Assessment of Extractables/Leachables (E/L) Data in ANDA Submissions – Part I

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Learning Objectives

- List examples of most common issues with container closure systems (CCS) E/L data in liquid-based drug product ANDAs
- Describe the type of information to be included in ANDA submissions for CCS E/L studies
- Describe FDA's assessment of CCS E/L data in ANDA submissions

Introduction

- Extractables and leachables assessment is an integral part of the evaluation of suitability of a container closure system and manufacturing equipment for a drug product

- See USP <1663> and <1664> for definitions and recommendations on assessment of extractables and leachables associated with container closure systems

Introduction – contd.

- Sources of Extractables:
  - Chemical entities and additives in individual packaging components (elastomeric/polymeric, glass, and metals)
  - Entities related to the dissolution of the packaging component itself (e.g., silicon extracted from glass)
  - Migrants from secondary and tertiary packaging components, such as inks, label adhesives, and volatiles from cardboard shipping containers, plastic storage bags, etc.
  - Chemical substances on the surfaces of drug product manufacturing systems
  - Etc. (See USP <1663> for additional sources)

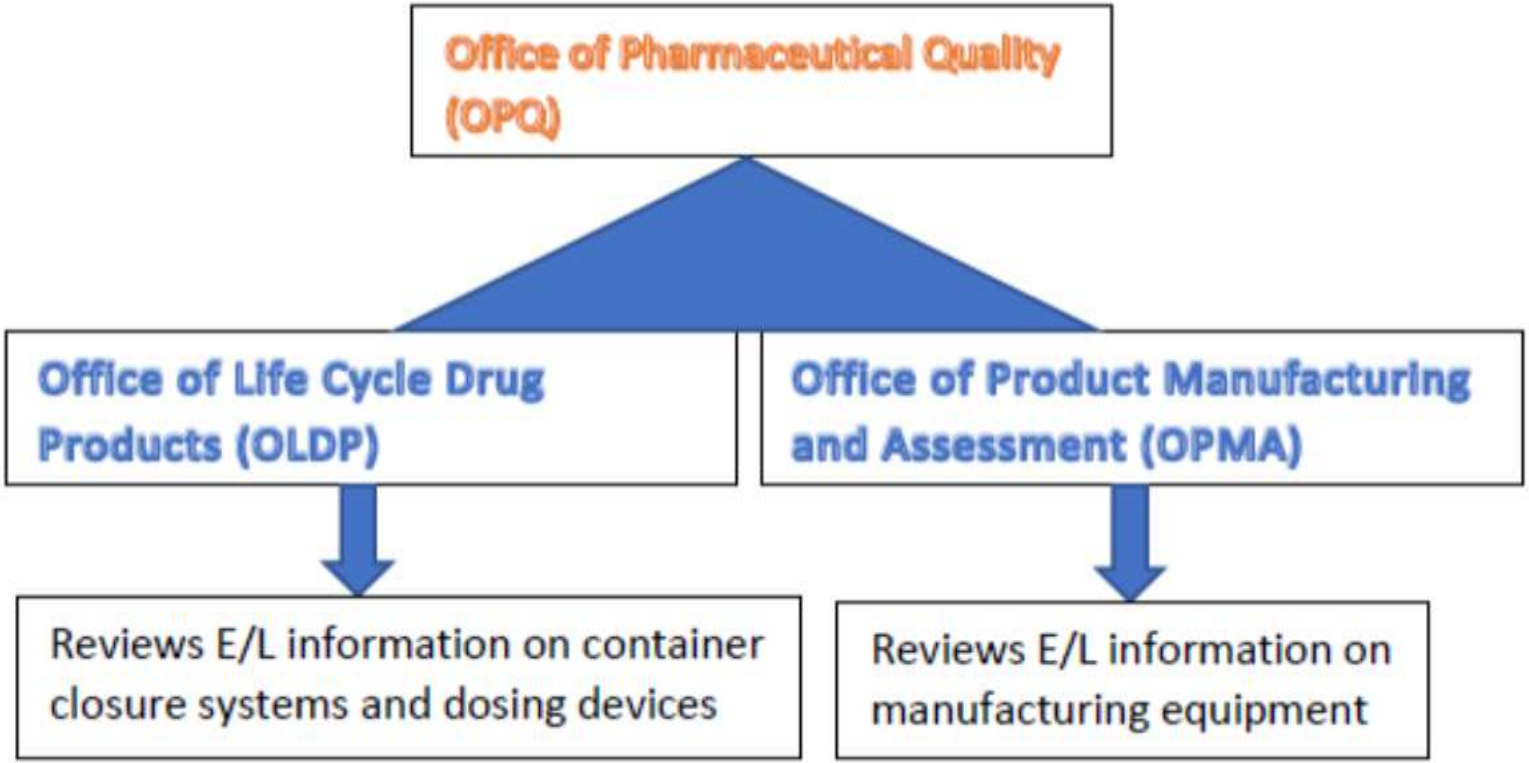
Introduction – contd.

- Per USP <1663>/<1664>:
  - Extractables have the potential to leach into a drug product under normal conditions of storage and use and thus become leachables
  - Leachables are present in a packaged drug product because of the direct action of the drug product on the source of the leachables
    - Typically, a subset of extractables or derived from extractables
    - Mostly derived from manufacturing and packaging equipment, and primary and secondary packaging components and systems

Introduction – contd.

- **Migrants** – Same definition as leachables per USP
  - Exception: Cross a physical barrier before accumulating in the packaged drug product
    - Typically, from secondary and tertiary packaging and ancillary components
- **Both leachables and migrants should be evaluated and controlled in the drug product, where applicable**

Review Responsibilities for E/L studies in ANDAs



Common Issues with CCS E/L Studies in ANDAs

Examples:

- Extractables/Leachables data not submitted in ANDA
- Extractables data submitted but no leachables or inadequate leachables data in application
- Use of incorrect analytical evaluation threshold (AET)/safety concern threshold (SCT)
- Inadequate or no method/method validation information
- High levels of leachables in drug product with no justification/inadequate justification

What does the Agency expect for CCS E/L studies for ANDAs? - contd.

- **Extractables study design** (per USP <1663> recommendations)
  - Designed to identify potential leachables and develop suitable analytical methods for measurement of leachables
  - Identification of potential extractables
  - Solvent selection and extraction conditions
  - Analytical Methods
    - Suitable for intended use
    - Appropriate detection & quantitation limits
  - Identification and quantification of extractables: AET calculation based on **correct MDD and SCT** for the product

What does the Agency expect for CCS E/L studies for ANDAs? – contd.

- **Leachables study design** (per USP <1664> recommendations)
  - Study conditions
  - Analytical methods: Validated and suitable for intended use
    - Similar to that for extractables study or adequately justified if different
  - Identification and quantification of leachables
    - AET calculation: based on **correct MDD and SCT** for the product
  - Number of drug product batches used for study
  - Analysis during stability study

What should be included in Extractables study report for ANDAs?

- Initial risk assessment for study approach
- Extractables studies data (per USP <1663>): accounts for primary, secondary, and tertiary packaging components (e.g., inks, label adhesives, volatiles)
- Information on extraction conditions (e.g., media, temperature, time, analytical techniques)
- Information on analytical methods and method validation
- Assessment of the resultant extractables profiles

What should be included in Leachables study report for ANDAs?

- Per USP <1664>, data from three primary stability batches, each of which should be followed through expiry
- Information on analytical procedures and method validation studies
- Safety assessment of leachables above AET/SCT
- Proposed acceptance criteria in drug product specifications (if leachable impurities are detected above AET)

How does the Agency evaluate E/L Data in ANDA submissions?

- Consider E/L risk for drug product: See FDA guidance on container closure systems for packaging human drugs and biologics

Table 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 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

How does the Agency evaluate E/L Data in ANDA submissions? – contd.

- If risk is high, request E/L information from ANDA applicants if not already submitted
- Evaluate adequacy of extractables study design and analytical methods (e.g., study conditions, AET, methods/method sensitivity, data, etc.).
  - Do methods adequately cover inorganic (metals) and organic impurities (including volatiles, semi-volatiles and non-volatile compounds)?
- Any extractable compound(s) greater than AET? If so, is leachable data submitted?

How does the Agency evaluate E/L Data in ANDA submissions? – contd.

- If leachables data is submitted, is the information acceptable?
  - (e.g., appropriate study conditions, correct AET and SCT, adequately validated methods, # of batches used, study time points, etc.)
- Is any leachable greater than AET?
  - If so, is leachable characterized and qualification data submitted and acceptable?
- If qualification data is not acceptable, CCS is not qualified

Changes to CCS Components

- **For pre-approval or post-approval changes**
  - A risk-based approach should be used for E/L studies
    - Should consider
      - Product risk (e.g., change in formulation, manufacturing system or process, product shelf life, storage or shipping conditions, etc.)
      - If new CCS that was not previously qualified/approved (high risk, full E/L study will be needed), OR
      - If change is to a previously qualified CCS
        - » Low risk if extractables profile of changed CCS is similar to that of previously qualified CCS (leachables study may not be needed)
        - » High risk if extractables profile of changed CCS is not similar to that of previously qualified CCS (leachables study may be needed)

Challenge Question #1

1. ***Firm ABC is developing a topical cream drug product that contains about 78% purified water and 20% organic solvents in the drug product formulation. Are extractables-leachables studies (per USP <1663> and <1664>) necessary for this product?***

A. Yes, because extractables-leachables studies are required for all drug products.

B. No, because the FDA guidance on container closure systems for packaging of human drugs and biologics classifies the degree of concern for extractables and leachables for this route of administration (i.e. topical) as low.

C. Yes, because the drug product formulation contains about 20% organic solvents which could enhance the leaching power of the proposed drug product.

D. No, because the topical cream drug product is viscous which reduces the likelihood of packaging component-dosage form interaction.

Challenge Question #2

Firm XYZ has developed methods for extractables studies of the container closure systems (CCS) for packaging of their proposed ophthalmic suspension drug product but did not validate the methods prior to the study. Should firm's methods be validated?

A. Firm should not validate the methods because the methods are exploratory in nature and not designed as target compound specific methods.

B. Firm should verify at least the limit of detection (LOD) and limit of quantitation (LOQ) for the methods (at ≤ AET - calculated based on SCT and MDD for the product) to increase the degree of scientific certainty for quantitation of the extractable impurities.

C. Firm should fully validate the extractables methods as per ICH Q2(R1) recommendations to ensure the methods are suitable for their intended use.

D. Firm does not need to validate the methods for extractable studies since they will validate the method used for leachables study of the drug product.

Resources

- Container Closure Systems for Packaging Human Drugs and Biologics
- USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
- USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems

Summary

- A risk-based approach should be used for E/L studies of your CCS
- Extractables and Leachables studies should be performed per USP <1663> and <1664>, respectively
- The extractables and leachables from your CCS should be evaluated from a patient safety perspective to ensure safe exposure to leachables in the drug product
- The E/L study information in your ANDA should include initial risk assessment, the E/L testing data/reports and toxicological risk assessment of leachables above AET (with AET based on correct MDD and SCT)

Closing Thought

Ensure your extractables/leachables studies are adequately designed and executed per USP <1663>/<1664>, and adequate information is submitted in your ANDA to justify safe levels of leachables in your drug product.

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- Thank you!