# ANDA SUBMISSION: RISK-BASED EXTRACTABLE AND LEACHABLE QUALITY INFORMATION

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# Disclaimer

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# Presentation Outline

- Introduction
- Safety Concern Thresholds
- Extractables and leachables from manufacturing equipment
- Extractables and leachables from container closure systems

# Introduction

- Extractables –
  - Chemical entities released from a manufacturing equipment or CCS into an extraction solvent under laboratory conditions.
- Leachables –
  - Chemical entities released from a manufacturing equipment or CCS leached into a drug product during manufacturing and storage.
- USP<1663> / <1664>
- FDA guidances
- Technical references - PQRI publications

# Safety Concern Thresholds (SCT)

| Route of Administration | Duration of Treatment >10 years | Duration of Treatment ≤ 10 years |
|---|---|---|
| Most routes[1] | 1.5 µg/day | 5 µg/day |
| Topical ophthalmic products[2] | Reporting Threshold: 1 ppm<br>Identification Threshold: 10 ppm<br>Qualification Threshold: 20 ppm | |

1. Some very high-risk administration routes (e.g., epidural) may require lower SCT (e.g., 0.15 µg/day). Consult FDA/OGD via Controlled Correspondence as needed.
2. FDA Guidance for Industry: Quality Considerations for Topical Ophthalmic Drug Products (12/2023). PPM is used due to the risk of local toxicity to the eye.

# Information Assessed in the ANDA Submissions: Manufacturing Equipment

- **Study protocols**
  - Relevant polymeric surfaces, extraction conditions, worst case scenarios
- **Analytical procedures**
  - Fit for purpose, Details, Reference Standards, Method qualifications
- **Data**
  - Identification and quantification of individual extractables
  - Identification and quantification of individual leachables if leachable studies performed
- **Mitigation** of extractables above AET
  - Engineering controls and/ or leachable studies
- **Mitigation** of leachables found above AET
  - Engineering controls/ Safety assessment

# Structured E/L Summary to Assist E/L Information Assessment

- Current ANDA submissions: E/L information from manufacturing equipment submitted in multiple sections of eCTD

- Structured Summary is recommended in addition to manufacturing equipment E/L information:
  - Summary can be submitted in a structured format
  - E/L information summarized alongside product and process variables
  - Conducive to analysis using attributes in summary
    - Formulation parameters
    - Process design and parameters
    - Safety and analytical thresholds

# Structured E/L Summary – Overview Tab

Column for labels and column for data

| | A | B |
|---|---|---|
| 1 | **Application ID** | A222444 |
| 2 | **Reference Product ID, if applicable** | N022333 |
| 3 | **Drug substance name(s)** | Drug Substance |
| 4 | **Route of administration** | Injection |
| 5 | **Lowest strength** | 1.0 mg/mL |
| 6 | **Commercial batch size for lowest strength (L)** | 50 |
| 7 | **Maximum daily dose (MDD) mg/day** | 5.0 |
| 8 | **Maximum daily volume for lowest strength (mL)** | 5.0 |
| 9 | **Bulk product minimum pH** | 3.2 |
| 10 | **Bulk product maximum pH** | 4.0 |
| 11 | **Bulk product organic solvent concentration (%)** | 50.0 |
| 12 | **Bulk product surfactant concentration (%)** | 0.0 |
| 13 | **For each organic solvent or surfactant: name and amount** | Ethanol 450 mg/mL; Glycerin 5 mg/mL |
| 14 | **Maximum treatment duration** | Chronic |
| 15 | **Safety Concern Threshold (SCT) mcg/day** | 1.5 |
| 16 | **Any process equipment-related leachable present above SCT?** | Yes |
| 17 | | |
| 18 | | |
| 19 | | |

Multiple tabs

Overview | Equipment | Leachables

# Structured E/L Summary – Equipment Tab

Column for each distinct brand name & contact material combination.

| | A | B | C | D |
|---|---|---|---|---|
| 1 | Item description | Filter | Tubing | Bag |
| 2 | Manufacturer | FilterCo | TubingCo | BagCo |
| 3 | Brand name | FilterBrand | TubingBrand | BagBrand |
| 4 | Primary contact material | PVDF | Silicone | LDPE |
| 5 | Catalog numbers | DFG789012CC1; DFG789012TT1 | ABC123456; XYZ336699 | BAG271828 |
| 6 | Pre-treatment sterilization methods | Irradiation; Moist Heat | Moist Heat | Moist Heat |
| 7 | Pre-treatment sterilization conditions | Gamma, 25 kGy; 121°C, 20 min | 121°C, 20 min | 121°C, 20 min |
| 8 | Contact area used for compounding step (cm^2) | 0 | 0 | 0 |
| 9 | Contact area used for offline filtration (cm^2) | 1900 | 1140 | 0 |
| 10 | Contact area used for intermediate bags (cm^2) | 0 | 0 | 20000 |
| 11 | Contact area used for inline filtration / filling (cm^2) | 1900 | 2850 | 0 |
| 12 | Maximum contact duration (h) | 12 | 12 | 16 |
| 13 | Maximum contact temperature (°C) | 25 | 25 | 25 |
| 14 | Flushing volume for inline filtration / filling (L) | 1.25 | 1.25 | 0 |
| 15 | Flushing volume after pause (L) | 1.25 | 1.25 | 1.25 |
| 16 | EXTRACTABLE STUDY REPORTS | | | |
| 17 | Sample used in extraction study has same brand (row 3) and primary contact material (row 4) | Yes | Yes | Yes |
| 18 | Was the LOQ of the analytical methods sufficient to detect impurities at the SCT? | Yes | Yes | Yes |
| 19 | Largest extractable (mcg/cm^2) | 2.63 | 15.20 | 0.475 |
| 20 | Largest extractable name/description | Irgafos 168 | Octamethylcyclotetrasiloxane | Stearic acid |
| 21 | Solvent system & study conditions | 50% ethanol/water, 30°C, static, 48h | 50% ethanol/water, 30°C, circulation, 12h | 50% ethanol/water, 30°C, static, 24h |
| 22 | eCTD location and name of study report | 3.2.P.2 "Filter extractables report" | 3.2.P.2 "Tubing extractables report" | 3.2.P.2 "Bag extractables report" |
| 23 | | | | |
| 24 | | | | |
| 25 | | | | |

Overview | Equipment | Leachables

# Structured E/L Summary– Leachables Tab

| | A | B |
|---|---|---|
| 1 | Manufacturing Batch ID(s) | EB12345 |
| 2 | Did the study design enable detection of process equipment-related leachables (PERLs)? | Yes |
| 3 | Did the study represent worst-case manufacturing conditions including minimum commercial batch size? | Yes |
| 4 | Was the LOQ of the analytical methods sufficient to detect impurities at the SCT? | Yes |
| 5 | Were process equipment-related leachables (PERLs) indentified in the leachables analysis? | Yes |
| 6 | Largest process equipment-related leachable level (mcg/mL) | 0.60 |
| 7 | Name/description of largest process equipment-related leachable | Benzo[a]pyrene |
| 8 | eCTD location and name of study report | 3.2.P.2 "Leachables study report" |
| 9 | Are there leachables that may present safety issues? | Yes |
| 10 | | |
| 11 | | |
| 12 | | |
| 13 | | |
| 14 | | |
| 15 | | |
| 16 | | |

Overview | Equipment | Leachables

# Uses for Structured E/L Data

- Increase review efficiency and consistency
  - Rapid identification of deficiencies
  - Reduction in information requests
  - Data-driven evaluation

- OPQ/OPMA can receive structured E/L data in 3.2.R in .xlsx format

# Question

In what module of the application the E/L structured data should be submitted?

a. 3.2.P.2 Pharmaceutical Development
b. 3.2.P.3 Manufacture
c. 3.2.R Regional Information

# Extractables and Leachables from CCS

- Design of extractable studies –
  - Data from CCS manufacturers, literatures, applicants' internal prior knowledge
  - Solvents and extraction conditions
  - Analytical method for the identification and quantitation of extractables
- Design of leachable studies –
  - Study conditions (e.g., on 3 formal stability batches) and test frequency to inform trending of leachables
  - Analytical method for the identification and quantitation of leachables
    - e.g., LOQ should be validated below Analytical Evaluation Threshold (AET)

# Extractables and Leachables from CCS

- AET calculation –
  - Derived from MDD and SCT (USP<1664>)
  - Inclusion of an Uncertainty Factor (e.g., x0.5)
- Toxicological assessment –
  - Any leachables towards end of shelf life at levels > AET
    - Identification of chemical structures
- Extractable – leachable correlation
  - Allows for the control of leachables upstream at the QC stage of CCS or manufacturing equipment, if needed.
  - Informs post-approvable changes

# Risk-based Approach to E/L Data Submission

- Prior knowledge –
  - Applicants' internal knowledge and open literature
  - Comparison of leaching propensity, route of administration and maximum daily dose of different products
- Route of administration and dosage form –
  - Reference to 21 CFR 174-186 (indirect food additives regulations) may be sufficient without E/L studies for oral drugs, if –
    - Materials of construction, use conditions, specification and test results comply with the regulations
    - Comparison of leaching propensities – drug vs. food

# Question

FDA published Guidance for Industry – “Container Closure System for Packaging Human Drugs and Biologics” in

**a)** **1989**
**b)** **1999**
**c)** **2009**
**d)** **2019**

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