Product & Quality Threats and Opportunities

Priti Jagani
(Sr. Director, Analytical R&D, Amneal Pharmaceuticals)

October 22, 2024

Disclaimer

The Views expressed in this presentation are my personal opinions and do not reflect the views or positions of Amneal Pharmaceuticals.

Overview

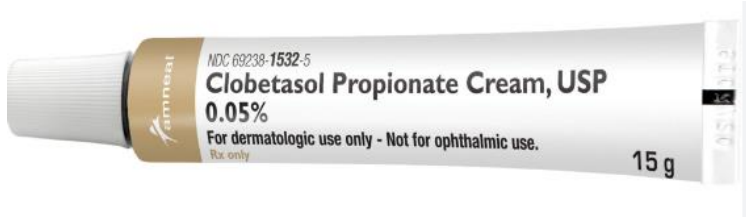
- Extractables & Leachables
- Product Threats
- Quality Threats
- Approach for Assessments
- Qualification Strategies
- Regulatory Compliance
- References

❖ Extractables & Leachables

- **Extractables :** Chemicals entities that can be extracted from pharmaceutical packaging materials (PM's) or Manufacturing process equipments by subjecting them to exaggerated and controlled conditions in the laboratory.

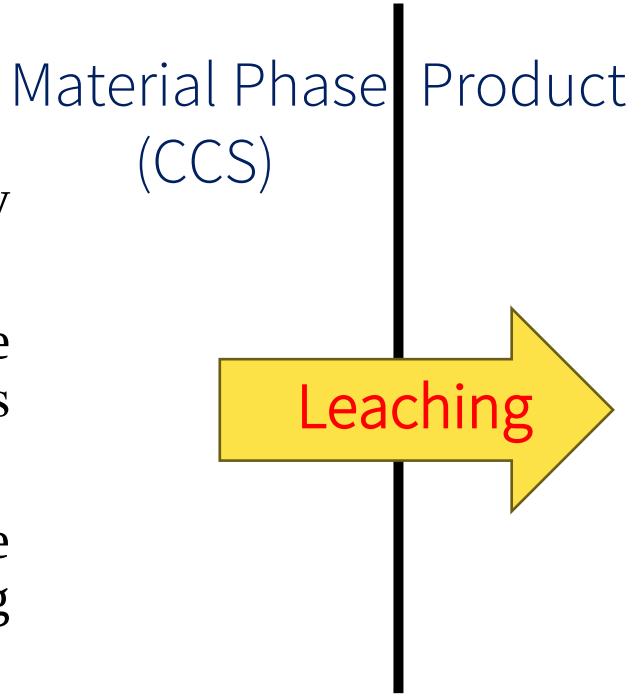
- PM's can have direct contact with the drug product (e.g., Bottles, Closures, Tubes, Backing Film, Release Liner, etc.) or may have indirect/transient contact such as during in-use conditions of drug product (e.g., Pouch, Actuators, Mouth-piece, Nasal Spray Pumps etc.)

- **Leachables :** Chemicals entities that has the potential to migrate (leach) from the PM's and/or Process equipments into the drug product.



❖ Product Threats

- Pharmaceutical Products: Formulated and administered to maximize the therapeutic benefit derived from the product.
- Any action that modifies the formulation composition can adversely impact the derived benefit.
- Contact between the product and its associated system provides the opportunity for an interaction between the formulation and system's material of construction.
- One such interaction is Leaching (additive interaction) where the leachable could impart an undesirable characteristic on the drug product.



❖ Product Threats

- **Risk of Contamination:**
  - Leachables can introduce harmful chemicals, altering the formulation composition and potentially causing **reduction in the stability** of the drug product.
  - Development of undesirable aesthetic effects (e.g., smell, taste, discoloration, clarity)
  - Formation of extraneous matter (e.g., particulate).
  - Alteration of impurity profile.
- **Impact on Efficacy:** Leachables may interact with the active ingredient potentially altering the efficacy of the drug product.
- **Regulatory Compliance:** Failure to identify and quantify extractables/leachables could result in non-compliance with regulatory standards, leading to delays in approval or market withdrawal.
- **Patient Safety Concerns:** Presence of leachables could be toxic and lead to serious adverse effects in patients compromising their safety and well-being.

❖ Threats to Quality

- **Packaging Material Quality:**
  - Poor quality materials used for Pharmaceutical packaging.
  - Coated versus Uncoated Rubber Stopper (Vials), Rubber Plungers (Syringes).
  - Type of internal coating in Aluminum canisters used for Inhalation products.
  - Barrier properties of multilayer films (e.g., Pouch stock used in TDS).
  - Quality of Ink, its curing and printing processes in TDS.
- **Process Equipment Material Quality:**
  - Tubes used for Filling/Transfer process (Inert Materials such as PTFE, FEP etc. preferred).
  - Quality of Aseptic Bags/Bio-containers and associated components used for mixing/storing concentrates.
- **Product Integrity:**
  - **Degradation** of the PM over time can compromise product integrity.

➢ Case Study

- **Leachables can originate from variety of sources and have a diversity of molecular structure.**
  - Background**:** Unknown impurity was found in Drug Substance.
  - Challenge: Source and Identification of Unknown Impurity
  - Investigation:
    - UV spectra of unknown peak different from the API peak.
    - LC/MS analysis was accomplished with both APCI and ESI processes with negative ion mode based on sensitivity of unknown peak.
    - LC-MS Analysis - Isotope Pattern of molecular ion and molecular weight of 190 indicated presence of two chlorine atoms.
    - LC-MS-MS Analysis – Significant negative ion sensitivity in ESI along with collision induced dissociation showed a primary loss of CO_2 suggested the unknown was carboxylic acid.
    - LC-MS, LC-MS-MS and UV results suggested the unknown was an aromatic carboxylic acid with two aromatic substituted chlorine atoms.

➢ Case Study

- Outcome:
  - An isomeric dichlorobenzoic acid was consistent with all of the available mass spectrometric data on the unknown.
  - LC/UV and LC/MS analysis on authentic reference compound confirmed that 2,4 – dichlorobenzoic acid was the unspecified impurity.
  - 2,4 – dichlorobenzoic acid was not structurally related to the API nor was it employed in the API synthesis process, it was confirmed to be a leachable and search was initiated to confirm its source.
- Conclusion:
  - Silicone Rubber tube attached to processing equipment used for the API synthesis was the source of the 2,4 – dichlorobenzoic acid. Bis (2,4-dichlorobenzoyl)peroxide which can easily degrade to yield 2,4 – dichlorobenzoic acid was used for vulcanization of the silicone rubber in that particular tubing.

❖ Approach for Assessments

- Materials should be chemical and bio compatible, highest quality and 21 CFR compliant.
- Ensure cleaning procedures are validated to prevent cross-contamination from previous batches or residuals which can lead to false positives
- Stability testing to evaluate how different storage conditions (e.g. temperature, humidity and proposed shelf-life) and orientation can impact leachables
- Ensure the PM maintain their integrity throughout the product's shelf-life.
- Assess the potential for E&L from process equipments and PM that comes in direct contact with drug formulation.
- Process Controls: Monitor and control manufacturing process to avoid conditions that could exacerbate E&L issues, such as high temperature and prolonged contact times.
- Implement risk management strategies to identify and mitigate potential E&L issues in early development phase.

❖ Approach for Assessments

- **Screening:**
  - Preliminary Screening: Conduct initial screenings to identify potential extractables from materials used in Packaging and Manufacturing.
  - Utilize hyphenated techniques such as Headspace-GC/MS, Direct Injection/GC/MS, LC/MS, ICP/MS and ICP/OES.
- **Quantification and Identification:**
  - Perform comprehensive analysis to identify and quantify leachables in the drug product. This often involves testing under accelerated conditions to simulate long-term storage.
- **Stability Studies:**
  - Conduct stability studies at multiple time-points to monitor the impact of E&L over time to understand the impact of leachables on stability and efficacy.
- **Regulatory Compliance:**
  - Follow regulatory guidelines from organizations such as FDA, EMA, ICH regarding testing regimens, documentations, risk assessments, and any corrective actions taken.

❖ Qualification Strategies

- **Material Qualification:** Verify that manufacturers & suppliers provide materials that meet E&L requirements, Conduct supplier audits if necessary.
- **Packaging Qualification:** Perform extractable studies on packaging materials with simulated solvents to evaluate potential leachables.
- **Material Specifications:** Define and document specifications for materials including acceptable levels of extractables and leachables.
- **Process Controls:** Maintain clean room standards and proper handling of materials to minimize the risk contamination (e.g. grease, dust etc.) which can lead to false positive results.
- **Storage Controls:** Regularly monitor environmental conditions such as temperature and humidity where materials and drug products are stored and handled

Regulatory Compliance

- **Adhere to Guidelines:** Follow applicable regulatory guidelines and standards for E&L testing and management such as those issued by FDA, PQRI, ICH etc. Follow all the internal SOP's pertaining to handling of testing and documentations.
- **Submission Documentation:** Provide detailed E&L information in regulatory submissions including stability testing results, risk assessments, mitigation strategies.
- **Timely Submission:** Provide timely submission of agency's queries with appropriate data, supplementary information and/or justifications.
- **Training and Awareness:** Proper training and awareness of E&L issues and their risk in the delaying of product approvals to all the personals involved throughout the life-cycle management.

References

- *FDA guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics.*
- *Leachable and Extractable Handbook: Edited by Douglas J. Ball, Daniel L. Norwood, Cheryl L. M. Stults, Lee M. Nagao.*
- *USP general chapters: <1663>, <1664>, <661.2>, <87>, <88>.*
- *The regulatory Environment for Extractables and Leachables: "Low-risk" Dosage Forms (Cristina Manolescu, Scott Pennino, Daniel L. Norwoood, Ph.D.)*

Acknowledgement

- *Dr. Srinivas Kone Chief Scientific Officer, R&D Generics*
- *Dr. Balasbramaniyam Lingam, Associate Director, Analytical R&D*
- *Maryll Toufanian SVP, Regulatory Strategy and Government Affairs*
- *Janie Gwinn , Vice President, Regulatory Affairs*

Thank You

Priti Jagani

pritij@amneal.com


amneal