In-Use Stability Studies:

Is there a common approach?

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1. When are “In-Use” stability studies typically needed?
   - Is there a common definition within the industry/FDA?
   - In-Use vs. admixture study – what is the difference?
   - Recent deficiency questions from FDA

2. What should be considered in an In-Use study?
   - Critical quality attributes – physicochemical testing
   - Why would microbiological testing be required?
   - What is length of study and how is it defined?

3. A Case Study – Pre-mix bag
   - Overview of study requirements- when no information is included in PI
What are considered to be “In-Use” studies and why this is challenging?

- There is currently no common definition of “In-Use”.
- The duration of in-use is often the most difficult to prove...especially when no duration is provided in package insert.
- Is in-use defined when the medication is delivered to a patient or when it is being prepared by the pharmacy?
  - Particularly important for products that may require light or oxygen protection – label statements may make claim “retain in carton until time of use”.
  - Also important for solid oral dosage forms when medication is delivered to patient in a pharmacy dispensed container closure system.
  - Would it be acceptable for industry to use any commercially available pharmacy container closure system to perform these studies??
What are considered to be “In-Use” studies and why this is challenging?

- Inconsistency within Agency on when an “In-Use” study is required
  - Especially true with lyophilized products after reconstitution.
  - Is a study always required after recon or does it depend on length of time established in the RLD PI?
    - Have experience where a study has been requested when RLD PI states product is only stable for 4-6 hours post-recon

- Inconsistent use of terms for admixture vs. reconstitution vs. in-use stability in deficiency questions received from Agency (examples on following slides)
Example from OPQ of when studies may be requested:

- High risk scenario which may trigger this request:
  - When the limited stability studies provided in the application indicate the drug product is formulated near the edge of stability failure. Additional in-use studies may be needed to ensure patients are not taking generics products with compromised product efficacy (due to low potency) or safety (due to elevated impurities).

- In efforts to ensure greater transparency, OPQ is in the process of developing a MAPP to clarify scenarios where traditional ICH stability studies may need to be complemented with additional in-use studies. In addition, this MAPP will establish guidelines for the in-use stability protocol.
## In-use vs. Recon vs. Admixture Studies – What are the differences?

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<thead>
<tr>
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<th><strong>Reconstitution Study</strong></th>
<th><strong>Admixture Study</strong></th>
<th><strong>In-Use Study</strong></th>
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<tbody>
<tr>
<td><strong>Common Definition</strong></td>
<td>Some drugs must be stored in powdered form because they rapidly lose their potency once they are mixed into a solution. These drugs will have to be <strong>reconstituted</strong>, or mixed with a liquid, before they can be administered.</td>
<td>Some drugs require further dilution prior to administration. Or Can be co-administered with another drug product (i.e. Neostigmine and Glycopyrrolate)</td>
<td>Is often used synonymously with admixture studies. Commonly performed to &quot;simulate&quot; in-use practices by end user groups (i.e. nurses, pharmacy, home care)</td>
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<td><strong>Study Parameters</strong></td>
<td>Typically performed to confirm specification for reconstitution time listed in Package insert. Require comparison against RLD.</td>
<td>Usually based on directions included in PI to define duration of stability (i.e. 24 hours after dilution). Study can often include evaluation of physicochemical properties as well as microbiological study to confirm if there is growth promotion after solutions are combined.</td>
<td>Can often not have a set-time point for performing study. Examples include: demonstrating how long a pre-mix bag product is stable once overwrap is removed. How long is solid oral tablet stable once it is transferred into a pharmacy dispensed container... or if you open the bottle one time per day over 30 days would your product be stable?</td>
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Common Deficiency Questions
Lyopholized product example: In-Use

- Although you have provided *admixtire studies*, no data was provided to support proposed package insert labeling that states: “physical and chemical *in-use stability* of the infusion solution prepared as recommended has been demonstrated *in non-PVC bags up to 48 hours* when stored between 2°C and 8°C (36 and 46°F).” Therefore, please provide *admixtire studies* for up to 48 hours.

  - **CHALLENGE:** Agency requested study be performed in non-PVC bags... is the generic company expected to identify and test all potential suppliers of non-PVC bags?
  - *Should study only be performed out to 48 hours based on PI or should study be extended to cover potential off-label usage?*
Lyopholized product examples: In-Use

- **Product X reconstituted single dose vials can be used in ambulatory intravenous infusion pumps.** Your study should demonstrate that the stability of Product X is not affected when administered using an ambulatory intravenous infusion pump. Please provide in-use stability studies to support the following text in the package insert: ‘Stability of Product X in an ambulatory intravenous infusion pump has been demonstrated for a period of 12 hours at room temperature.’

- **CHALLENGE:** there are many variations of ambulatory infusion pumps. For a generic injectable company, how would the company obtain access to such pumps and how many “variations” must be tested?
Example of “Co-Administration”

- Per the drug product labeling, the product is administered as an intravenous push over 3-5 minutes via the side port of a free-flowing 0.9% Sodium Chloride Injection. We could not locate the information on in-use stability study of the product per labeling instruction. To demonstrate compatibility of the product with the 0.9% Sodium chloride injection, please provide data for in-use stability study of the proposed drug product.

  - **CHALLENGE:** How long should in-use study be since PI states IV push over 3-5 minutes only? The drug is in contact with the 0.9% NaCl for virtually a negligible amount of time...
KEY TAKE-AWAYS

- Current trend within FDA seems that admixture and in-use studies are being requested much more frequently for parenteral drug products... even if the contact time with the diluent or container is extremely short
- The term admixture and in-use seem to be used interchangeably in the parenteral injectable world... perhaps there is a clearer distinction within solid oral dosage forms
- Due to the high variability in study designs, there is no common practice currently being followed by generics.
- OPQ has committed to the development of a MAPP to provide additional guidelines for when a study may be required and how protocol should be developed
Design of In-Use Stability study

- Comparative Physicochemical Testing against RLD
  - Typically evaluate Appearance, Particulate Matter, pH, Assay, and Impurities.
  - Should product samples be aged in order to demonstrate in-use stability of the product over the entire shelf-life?
    - FDA has asked to pull samples from various ICH stability time-points (i.e. T=0, T=6 month accelerated, T=12 and T-24 month long-term) to show that as the product ages there is no impact on the in-use stability.
    - It is best to use “aged” samples (even simulated aged samples) in an in-use study in order to cover proposed shelf-life
  - Recent experience has shown that FDA does not want a company to “bracket” the diluents... have requested that all diluents in PI be used in study
Design of In-Use Stability Study

- **Micro requirements- GROWTH PROMOTION STUDY**
  - Please provide a risk assessment summarizing studies that demonstrate adventitious microbial contamination does not grow under the specified storage conditions after further dilution with the specified diluents.
  - Include a description of the test methods and results of studies that are designed using a minimum countable inoculum to simulate potential microbial contamination that may occur during product dilution.
  - Perform the test using the storage conditions (temperature and duration) and diluents specified in product labeling. Provide justification for the selected test conditions and/or diluents as necessary. Periodic intermediate sample times are recommended, as well as extended sample time points demonstrating that the diluted product does not support microbial growth for at least the maximum storage periods under the specified storage conditions. The RLD may be tested in parallel to demonstrate equivalence.
KEY TAKE-AWAYS

- Always perform comparative analysis against RLD
- Trend within FDA seems to be requesting physicochemical testing and not just typical stability indicating tests like pH, assay, and impurities
- Use all diluents listed in PI (when possible)
- Even if in-use time period is short as defined in the package insert (i.e. less than 24 hours), there seems to be an increased trend for FDA to ask for microbial growth promotion studies
  - Can Agency define if there a “cut-off” for when micro studies may be required- i.e. when in-use time period is greater than 72 hours??
A Case Study: Pre-Mix Flexible Bag

- Why was a study performed?
  - Flexible plastic pre-mix bags typically require long-term storage in an overwrap due to moisture vapor transmission or need for light protection
  - Most package inserts for pre-mix bags do not address the stability of the bag once it is removed from the overwrap
  - Customers commonly ask how long product is stable outside the overwrap
    - Commonly occurs in the “in-use” setting – a nurse may prep a bag for one patient (remove from overwrap) but patient may not require product immediately.
    - Central hospital pharmacy removes overwrap to prepare for transport up to treatment floor but patient ends up not requiring medication – can this product be used for another patient?
Pre-Mix Flexible Bag: Design of Study

- Maximum duration for study was 30 days
  - It is highly unlikely a product would ever be stored outside of the overwrap for this length of time. In common practice, it will likely only be hours but study was designed using worse-case parameters

- Study Design:
  - Only evaluated critical stability indicating parameters
  - Micro testing should not be required because assumption is made that bag will remain sterile. Package Insert clearly states that if bag is punctured, clinician must throw it away.
QUESTIONS?