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

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David B. Lewis, Ph.D.
Office of New Drug Quality Assessment
CDER/FDA

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**

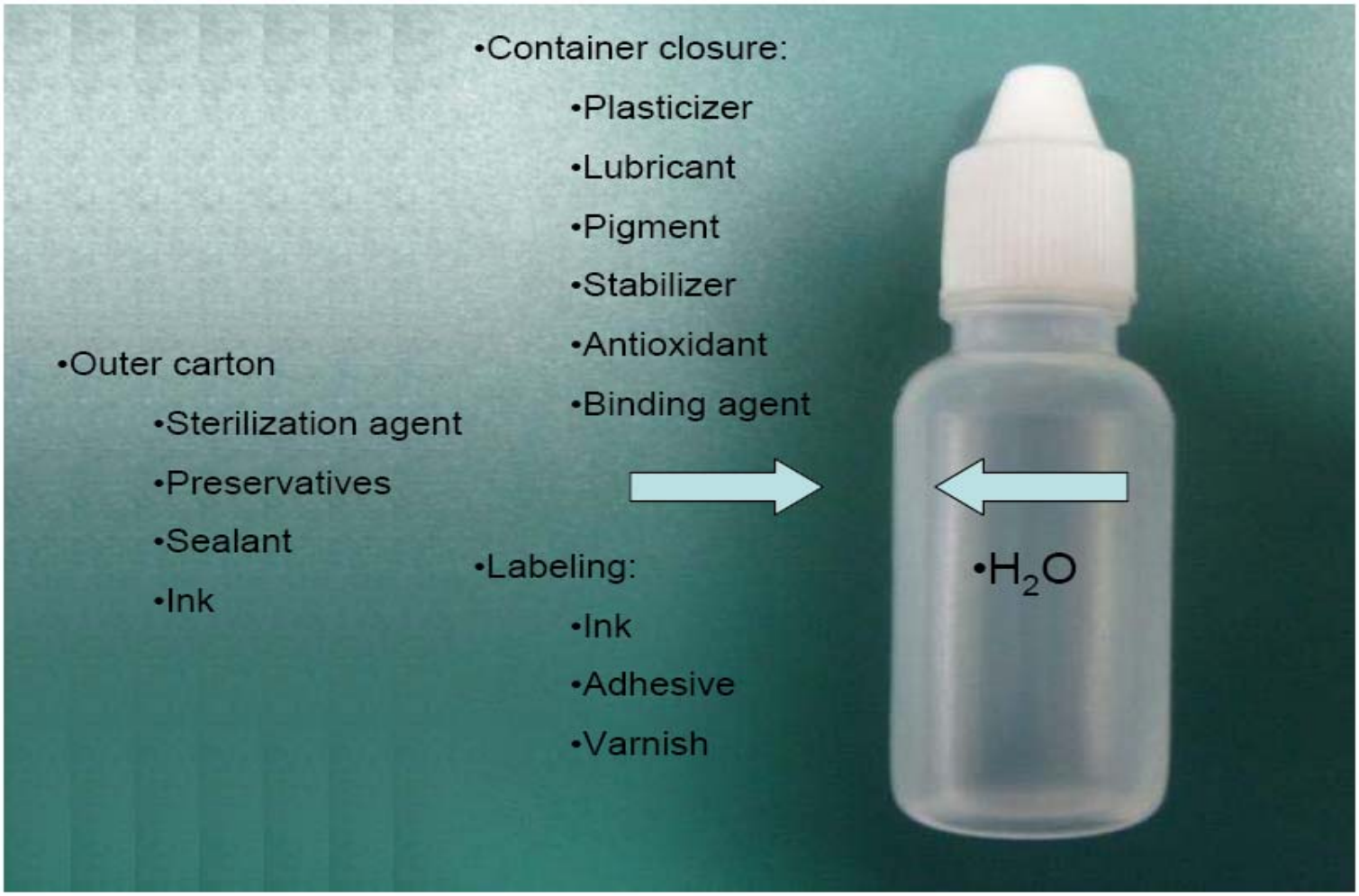
FDA practice regarding E/L

- *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

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 Solutions; Injections and Injectable Suspensions[a]	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

Leachables


•Container closure:
•Plasticizer
•Lubricant
•Pigment
•Stabilizer
•Antioxidant
•Binding agent
•Outer carton
•Sterilization agent
•Preservatives
•Sealant
•Ink
•Labeling:
•Ink
•Adhesive
•Varnish
•H_2O

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

- **<u>Lipid emulsions</u>**
  - 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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