Leachable Studies and Routine Extractables Testing

PQRI Workshop on Leachables and Extractables
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Best Practices

- Recommendations
- Application
- Goals
- Method Development
- Special Case Compounds
- Correlation
- Validation
- Specifications and Acceptance Criteria

PQRI Recommendations

- Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing and Controls Documentation
- Nasal Spray and Inhalation Solutions Suspensions, and Spray Drug Products Chemistry Manufacturing and Controls Documentation

Summary of Recommendations

- Leachable Evaluations Should be Based on Methods/Techniques Used in Controlled Extraction Studies
- Analytical Methods Should be Guided by the AET
- Comprehensive Correlation May Obviate the Need for Routine Implementation of Drug Product Leachable Specifications and Acceptance Criteria
- Acceptance Criteria for Leachables Should Apply Over the Proposed Shelf-Life and Include Quantitative Limits for Known and New/Unspecified Leachables

Summary of Recommendations

- Extractable Testing Should be Based on Methods/Techniques Used in Controlled Extraction Studies
- Specifications and Acceptance Criteria Should be Established for all OINDP Critical Components Prior to Drug Product Manufacture
- Leachable and Extractable Methods Should be Validated According to ICH Validation Characteristics
- Special Case Compounds Require Evaluation by Specific Analytical Techniques and Defined Thresholds
- Safety Consultation Should be Incorporated in the Early Stages of a Leachable Study

Leachable Study

- A Leachable Study is a laboratory investigation into the qualitative and quantitative nature of a particular OINDP leachables profile(s) over the proposed shelf-life of the product.

Application

- Comprehensive Leachable Studies
  - MDI
  - Nasal Spray
  - Inhalation Spray
- Stability or “One-Time” Leachable Studies
  - DPI
    - If potential leachables have safety concerns
- Leachable Study Not Required
  - Inhalation Solution
    - Aqueous Drug Product and no Extractables at AET
    - No Evidence of Migration through Container

Leachable Study Goals

- To help establish an extractables/leachables correlation.
- To understand the trends in drug product leachables levels over the shelf-life of the product.
- To determine maximum leachables levels up to the proposed end of shelf-life of the product.
- To support a comprehensive safety evaluation of drug product leachables.
- To establish drug product leachables specifications and acceptance criteria, should these be required.

Leachable Methods

- Based on Analytical Techniques used in the Controlled Extraction Study
- Optimize Measurement and Recovery of Potential Leachables
- Guided by the AET
  - "how low to go"
- Must be Fully Validated According to Accepted Parameters and Criteria

Special Case Leachables

- Lower Thresholds
- Dedicated Methods
  - Optimized
  - Validated
- Appropriate Specifications
- Qualification
- Risk Assessment

Polynuclear Aromatic Hydrocarbons

- Naphthalene
- Acenaphthylene
- Fluorene
- Phenanthrene
- Fluoranthene
- Anthracene
- Pyrene
- Benzo(a)anthracene
- Chrysene
- Benzo(b)fluoranthene
- Benzo(k)fluoranthene
- Indeno(1,2,3-cd)pyrene
- Benzo(a)pyrene
- Benzo(e)pyrene
- Dibenzo(ah)anthracene
- Benzo(ghi)perylene

Nitrosamines

- N-nitrosodimethylamine
- N-nitrosodiethylamine
- N-nitrosodi-n-butylamine
- N-nitrosopiperidine
- N-nitrosopyrrolidine
- N-nitrosomorpholine

Leachable Method Development

- Recovery of Leachables
  - Type of Drug Product
  - Spiking Studies
- Linear Dynamic Range
  - Based on Levels of Potential Leachables
- Limit of Quantitation
  - Consideration of AET

Validation of Leachable Methods

- Validated according to ICH Guidelines
  - Characteristics of a quantitative impurity test
    - Accuracy, Precision, Specificity, LOQ, Linearity and Range
  - Validation Parameter Acceptance Criteria
  - Characteristics of Limit Tests
    - Specificity and LOD

L&E Correlation

- Comprehensive
  - Qualitative
  - Quantitative
  - Multiple Batches of Drug Product
  - Multiple Lots of Critical Container Closure Components
  - All Product Orientations
  - Accelerated Storage Conditions
  - Full Shelf-Life
- End of Shelf-Life Profiles
  - Leachable less than or equal to extractables

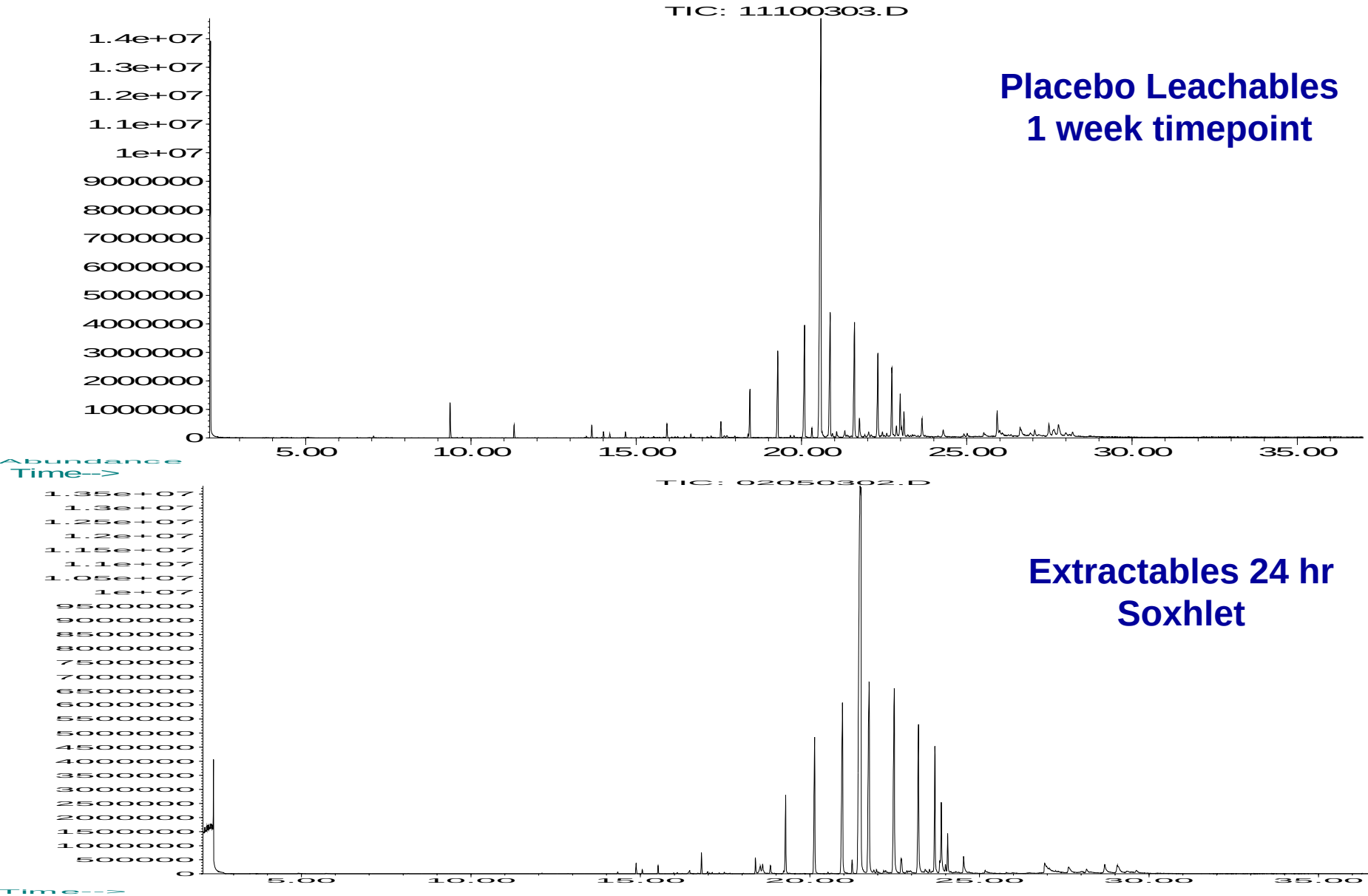
Qualitative Correlation

- A *qualitative correlation* can be established if all compounds detected in validated leachables studies can be linked qualitatively either directly or indirectly to an extractable identified in comprehensive Controlled Extraction Studies or during Routine Extractables Testing.

Quantitative Correlation

- A *quantitative correlation* between a leachable and an extractable can be made if the level of the leachable is demonstrated to be consistently less than that of the extractable(s) to which it is qualitatively correlated.

MDI Leachables/Extractables Profile Comparison



Placebo Leachables
1 week timepoint

Extractables 24 hr
Soxhlet

Leachable Trending

- Qualitative and Quantitative Profiles
  - Leachable Profiles of at Least 3 Drug Product Registration Batches
  - Extractable Profiles of Container /Closure Components used in the Registration Batches
- Consistency of Correlation
  - Multiple Extractables and Leachable Profiles
- Profile Evaluation
  - Suitability of Extractable Leachable Methods
    - Variability in Component Composition/Manufacturing
    - Drug Product Formulation Changes
    - Drug Product Reaction Products

Leachable Specifications

- Quantitative limits for known drug product leachables monitored during registration stability studies
- A Quantitative Limit for ‘new” or unspecified” leachable not detected or monitored during product registration stability studies.

Quantitative Acceptance Criteria

- Based on Leachable Levels
- Trends of Leachable Levels Over Time and Across Various Storage Conditions and Orientations During Product Registration Stability Studies
- Appropriate Statistical Analysis

Leachable Control
"IF Tested Will Comply"

- Assume Appropriate Correlation
  - Adequate Information from Critical Component Suppliers with an Adequate Evaluation of this Information
  - Understanding of Critical Component Fabrication and Manufacturing Processes
  - Validated Leachable Methods and Comprehensive Leachable Study
  - Validated Routine Extractable Testing and Adequate Data Base of Critical Component Extractable Profiles
  - Appropriate Specifications and Acceptance Criteria for Extractables from Critical Components

Establishment and Implementation of Leachable Specifications and Acceptance Criteria for any OINDP is Regulatory Policy and Outside the Scope of the Working Group's Consideration

Routine Extractables Testing

- Routine Extractables Testing is the process by which OINDP container closure system critical control components are qualitatively and quantitatively profiled for extractables, either for purposes of establishing extractables acceptance criteria or release according to already established acceptance criteria.

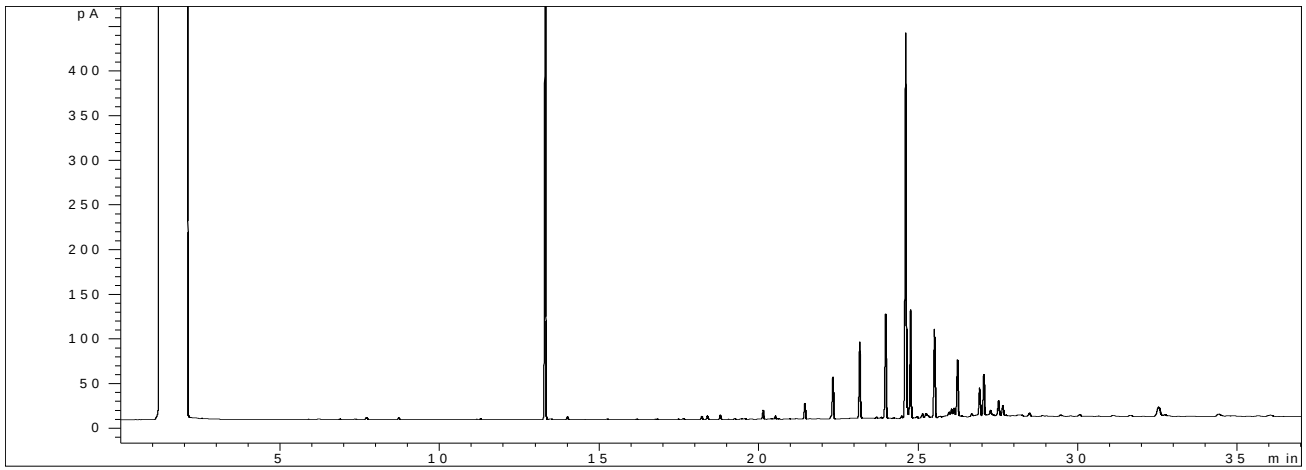
Extractable Testing Goals

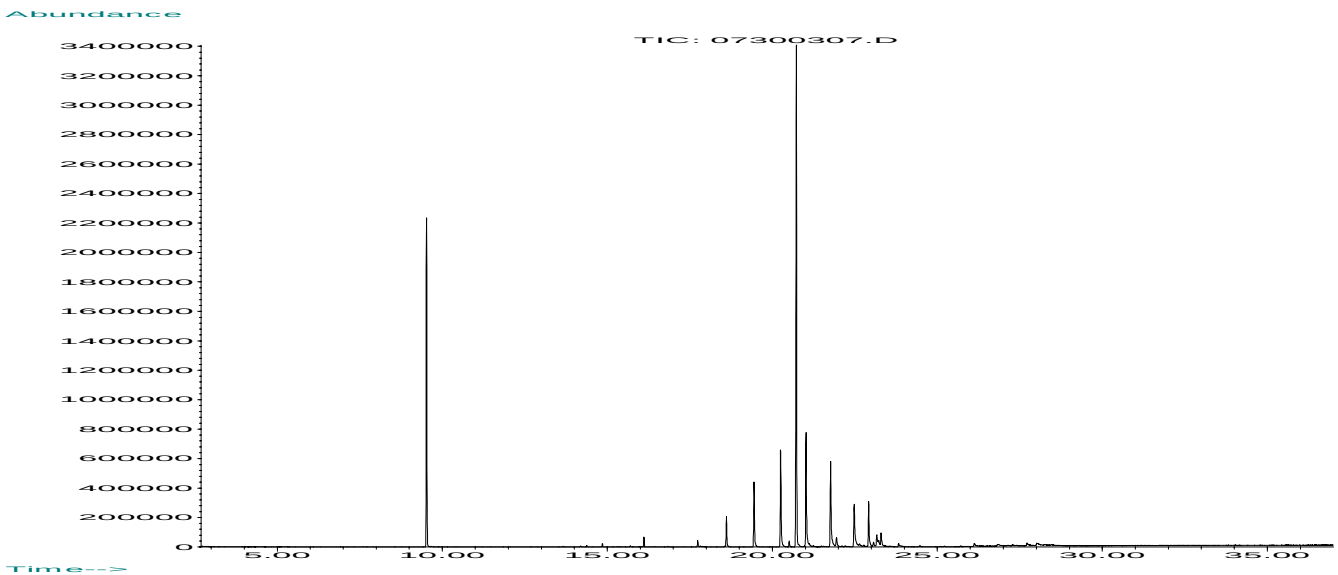
- To establish extractables specifications and acceptance criteria for OINDP critical container closure system components.
- To help ensure that the leachable profile in the drug product is maintained within appropriate limits.
- To release OINDP container closure system critical components according to established specifications and acceptance criteria, which are designed to:
  - Control the identities and levels of extractables identified during Controlled Extraction Studies;
  - Detect “unspecified” extractables which could be present as the result of component ingredient changes, manufacturing changes, external contamination, or other causes

Routine Extractable Methods

- Based on Controlled Extraction Studies
- Special Case Compounds Evaluated by Specific Analytical Techniques
- Detect and Quantify All Extractables Characterized in Controlled Extraction Studies
- Identify Unspecified Extractables which could Result from Unanticipated Changes in the Critical Component Ingredients or External Contamination
- Optimized to be Rugged and Robust to have Ability to Transfer to Quality Control and Manufacturing Environments
- Fully Validated According to Accepted Parameters and Criteria

Extractables Profile Sulfur-Cured Elastomer





Extractable Method Development

- Recovery of Extractables
  - Extraction Procedure
    - Asymptotic Levels
    - Spiking Studies
- Linear dynamic Range
  - Based on Levels of Potential Leachables
- Limit of Quantitation
  - Consideration of AET

Validation of Extractable Methods

- Validated According to ICH Guidelines
  - Characteristics of a Quantitative Impurity Test
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  - Charactertics of Limit Tests
    - Specificity and LOD

Routine Extractable Testing

- Performed on Critical Control Components
- Acquire Data Base of Identified, Unspecified and Special Case Compounds
- Develop Specifications and Acceptance Criteria
- Provide Data to Toxicologists to Assess for Potential Safety Concerns
- Control of Critical Components for Release
- Monitor for Level of Potential Leachables

Extractable Specifications

- Critical components should be released to drug product manufacture based on defined specification and acceptance criteria
- Specifications depend on the type of critical component and adequacy of leachable and extractable correlation

Extractables Acceptance Criteria

- Confirmation of Extractable Identified in Controlled Extraction Studies
- Quantitative Limits for Extractables Identified in Controlled Extraction Studies
- A Quantitative Limit for New or Unspecified Extractables Not Detected during Controlled Extraction Studies.

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