of glass (vials, bottles, syringes)
Leachables Testing in Ophthalmics and Parenterals

- Stability issue and/or a container qualification and compatibility issue
- Leached compounds are often unknown to applicant (proprietary information from packaging DMF holders)
  - Type, level, properties, toxicity
  - Penetration level and rate
Potential Approaches

• Shared information between CCS components suppliers, applicants, and FDA
  – Composition of CCS components and raw materials of fabrication
  – Some of this information is already public via MSDS, specification sheets, and technical descriptions
Potential Approaches, cont’d

• Applicant designs analytical methodology to aid in detection and determination of compounds in the CCS components
• Supplier can use DMF to convey confidential information to the Agency
• Agency reviewer may confirm that studies performed by the applicant are capable of detecting/determining leachables
Evaluation of Leachables

• One-time study (container qualification)
• Performed for new applications and in support of CCS changes
• Comparative studies should use appropriate controls and standardized conditions
• Test at least one batch on stability (6M accelerated and long-term through expiry) for leachables
Evaluation of Leachables, cont’d

• Need proper detection and screening techniques (such as GC or HPLC) with acceptable LOD and LOQ

• Leachable analytes may be compared to established in-house standards generated from:
  – Extractables study
  – Knowledge of CCS component composition
  – Additional information from CCS suppliers
Reporting of Leachables Data

• Leachable impurities typically reported in units of ppm
• Should be identified when possible (e.g., CAS Registry number, structure, name) to allow toxicological assessment
Reporting, ID, and Qualification

• Typically, leachables are
  – Reported at above 1 ppm
  – Identified at 10 ppm
  – Qualified at 20 ppm
  – Only included in the drug product stability protocol if detected at levels representing toxicological risk (via consult with Pharmacology and Toxicology staff)
  – Source: current practice within DAIOP
Parenteral products – likelihood of CCS-dosage form interaction

• Many parenteral DP’s are aqueous solutions at near-neutral pH
• Packaged in plastic or glass containers
• Relatively few “novel” CCS materials
  – Different applicants utilize same containers/closures
  – Individual applicants package dozens of products in the same CCS
• Often parenteral DP’s can be treated as a general class regarding E/L
E/L for Parenterals, special cases I

• **Lipid emulsions**
  – Higher potential to extract from plastic and rubber components
  – CCS could effect critical formulation parameters, e.g., globule size distribution, emulsion stability, etc.
E/L for Parenterals, special cases II

• **High-pH formulations**
  – Can be “vigorous” extractors
  – Extraction of silicone oil (used to lubricate closures on conveyance)
  – Extraction of trace metals from plastic containers
E/L for Parenterals, special cases III

• **Diluents** (e.g., D5W, NS, Ringer’s)
  – Used to constitute “for injections”
  – The drug to be constituted may not be compatible with the CCS for the diluent
  – Diluents available from multiple sources, packaged in different CCS
  – Responsibilities for E/L
    • Diluent manufacturer
    • “For injection” drug manufacturer
E/L for Parenterals, special cases IV

- **TPN admixture components**
  - Required to be tested for aluminum content by Federal regulation 21 CFR 201.323
    - LVP: NMT 25 ppb
    - SVP: report maximum level and label
  - Main concern from glass containers
  - Leachables more critical than extractables
Take-home message

• Some situations call for a more extensive E/L evaluation (comprehensive E/L studies, resembling those used for MDI)
• Some situations allow for a risk-based evaluation (potential for extraction, knowledge of CCS from other applications which the FDA is authorized to access, etc.)
Summary

- Leachables are usually low-molecular weight volatile compounds that migrate through semi-permeable containers.
- Appropriate testing should be designed to monitor leachables.
- Cooperation between CCS suppliers, applicants, and the Agency may facilitate method development for leachable testing.
Acknowledgments

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