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Extractable and Leachable Challenges...

From a generic injectable drug development perspective

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PROGRESS

Disclaimer

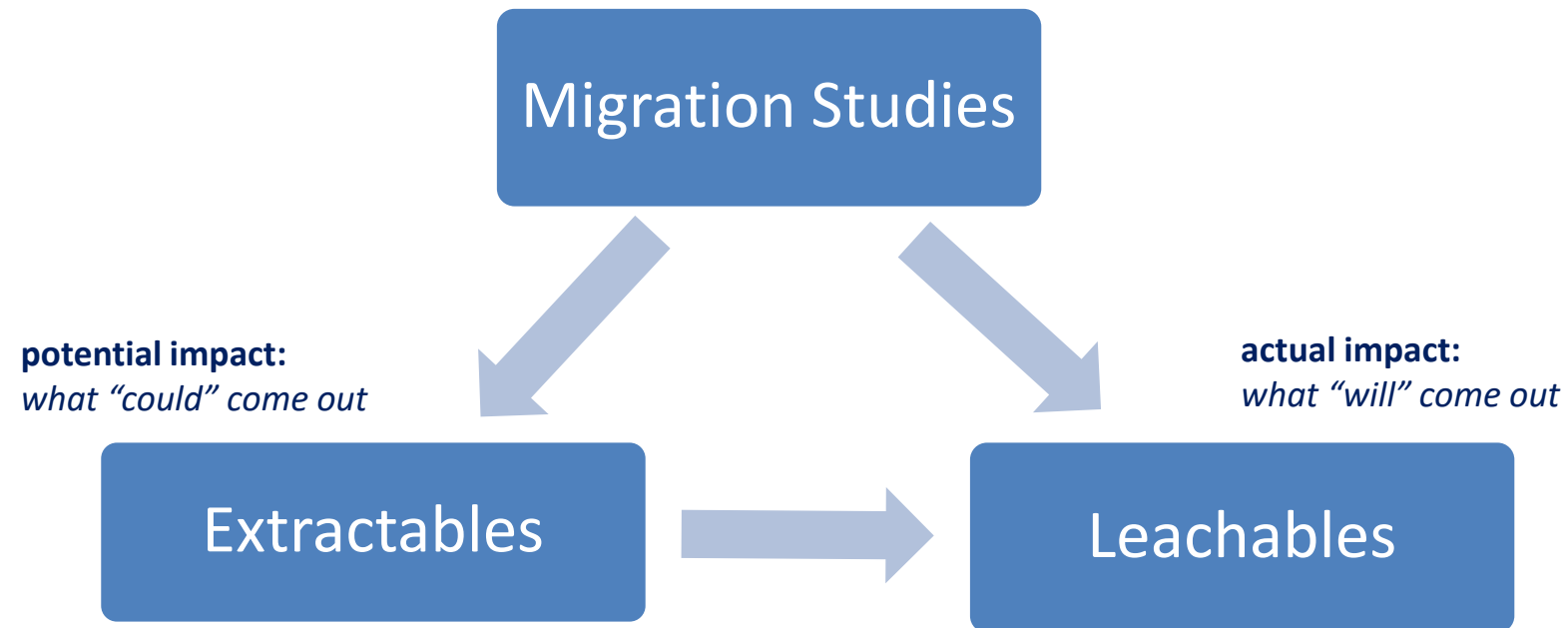
- This presentation contains a summary of the opinion and perspective from industry representatives on the topic of Extractable and Leachable Challenges.
- This presentation does not necessarily represent the opinion of the presenter nor its employers.

Generic Small Molecule Perspective

1. Landscape of E/L studies in injectable product development
 - Manufacturing components with bulk solution
 - Finished Products
 - Plastic containers with label-ink
 - Lyo products and recon solutions
 - Liquid products in glass vials or PFS
2. Challenges and Strategies
 - Challenges in workload, cost and timeline
 - Consolidation of choices and centralized extractable database
 - Simulation Study for waiving stability sample monitoring
 - Bracketing of stability samples for leachable testing



Overview of Common Terminology



- Chemical entities that can be “pulled” from a pharmaceutical packaging/delivery system
- Needed for all container closure components with direct product contact, including label (with ink and adhesives) and secondary packaging (for plastic containers)
- **Not in drug product**

- Chemical entities that can “migrate” into an associated drug product formulation
- Typically a subset of extractables or are derived from extractables.
- Evaluated over drug product shelf-life
- **Performed in product**– can be performed during stability batch testing

Manufacturing Components

- Examples of Component Types
- Qualification Approaches
- Recent FDA Deficiency Examples

Component Types

Components possibly to contact with bulk solution

- Tank: Stainless steel, Glass-lined tanks
- Tubings: Tygon; Silicone; Cflex; Cflex Ultra; Pharmed; PFA (teflon); Silicone Pharma 50; Stainless steel
- Diaphragms: Red TL silicone; clear TL silicone
- Filters: PVDF; PES; Nylon66
- Filler: Stainless steel, ceramic



Qualification Approaches

- COMPATIBILITY STUDIES \neq EXTRACTABLE/LEACHABLE STUDIES
- Compatibility studies often only look at physicochemical properties of DP when in contact with manufacturing components... don't always include E/L assessment.
- First place to go is to vendor! Use extractable report to justify no need for leachable testing
- Justify leachable not required due to limited product contact time
- Justify that testing extractables under prolonged stagnant contact time represents “worst-case” as compared to the transient exposure time the product has with components during routine manufacturing conditions
- Institute a total contact time (if necessary) for routine manufacturing
- If leachables were present from the components, this would be detected in the finished product leachable samples as the method would be capable of detecting any peaks.

Example Deficiency Questions – Small Molecule Aqueous Solutions

FDA Deficiency Question: “During the manufacturing process, the drug product exists as a solution and thus has the potential for leachables and extractables from materials. Other than the extractable studies for the proposed filters, extractable/leachables data was not provided for the processing components (e.g., stainless steel vessel, jacketed vessel, silicon tubing) used in the proposed manufacturing process. Please provide this information to demonstrate compatibility between the equipment contact materials and the bulk solution.”

Response:

- **Consider product properties versus stainless steel**
- **Consider available vendor data**
- **Consider actual contact times**
- **Run studies if still deemed necessary**

Co-solvent Bulk Solutions or Drug Product + Diluent

FDA Deficiency Question: Please provide additional information to demonstrate that the hold and flush strategies as employed during the manufacturing of the diluent are adequate to mitigate the risk of leachables or to reduce them to levels which are considered acceptable. We note that the control strategies suggested for the bulk solution of drug product are based on compatibility studies; however such compatibility studies as described in the pharmaceutical development report did not discuss potential leachables. Explain why such control strategies applied for Drug Product (DP) manufacturing is adequate and why similar holding and flushing strategies as applied for diluent are not warranted.

Response:

- **Consider product properties**
- **Consider available vendor data**
- **Consider actual contact times**
- **Run studies if still deemed necessary**

Finished Product



Glass Vials



Flexible Plastic PreMix bags



Pre-Filled Syringe or AutoInjectors

Special Considerations – Small Molecule

- **GLASS**

- If glass is coated (with silicone), a study may need to look specifically for extractables that are coming from coating. Needs to be determined based on the drug product formulation and the potential for it to interact with the coating.
- Labeling components typically do **NOT** need to be evaluated

- **PLASTIC:**

- Are deemed semi-permeable so also need to consider the secondary packaging as well as port system components (for bags and pre-filled syringes)
- It is critical to evaluate all labeling components in the extractable study, inclusive of inks, glue, adhesives, etc.

- **LYO PRODUCTS:**

- Typically are not performing leachable studies on lyo products
- May need to perform leachable studies on reconstituted solution if **recon stability times exceed 7 days based on PI (have received deficiency questions from FDA even for shorter recon times)**

Basic Extractable Screening Study Design

1. What to Study:

- Obtain information from vendor of packaging components with direct product contact (includes inks and label adhesives)

2. Selection of Test Method: Based on proposed drug product formulation

- HPLC
- GC/MS
- ICP

3. Baseline Extractable Screening Study:

- Select a range of representative test solutions in order to develop product “families” that can be used to cover different drug product vehicles (aqueous products, non-aqueous products (i.e. oil based, emulsions), etc.)
 - pH adjusted water (pH 2.0 and pH 10.0)
 - Alcohol mixture (15% ethanol / water or IPA)
- Subject the test solutions to “worse-case” parameters (i.e. processed under high sterilization temps)
- Determine extraction time based on proposed drug product formulation
- Performed on lab batches filled in the final container closure system- primary container, labels with ink (for plastic), and secondary packaging-if needed

Deficiency Question Examples

- Recent FDA deficiency questions received:
 - Have asked that extractable studies performed on plastic bags be performed on larger range of solutions, including pH-adjusted water and alcohol
 - Have asked to lengthen the extraction time to > 1 hour
 - Have asked questions specific to potential extractables coming from labels, including ink and adhesives – critical to get all available information from relative supplier
 - Recent deficiency question received on Premix Flexible Container:

Ink Qualification Studies for Plastic Containers

- Qualification of Inks for Primary Container Label:
 - Information on ink and label adhesive must be obtained from relevant suppliers
 - One-time baseline extractable evaluation of label + new ink must be performed on multiple solvents (not just water)
 - pH adjusted water at pH 2.0 and pH 10.0
 - Alcohol (50:50 ethanol / water mixture)
 - Additional organic solvent as determined by drug product vehicle
 - A new one-time baseline extractable study should be performed on every new ink
 - Could consider development of a “multi-color” label to serve as worse-case test condition

Example of Lyo Product

Limited to no direct stopper contact

- E&L studies were not typically performed on lyo products due to short contact time (even after reconstitution)
- Lyophilized products: no direct contact (no extracting force) with stoppers.

Recon Solution

- Leachable study required for Label-claimed prolonged in-use time (>7 days)
- If multiple recon solutions in PI, may need to perform a leachable study using different recon solutions

Example FDA Deficiency: “Submit extractable & leachable studies for proposed stopper.”

Label Claim: Recommended duration for treatment is **5 – 14 days**. Once reconstituted, product may be stored at room temperature(not to exceed 25°C/77°F) for up **to 24 hours** (up to 6 hours in the vial and the remaining time in the intravenous bag).

KEY TAKE-AWAY: Even with limited contact time after recon (24 hours!!), FDA still required extractable AND leachable evaluation. An “in-use” leachable study was performed. A representative sample of drug product was reconstituted with each diluent and stored inverted at an elevated temperature of 40 °C for 24 hours for assessment of leachables.

Leachables

- Leachables Study Design
- Example Deficiency Questions



Leachables Study Design

1. What to Study:

- Based on extractable test results, determine what chemical entities need to be evaluated over product shelf-life

2. Method Development/Verification:

- Standard “extractable” methods may not be appropriate due to interference with API. Product specific leachable method may be required.
- The leachable method validation should meet all appropriate ICH validation parameters

3. Study Design:

- Studies are product specific (evaluate proposed commercial product formulation)
- Studies must be performed using the proposed commercial product presentation:
 - Including label, inks, and aluminum overwraps for plastic containers
 - For glass containers, labels are not required.
- Are typically performed using samples from the ICH stability batch manufacture and evaluated during stability testing over product shelf-life

Proposed Study Requirements

- Leachable testing should be performed on samples from **all** exhibit batches
- For glass or plastic vials, perform leachable testing on inverted samples only
- A toxicological evaluation must be performed on any leachables seen during stability batch testing
 - Justification needs to be provided based on outcome of literature studies and PPD
- Proposed stability test requirements:

Storage Conditions	Initial	3	6	9	12	18	24	36
Long-term	X	X	X		X	X	X	X
Accelerated	X	X	X					

NOTE: Additional time points may be required based on drug product formulation, proposed dosage form, and route of administration



Example Deficiency Questions



Case Study: Flexible Plastic Bag

- Recent FDA deficiency question received:
 - Leachables were not performed on all stability batches
 - Leachables were evaluated at minimal time-points
 - Due to the above issues, FDA has requested that testing for leachables be added to both release and shelf-life product specifications
 - No toxicological evaluation was performed on leachables. FDA has asked for literature to support that leachables have no potential toxicological effects.
 - Excerpt from recent FDA deficiency question:

Leachable data **on one batch at six months** is insufficient to justify the exclusion of leachable testing in the drug product specification. Include monitoring leachable levels on stability until end of shelf-life for the three ongoing registration stability batches, and for each annual batch as part of post-approval stability protocol. Test the leachable levels in the three registration stability batches and the batch for which the six month leachable data were provided. If data from a sufficient number of commercial scale batches show negligible levels of leachables or data are generated to provide accurate PDE for each leachable you may propose to eliminate the leachable test.

Case Study: Pre-Filled Syringe Product

- Please explain why some of the detected leachables were not detected in the extractable study
 - *Extractable studies were performed by different lab with different methods than lab used for leachable studies. As a result, some of the detected leachables from the migration study were not detected in the original extractable study*
- Please clarify how the migration study was initiated in the absence of fully validated methods.
 - *Methods were not validated until after the T=3 month stability pull date*
- We are unable to locate the extractable and leachable testing to qualify the use of the elastomeric tip cap and plunger stopper
 - *Components were not included in original extractable evaluation so study had to be repeated with all components in order to correlate peaks seen in leachable study to potential extractable compounds*
- It appears that your extractable and leachable studies do not consider the label on the COC syringe. We recommend that the leachable (migration) studies be conducted in the primary container closure which is inclusive of the label on the syringe barrel.

Challenges and Strategies

- Challenges Faced
- Overview of Simulated Leachable Approach

Challenges Faced

Analytical Methods

- Validation work not completed by T=3 months (for both general screening methods and product-specific methods)
- Different methods being used for extractable testing vs product specific leachable studies to quantify the same compounds. Since different methods are being used, may not get adequate correlation between potential extractable compounds and leachable peaks

Identification of Source

- Need to clearly identify where extractables are coming from (i.e. primary bag film, stopper, overwrap, etc.)
- If source is not identified, may not be able to confirm where leachable peaks are coming from

Toxicological Assessment

- Can be time consuming and expensive
- First approach should be to try and use literature based approach
- Safety levels is based on Permitted Daily Exposure (PDE) and Maximum Daily Dose
- If leachable compound is not stable, may be difficult to isolate for evaluation in a toxicological study

Overview of Simulation Study Approach

Simulation Study for waiving stability sample monitoring

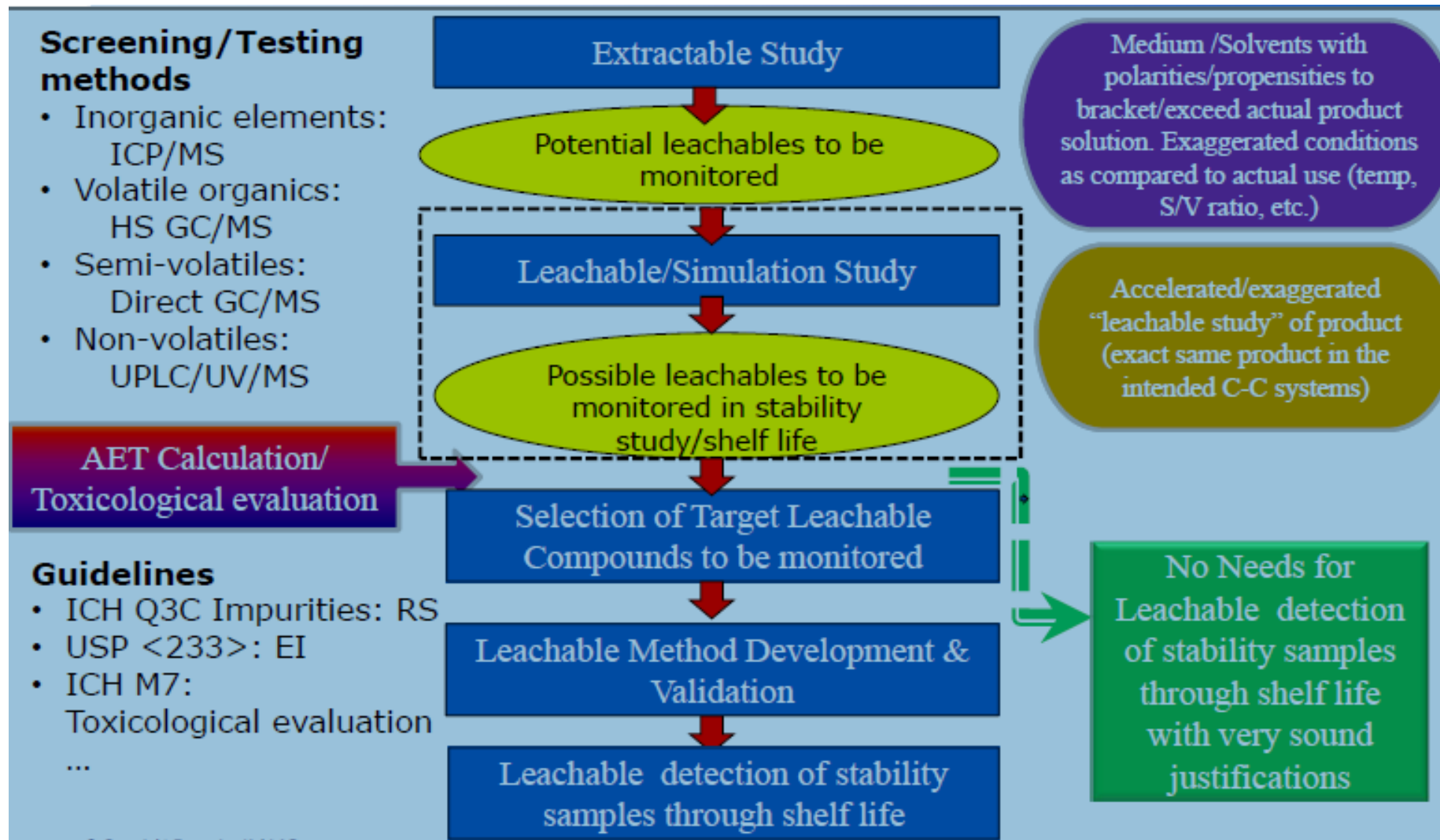
– E/L major time consuming and costly:

- Leachable method validation
- Leachable testing of stability samples

Two Conservative assumptions in the predictions of leachable levels:

- The extraction rates of extractable/leachable from the IV drug container material follow the Arrhenius equation.
- The accumulated amount of extracted compounds are linearly proportional to extraction time and may be extrapolated to the product shelf life.

Simulated Leachable Study Approach



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Simulation Study Case Study

A refrigerated product with 2 year shelf life

- **Extractable study**

- Head-space GC/MS for stopper. 8 compounds were detected.
- The Permitted Daily Exposure (PDE)/extractable amount is ≥ 27 .
- Liquid injection GC/MS & UHPLC/UV/MS for stopper:
- 65% ethanol /35% water extract. pH 2.5 formic acid extract.
- **The extractables do not pose toxicological concerns.**

- **Simulation Study at 55C for 2 weeks**

- The predicted leachable concentrations are estimated to be 3.2 times after two year storage compared to the ones in simulation study or $0.4 \text{ ppm} \times 3.2 = 1.3 \text{ ppm}$. **This is much less than the TTC (16.7 ppm)**. Also the inorganic leachable would be much less than the PDE.
- It is predicted that the potential organic and inorganic leachables would be many times lower than the TTC/PDE and therefore no target leachable monitoring will be performed.
- This approach accelerates and reduces the cost of medical product development.

Questions



Questions?

Thank You!