Chemistry Considerations for a Pre-Filled Syringe Case Study

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Outline

Goal – To provide a chemistry assessment for a pre-filled syringe case study

- Material evaluation
- Design of a controlled extractables study based on the PODP recommendations
- Generation of E&L mock data
- Data evaluation

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Pre-Filled Syringe Components

Case Study

The focus will be on the barrel and stopper.

Piston
PP

Drug Product
Very Complex Formulation

Barrel
PP

Stopper
Siliconized Halobutyl Elastomer

Needle

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PFS Components – Materials (1)

What do we know?

- Polymers
  - Residual Solvents, Monomers, and Oligomers
  - Primary Antioxidants (Hindered Phenols)
  - Secondary Antioxidants (Organic Phosphites)
  - Lubricants
  - Processing Aids
  - Fillers
  - Curing Agents
  - Plasticizers

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PFS Components – Materials (2)

- Acid Scavengers
- Colorants
- Antimicrobials
- Other Specialty Additives
  - Expected and Unexpected
- Additive Transformation and Degradation Products

- All of these chemicals have the potential to migrate from the CCS components and into the drug product

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Principles Governing Extraction

Migration - the transport of chemicals from polymer to the surrounding environment.

Two Physical Principles determine Total Migration:

- Thermodynamics – the *extent* to which material will migrate.
  - Partitioning of chemicals from plastics: solubility
  - Describes potential to migrate
- Kinetics – the *rate* at which chemicals will migrate.
  - Most important!
  - Diffusion coefficients are *usually* small, so diffusion time is long.
  - Chemical with favorable thermodynamic migration potential may migrate slowly due to slow kinetics.

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Diffusion

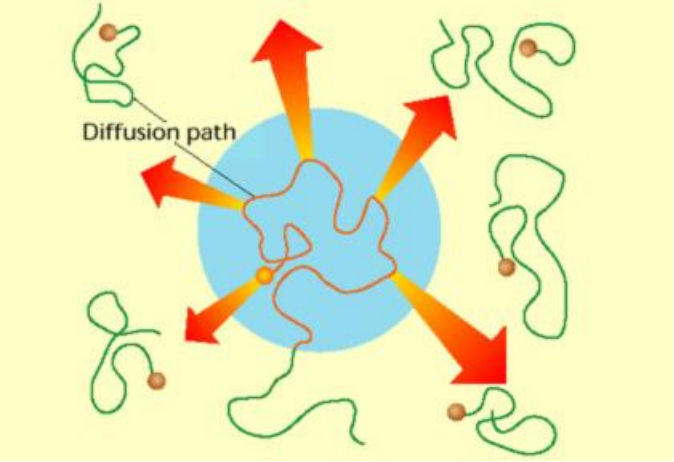
Migration of materials is proportional to the square root of time.

$$X = \sqrt{\frac{2kTt}{6\pi\eta r}}$$

- X – Mean Square Displacement
- t – Time
- k – Boltzmann constant
- T – Temperature
- η – viscosity
- *r* - radius

What factors influence extractions?

- Time
- Solvent
- Temperature
- Physical properties of the polymer



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Selecting Solvents for Extraction Testing

Consider…

- **Drug Product Formulation and Active ingredients**
  - **Extractive power of formulation**
  - **Acidity or Alkalinity of formulation**
- **Processing and Storage - Time and Temperature**
  - **How long will the formulation be exposed to the CCS component**
  - **End use temperatures**
- **Other Issues**
  - **Freeze / Thaw Cycles**
  - **Sterilization**
  - **Can affect the morphology of the polymer and subsequently the diffusion rate**
- Solvents that significantly swell a polymer are “aggressive”

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Case Study – Drug Product (1)

- Drug Product - Complex Formulation
  - Active Ingredient: Large Organic Molecule
  - Coarse Dispersion
    - Tonicity, Suspension, Viscosity, and Wetting Agents
    - 2 Antimicrobial Preservatives
    - Buffers
    - All Excipients, Except the Tonicity Agent and Buffers, are Organic

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Case Study – Drug Product (2)

What do we know?

- Very Aggressive Solvating Properties for a Parenteral
- Possible surfactants
  - Could swell the polymer
  - Increase the overall concentration of possible leachables
- High salt content
  - Reduce Migration of Organics “Salting In”
  - Increase Migration of Inorganics
    - Residual Catalysts, Fillers, Acid Scavengers, etc.
- Irradiation Prior to Filling
  - Could result in increased migration due to a change in polymer morphology
  - Possible presence of a violet / blue pigment to mask discoloration of the polymer

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Controlled Extractables Study

- Aqueous - pH 2.5
- Aqueous - pH 9.5
- Mixed – IPA / Water
- Organic – IPA
- Organic – Hexane

Select All

- Technique
  - Aqueous: Sonication and Sealed Vessel
  - Mixed: Reflux
  - Organic: Soxhlet and Reflux

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Selecting Analytical Methods

Analyzing the Extracts

- **Volatile Organic Compounds**
  - **Head Space, SPME, Thermal Desorption GC/MS**
- **Semi-Volatile Organic Compounds**
  - **GC/MS, GC/FID**
- **Non-Volatile**
  - **HPLC/UV, HPLC/MS**
- **Trace Metals**
  - **ICP/MS**
- Focus on Semi-Volatile and Non-Volatile for this Case Study

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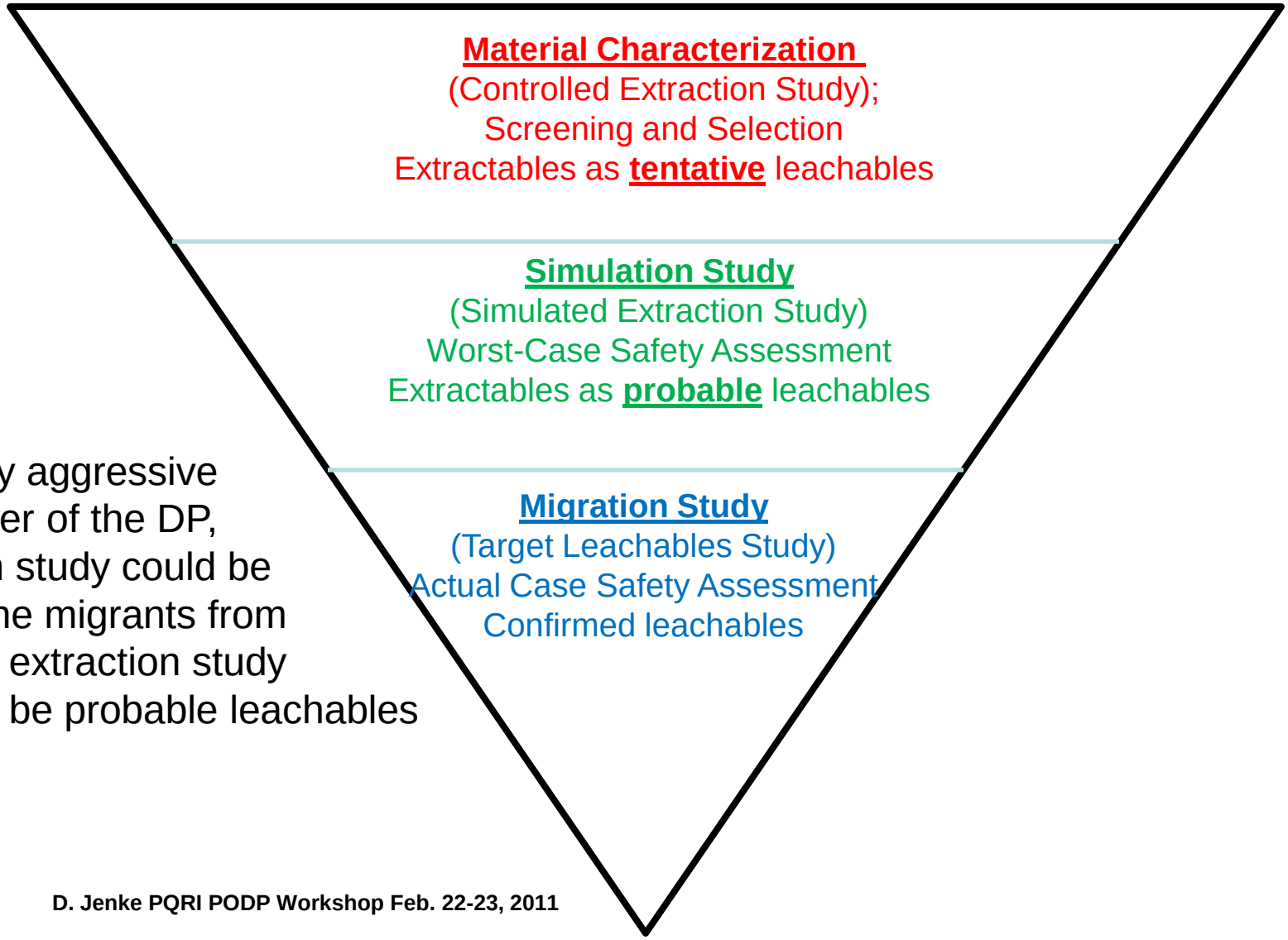
Consider the Safety Assessment Triad



Given the very aggressive solvating power of the DP, the simulation study could be omitted and the migrants from the controlled extraction study considered to be probable leachables

Hexane Extractables “Mock” Data

Organic Extractables	Component
Tris(2,4-ditert-butylphenyl) phosphite	PP - Barrel
Pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate)	PP - Barrel
Erucamide	PP - Barrel
3-(3’,5’-di-t-Butyl-1’-hydroxy-4’-oxacyclohexa-2’,5’-dienyl) propanoic acid	PP - Barrel
Unknown A	PP - Barrel
Unknown B	PP - Barrel
Benzo(a)pyrene	Rubber - Stopper
Docosane	Rubber - Stopper
Hexadecanoic acid	Rubber - Stopper
2,6-Di-tert-butyl-methylphenol	Rubber - Stopper
Octadecane	Rubber - Stopper
2-Bromo-4-(1,1-dimethyl-propyl)-phenol	Rubber - Stopper
Octamethylcyclotetrasiloxane	Rubber Stopper
Hexamethylcyclotrisiloxane	Rubber - Stopper
Unknown C	Rubber - Stopper
Unknown D	Rubber - Stopper
Unknown E	Rubber - Stopper

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Dealing with the Unknowns

- Determine the approximate concentration using a suitable internal standard and compare to the AET
- Compare the solvent used for the extraction to the drug product. If the migrant is a “Tentative Leachable” of low concentration, then it could be targeted in the Simulation Study
- If the unknown was detected in the Simulation Study and it is above the AET, it can be considered as a probable leachable and more structural information is required.
- Provide all the chemical data to a toxicologist for a formal safety assessment.

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IPAC-RS Proposed Identification Categories

Identification Categories for Structure Elucidation of Extractables and Leachables by GC/MS and LC/MS	
Category	**Identification Data**
A	Mass spectrometric fragmentation behavior
B	Confirmation of molecular weight
C	Confirmation of elemental composition
D	Mass spectrum matches automated library or literature spectrum
E	Mass spectrum and chromatographic retention index match authentic specimen

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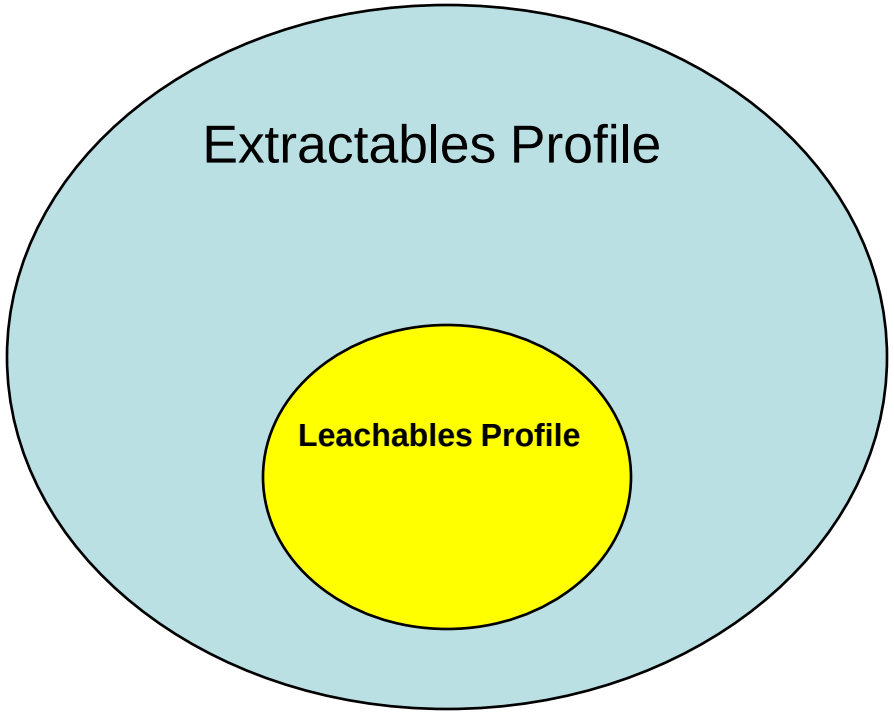
Leachables Testing – Correlation (1)



In theory, the leachables profile should be a subset of the extractables profile

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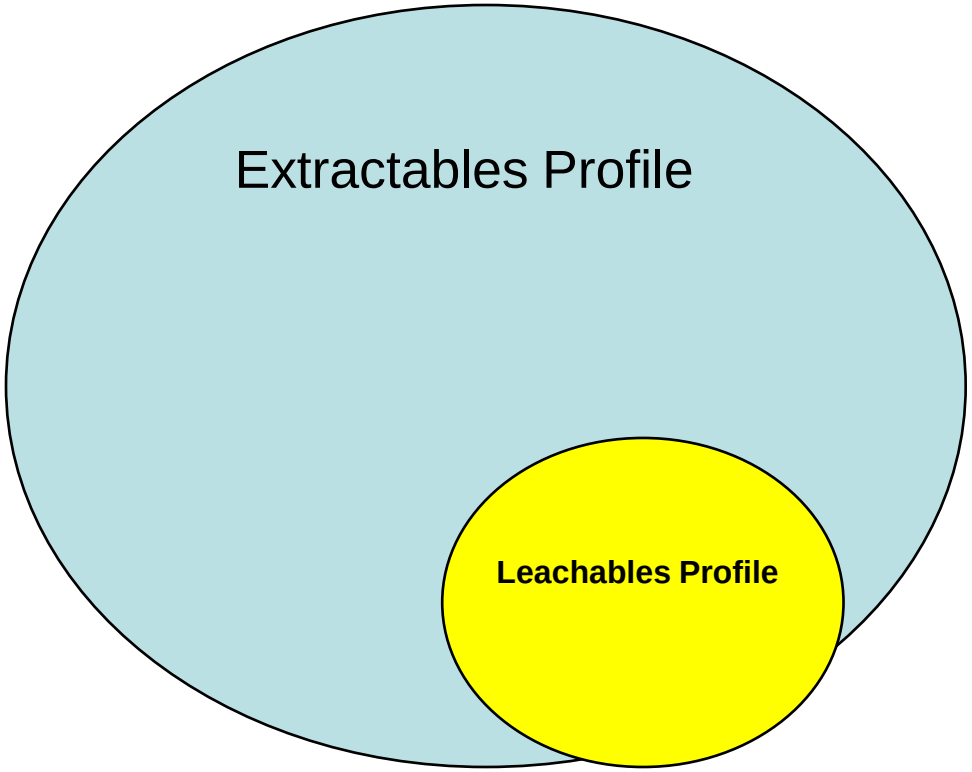
Leachables Testing – Correlation (2)



In reality, new components can be present if the leachable reacts with the drug product.

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Leachables Testing – Correlation (3)

- **Establish correlation between Leachables and Extractables**
  - **Qualitative**
  - **Quantitative**
- **Direct or Indirect Correlation**
  - **Component identified in extraction study**
  - **Component linked to extraction study**
  - **Component a reaction with drug product**

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Leachables Testing – Correlation (4)

- Look for trends
- Diffusion is a time based phenomenon
- Leachables should increase over time
  - Unless an equilibrium is reached
  - React or degrade over time
- New leachables could potentially appear late in the study
- Simulation Studies can often avoid surprises

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“Mock” Leachables Data

Leachable	Concentration (µg/device)
2,4-Bis(1,1-dimethyethyl)-phenol, 1,1’,1”-phosphate	0.09
2,4 Di t-butyl phenol	**1.3**
Erucamide	**1.5**
3-(3’,5’-di-t-Butyl-1’-hydroxy-4’-oxacyclohexa-2’,5’-dienyl) propanoic acid	0.05
Benzo(a)pyrene	0.03
Octadecane	0.06
2-Bromo-4-(1,1-dimethyl-propyl)-phenol	0.09
Hexamethylcyclotrisiloxane	0.08
Unknown A	**1.1**
Unknown C	0.05
Unknown E	0.07

Calculation of AET

Assumes SCT of 0.15 µg/day and 1 dose per day

AET = 0.15 µg/day 1 doses/day x 1 doses/device = 0.15 µg/device

- Not Detected in CES

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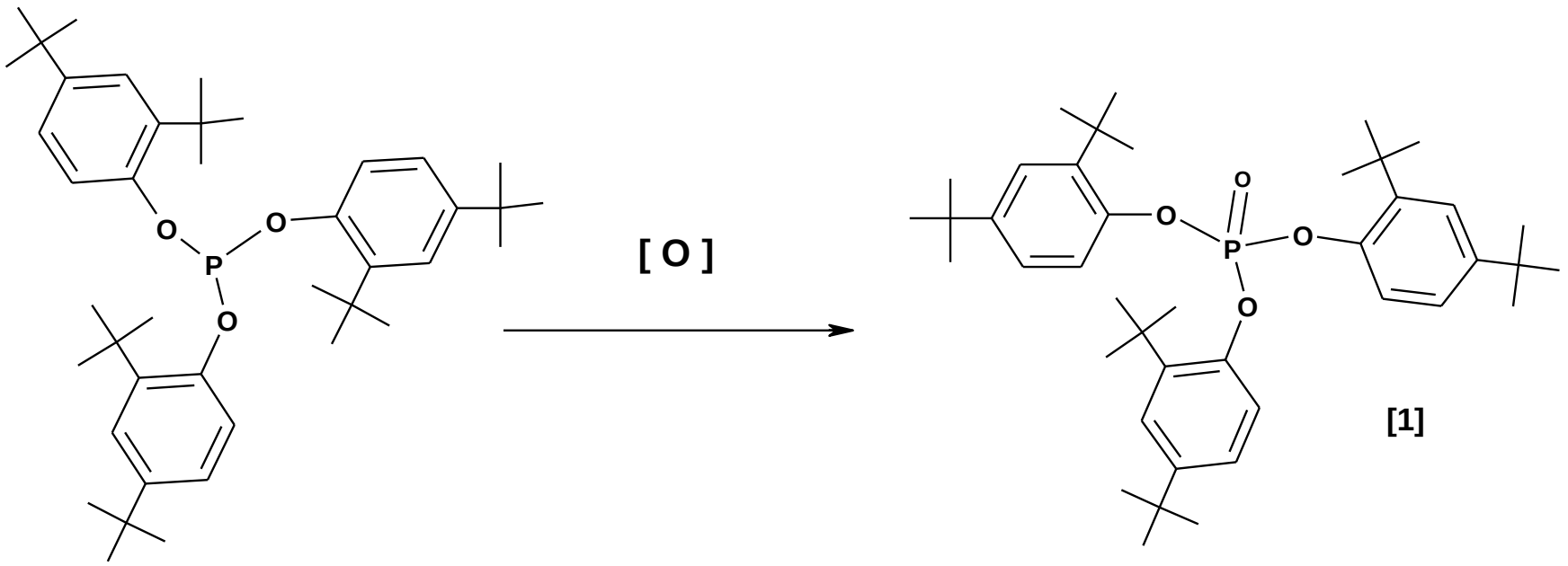
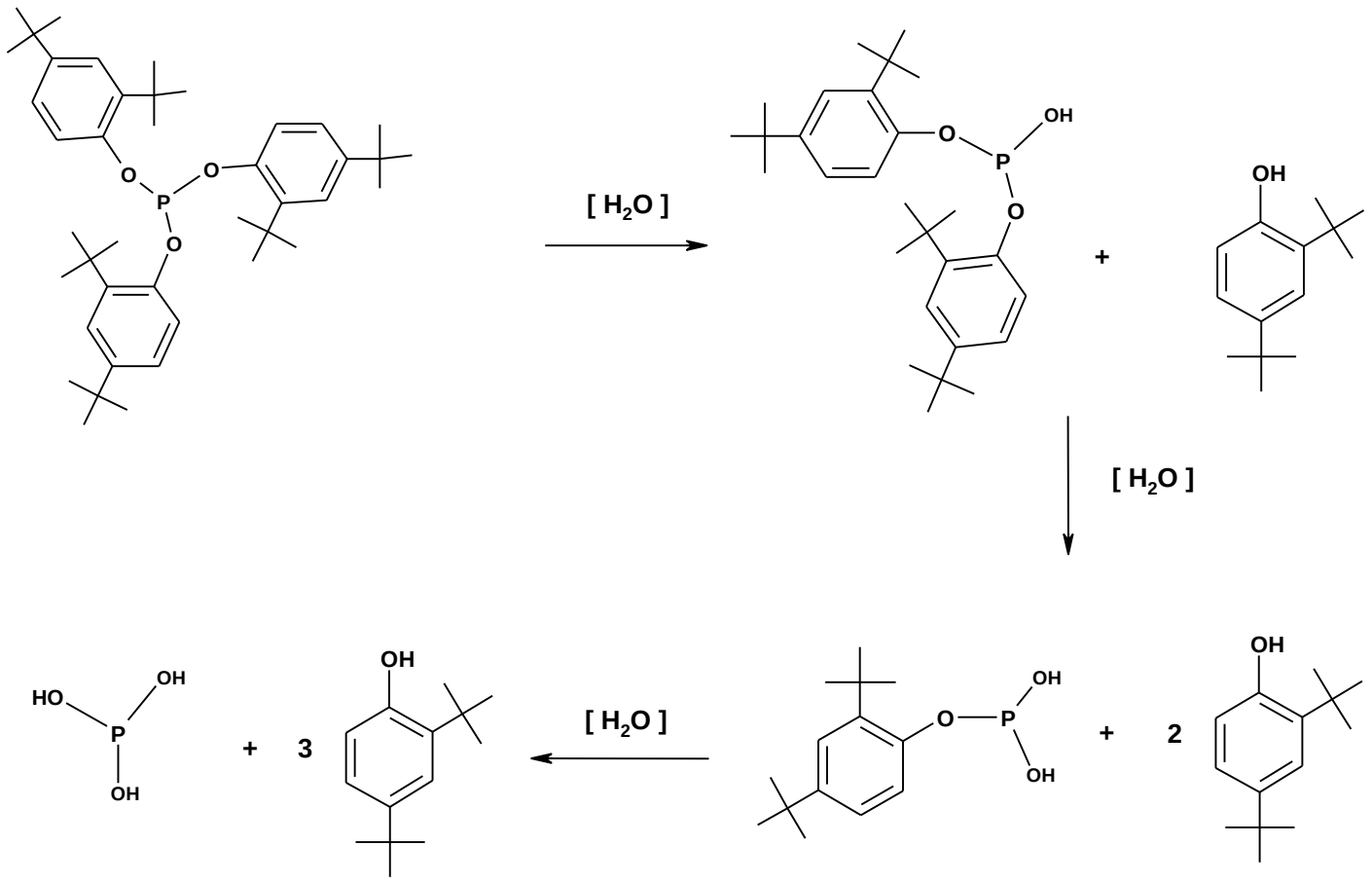
Phosphites – Transformation Chemistry



Phosphites – Degradation Chemistry



Chemistry Summary

- A material evaluation was performed on the pre-filled syringe components and possible target extractables were identified.
- A controlled extractables study was designed taking into account the materials used to construct the barrel and stopper as well as the solvating power of the drug product.
- Analysis of the E&L data revealed that two leachables were not detected in the extractables profile, but their origin was determined.
- Three leachables were present at concentrations greater than the AET.
- All E&L data was submitted for a toxicological assessment.

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