ANDA SUBMISSION: RISK-BASED EXTRACTABLE AND LEACHABLE QUALITY INFORMATION

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This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

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 Identification Threshold: 10 ppm 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

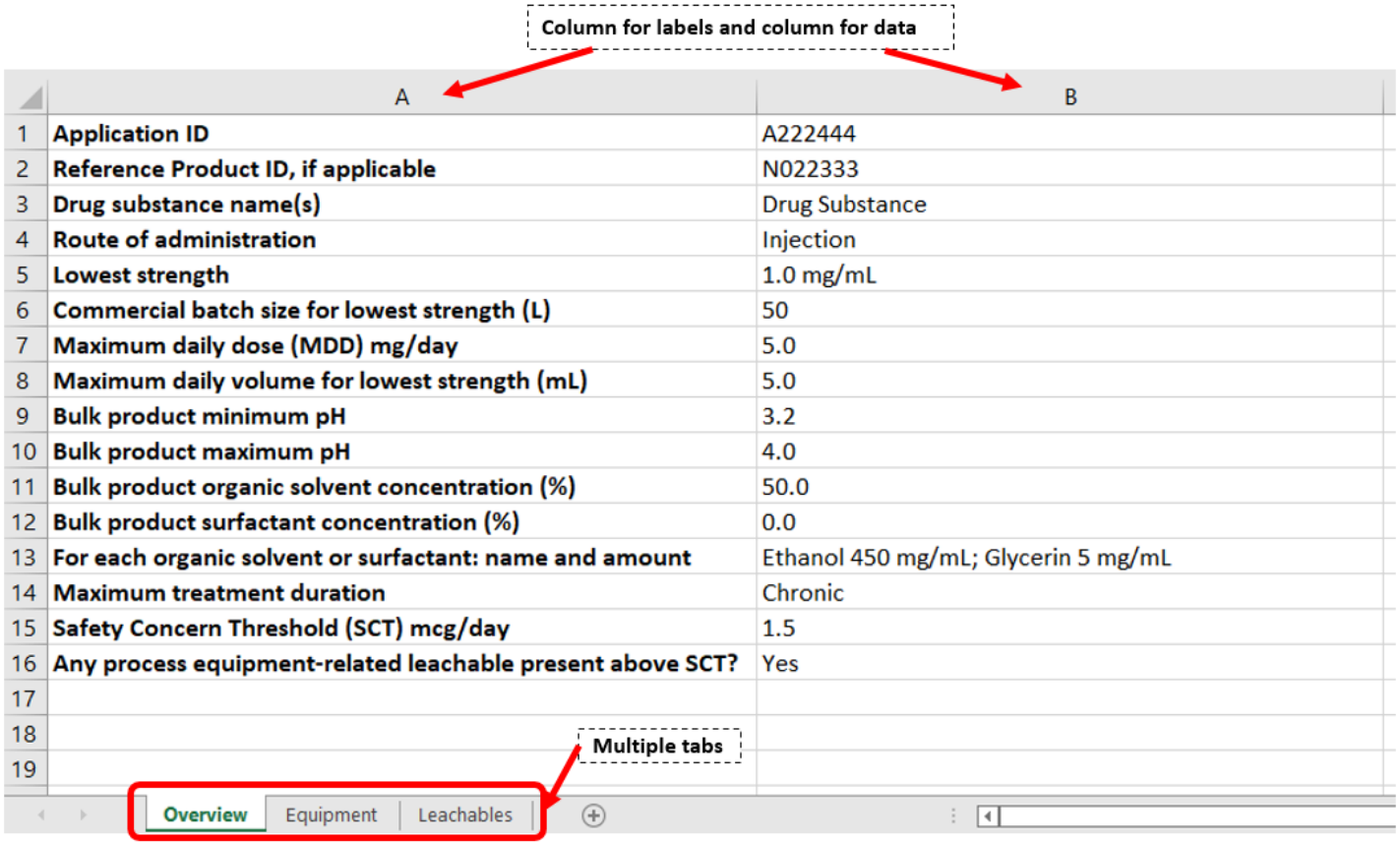
- **Study protocols**
  - Relevant polymeric surfaces, extraction conditions, worst case scenarios
- **Analytical procedures**
  - Fit for purpose, Details, Reference Standards, Method qualifications
- **Data**
  - Identification and quantification of individual extractables
  - Identification and quantification 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



	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		

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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