Assessment of Extractables/Leachables Data in ANDA Submissions- Part II Manufacturing Process Equipment

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What We're Covering Today

- Why do we assess manufacturing process leachables?
- What are the most common deficiencies in submissions?
- What information do we assess?
  - Protocols, procedures, data, mitigation
- How do we assess?
  - Adequacy of the studies and data
- Summary

Importance of Assessment of Manufacturing Process Leachables

- Leachables have potential to affect safety and quality of the drug product.

  leachables from filters, tubing etc. can have a significant impact on the outcome of drug product formulation stability e.g. protein formulations

- Polymeric materials and components are commonly used in pharmaceutical/biopharmaceutical manufacturing systems and must be suitable for their intended use.

  21 CFR 211.65: Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements

  ICH Q7 5.11: Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

Common Deficiencies in E/L Data in Submissions

- Not all relevant contact surfaces are included in the study
- Lack of correlation between extractable study conditions with proposed manufacturing process
- Lack of quantitative extractables data
- High levels of extractables (above AET*) with no justification or inadequate justification
  - e.g. No toxicology data or no leachables data or insufficient data
- Inadequate analytical procedures
- Risk assessment without data

Information Assessed by Agency for Manufacturing Equipment- related E/L Studies in the Submissions

Extractables Study

- Study protocol
  - relevant polymeric surfaces in the manufacturing process stream
  - Solvent selection and extraction conditions representing worst case manufacturing process conditions
- Data
  - Identification and quantification of extractables
- Mitigation of extractables above AET
  - toxicological justification or leachable studies

Information Assessed by Agency for Manufacturing Equipment- related E/L Studies in the Submissions

Leachables Study

- Based on extractables study
  - Evaluation of the extractables from manufacturing equipment found above AET in the bulk drug product or final drug product
- Analytical Procedures
  - Details
  - Validation
  - Relevant reference standards
- Mitigation of leachables found above AET

Expectations Regarding the Data in the Submission

- Adequacy of study protocols
- Adequacy of risk assessment by the applicant
  - Extractables above AET addressed for their potential risk as leachables in the final DP
  - Use of appropriate safety concern threshold (SCT)
- Mitigation of extractables/leachables above AET

Adequacy of Study Protocols

- Inclusion of all polymeric surfaces in direct contact with bulk used in the manufacturing stream
  - Filters
  - Tubing
  - Polymeric bags/ buffer tanks
- Use of appropriate exposure/surface area
- Use of appropriate incubation conditions
  - For extractable study: Use of exaggerated* conditions covering the worst-case manufacturing conditions
    - Duration, Temperature, Model Solvent
      - e.g. extraction using hexane at 90 °C is not appropriate for filter extractable study when formulation contains 5% ethanol and filtration at 25 °C
  - For leachable study: Use of conditions representative of the proposed process
    - Duration, Temperature, DP bulk solution or finished drug product

Adequacy of Risk Assessment

- Use of correct AET
  - AET calculated using appropriate safety concern threshold (SCT)

- Quantitative data for the extractables above AET

- Evaluation of extractables above AET as potential leachables in the final drug product

Mitigation of E/L above AET

- Extractables above AET
  - Adequate leachable studies to demonstrate the extractables found above AET in extractable studies (exaggerated process conditions) are not present above safety concern levels in the final DP under proposed manufacturing process conditions.

  OR

  - Toxicological justification with data to show extractables above AET do not pose risk to patient.

Mitigation of E/L above AET

- Leachables above AET
  - Appropriate process controls with supporting data to reduce leachables below safety concern levels

  OR

  - Toxicological justification with data to show leachables above AET do not pose risk to patient.

  OR

  - Control of leachable impurities throughout the life-cycle of the drug product

Summary

- Risk for manufacturing process leachables should be assessed based on drug product formulation and process conditions.
- Extractable/leachable studies should be performed on all equipment in direct contact with the bulk formulation.
- Extractables above AET should be justified for their levels or leachable study should be provided to demonstrate extractables above AET are not present in final drug product above safety concern levels.
- Any leachables above safety concern levels should be assessed for toxicological risk and adequate mitigation strategies should be provided.

Let's See What We have Learned

The drug product formulation contains 20% ethanol at pH 6.5, and sterile filtration is carried out at 2-8 °C, the extractables study was carried out using 1N HCl, pH 2. Which of the following statement is true.

a. The extractable study represents the worst-case scenario for the process leachables
b. The extractable study does not represent the worst-case scenario for the process leachables

Let's See What We have Learned

The tubing extractable study data shows total non-volatile residues (NVR) above AET. Which of the following steps are considered appropriate toward mitigation of risk of potential tubing leachables in the final drug product.

a. Identification and quantitation of individual compounds from the total NVR.
b. A leachables study that evaluated a few known tubing extractables, in the final drug product.
c. A leachable study that evaluated identified compounds from the extractable studies, in the final drug product.
d. Both a and c

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Thank you!