A RISK-BASED APPROACH TO EXTRACTABLES AND LEACHABLES EVALUATIONS

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Disclaimer

This presentation is not intended to convey formal FDA policy.

Presentation Outline

- Introduction
- Risk assessment
- Leveraging prior knowledge
- Using indirect food additive regulations (21 CFR 174-186) to support oral drugs
- Post approval supplements

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>
- Technical references - PQRI publications
- FDA Guidance - CCS for packaging human drugs and biologics (1999)

Risk Assessment – Product Specific

- Materials of construction and processing aids information from CCS manufacturers
- Prior knowledge
- Route of administration
- Duration of treatment
- Maximum daily exposure
- Formulation composition and leaching propensity
- Potential interaction between CCS and drug product
- Storage conditions and shelf-life

Leveraging Prior Knowledge in Initial Risk Assessments

- Prior knowledge with the same or a similar products using same CCS may be used to support new applications with proper justification -
  - Same route of administration
  - Same or similar product composition
  - Similar or less leaching propensity
  - Similar or less maximum daily exposure

Oral Drug Products

- Oral route of administration considered lower risk
- Compliance with 21 CFR 174-186 and relevant USP standards may be sufficient to support use of CCS for oral drugs –
  - Applicants should cite specific sections, subsection, and use conditions of the regulations, and provide supporting test results.
    - Materials of construction of the proposed CCS are consistent with those listed in 21 CFR 174-186
    - Use conditions are the same or less stringent than those listed in 21 CFR 174-186
    - Leaching propensity of the oral formulation is similar or less than the foods listed in 21 CFR 174-186
    - All testing results meet the acceptance criteria stipulated therein.

Post-Approval Supplements

- Extractable – leachable correlation
  - Allows for the control of leachables upstream at the QC stage of CCS or manufacturing equipment, if needed.
  - Informs post-approval changes
- Grouped supplements
  - Products of same administration route that use the same CCS
    - Risk assessments should evaluate each drug product in grouped supplements
  - Data from the product with the highest risk may be used to support the grouped supplements
    - Consider maximum daily exposure and product leaching propensity

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