Lessons Learned: Compatibility and In-Use Stability Studies

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Pharmaceutical Quality

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Drugs are no different.


Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence
in their *next* dose of medicine.

This talk reflects the views of the author and should not be construed to represent FDA's views or policies

Story of a Disconnect Between Bench and Bedside at IND Opening

- IND enabling compatibility studies for an antibody-based drug were described in a submission:
  - concentrations studied bracketed lowest and highest proposed concentrations for administration
  - product tested for product quality attributes and potency
  - hold time of several hours was tested
- IND considered safe to proceed

Story of a Disconnect Between Bench and Bedside at IND Opening (cont)

- Several months later, sponsor reached out that they had halted clinical studies
  - First dose cohort
    - at MABEL- no toxicities or adverse events
  - Second cohort-
    - half-log dose escalation, first dose well tolerated
  - Sponsor became aware of a potential issue in administration instructions (i.e., the pharmacy manual)
    - Compatibility studies included priming the line with a particular volume of diluted drug. Volume was in pharmacy instructions but not priming material.
    - Lines were being primed with saline prior to administration at trial site
    - Pharmacy manuals were corrected to specify priming with diluted drug

Story of a Disconnect Between Bench and Bedside at IND Opening (cont.)

- But then the second dose was administered to the first patient in the second cohort.
  - Resulted in severe cytokine release syndrome
- Trial was halted by the sponsor, and put on hold by the FDA
- Multiple rounds of IRs and soul searching……
  - **What did we miss?**

Pharmacy Manual: Important Piece of the Puzzle

- Information about preparation and administration can be found in an IND in
  - The protocol?
  - The Investigator's Brochure? (not usually, but sometimes)
  - **The Pharmacy manual**
    - **very rarely submitted to the IND, unless we ask**
    - **we're trying to ask for high-risk products when there's a pre-IND**

- Preparation and administration instructions provided to pharmacies has to carefully line up with what was demonstrated in compatibility study
  - Some submissions suggest that the manner in which dilutions are described and performed can also be a potential source of dangerous error

Pharmacy Manual:
Sample Information Request

Insufficient information was provided to the IND to assess whether the compatibility studies performed in Section X.X.X can support the accurate and consistent delivery of PRODUCT NAME to patients in the proposed clinical study. ***Submit the full instructions for drug dilution, preparation, and administration that will be supplied to the participating clinical trial sites (e.g., Pharmacy Manual) including instructions for priming the infusion system and the types of diluents, infusion bags, infusion lines and filters to be used.*** *Confirm that the instructions provided to the clinical sites is the same, or sufficiently similar to, the administration materials and conditions that were tested and proven to ensure accurate drug delivery in your compatibility studies.*

Multidisciplinary Communication During Review

- We also learned that early communication is essential with the team
  - Clinical reviewer
  - Pharm-tox reviewer
  - Clin Pharm reviewer
- For instance, compatibility may look fine, but you don't want to find out after you archive your review that
  - They've lowered the starting dose
    - Saber et al. Regul Toxicol Pharmacol., 2017- FIH dose selection for CD3 bispecific constructs
  - Sponsor will have to lower the diluted drug concentration to achieve it
  - Sponsor has no compatibility data to support it
  - Sponsor has no assay sensitive enough to perform the needed studies

Confirmation of Dosing

Normally, the PK assay is important for confirmation of patient dosing, but for highly potent drugs, it may not be sensitive enough to confirm exposure.

Under rare circumstances where the team considers the risk to be exceptionally high, and/or there is significant uncertainty regarding dose variability, you may receive an IR like this:

- *Due to the inability of the intended PK assay to confirm exposure at the lowest doses, dosing should be confirmed in real-time to ensure that your dose escalation is well controlled. Provide a description of how the actual drug product concentration delivered from the infusion system will be measured and verified for all patients participating in the study.*

Analytical Challenges with Dilute Drugs

- Finding product quality assays with adequate sensitivity, in the chosen diluent, is a challenge
- May need a more sensitive assay than used to determine potency for release and stability
- Qualification should include:
  - accuracy, precision, and limits of quantitation
  - special attention to the reliability of the assay in the range expected for the diluted drug tested in compatibility studies
  - It is possible that the starting dose might be lowered. Best to be prepared! (see above note on assay choice)

Multidisciplinary Communication During IND Preparation

We often see situations where

- the protocol/manual isn't informed by the compatibility studies.
  - Communication and collaboration are crucial and should occur between those who are
    - erforming the compatibility studies
    - writing the clinical protocol
    - writing the pharmacy manual
    - performing the pre-clinical studies

- there is insufficient detail in the pharmacy manual/protocol
  - The sponsor sometimes leaves it up to clinical trial sites to determine administration equipment; therefore, compatibility can't be adequately assessed

Assays and Timepoints to Support In-Use Stability and Compatibility

- A potency assay might be the only viable approach to assess protein concentration and drug product degradation for dilute products
  - other methods may not be sufficiently sensitive to quantify small amounts of protein and product-related impurities
- Visible and subvisible particles should be assessed.
  - For low dose products, these are unlikely to be an issue
- Testing samples at several (realistic) timepoints is recommended, in case your product is less stable under the administration conditions than anticipated.

Summary of Expectations (IND)

In-use stability/compatibility studies should:

- Simulate the administration of the product*
- Capture all potential product-contacting surfaces*
- Take samples from material that would be delivered to patient (ex., the needle tip)*
- Be performed in the proposed diluent(s)
- Be performed under worst-case conditions for duration, temperature
- Use multiple drug concentrations, reflective of proposed dosages of clinical studies; high and low is sufficient

* particularly for highly potent products

Expectations in Studies to Support Licensure

GOALS OF IN-USE STABILITY, COMPATIBILITY STUDIES CHANGE DURING DEVELOPMENT

At IND initiation:

Safety and interpretability of the data

At licensure:

To ensure accurate, safe dosing of drug under conditions that maintain quality

Summary of Expectations (BLA)

In-use stability/compatibility studies should:

- Simulate the administration of the product
- Capture all potential product-contacting surfaces
  - Typically, a broader number of materials to support wider use
- Take samples from material that would be delivered to patient (ex., the needle tip)
- Be performed in the proposed diluent(s)
  - When there has been a need for these, typically see more attention to compatibility and more complete data set
- Be performed under worst-case conditions for duration, temperature, light, etc.
- Use multiple drug concentrations, bracketing those described in the PI to support labeled dosages
- Utilize material close to or at the end of proposed expiry

Most Common Compatibility Issues

- Particle formation (sub-visible or visible)
- Protein loss
- Potency loss in absence of protein loss (associated with other product quality changes)
- Studies are just as important to inform incompatibilities as compatible materials
  - Sometimes, loss happens in bags, but can also be lines or catheter (or other components for other devices)
  - Incompatible with dextrose, saline, or both (in which case diluent may need to be developed to improve compatibility for administration)

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What about at Emergency Use Authorization?

Emergency Use Authorization: Case Study

Fact Sheet for Health Care Providers

- "Dilute into infusion bags made of polymer 1 or polymer 2...."
- "Use of a polymer 3 filter is strongly recommended"

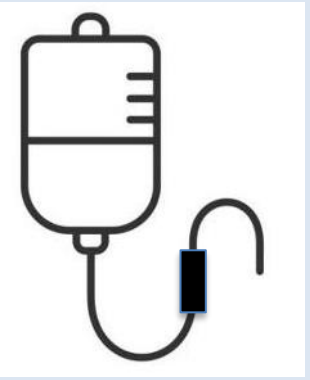
P.2. Compatibility Testing

Compatibility with a

- 100 mL ***intravenous (IV) bag (?)*** with 0.9% saline and
- ***a polymer 2 administration set***
- ***with a 2 µm in-line filter (?)***

was assessed.

- pH
- Sub-visible particles
- Potency
- Size and Charge
- 25 ºC and 5 ºC
- Multiple timepoints, 0 - 48h
- Microbial challenge



Emergency Use Authorization: Case Study

Information request was sent to request data to support compatibility with polymer 1 and polymer 3 components:

- What material was the IV bag? If not polymer 1, what other materials have been tested for compatibility?)
- What filter materials were tested? Polymer 3? Others?

Response/justification from the sponsor:

- A number of IV bag materials had been tested with no incompatibilities, some of which are similar to polymer 1.
- Multiple other materials of construction were tested across different components of administration set up without significant impact.
- Polymer 1 bags and polymer 3 filters are among most common in healthcare settings.

Justification	Pros	Cons
• Does the lack of incompatibility (or measurable impact) of a number of similar materials support the use of other materials? (For example, PE and PP support all polyolefins?)	• Strictly speaking, these materials had been tested for compatibility, and had been held with product over a long period	• Far less contact area with tubing, catheter, and filter than an IV bag. • Also, there are many, many types of polyolefins.
• Polymer 1 bags and polymer 3 filters are commonly used in healthcare settings	• Don't want to restrict use of mAbs under EUA or cause confusion	• If incompatible, problems could be widespread

- **Ultimately, we have had a great deal of experience with monoclonal antibodies in the ~10 mg/mL range, diluted in saline, in a variety of bags, infusion sets, and filters, particularly polymer 3.**
- **Most of the time they are compatible.**
- **In fact, these particular mAbs were tested with several materials of contact and no incompatibilities were observed.**
- **Given the urgent need, and with a commitment to do these studies ASAP, it was decided that the HCP-FS could propose the use of the proposed bags and filters.**

Compatibility Lessons Learned

- When receiving an IND for a highly potent product, we should reach out early
  - If under IND, set up a cross-disciplinary meeting ASAP
  - Tcon with the sponsor earlier in the 30-day window can be helpful
  - If have a pre-IND for highly-potent biologics, we provide comments regarding our expectations (Pharmacy Manual, assay qualification, possible confirmation of dosing, etc.)

  Sponsors should similarly collaborate with all relevant groups to support accurate dosing in proposed phase 1 studies
- Both the design of in-use stability/compatibility studies and the way that the data are presented should match the instructions that they support to ensure safety and efficacy
  - Pharmacy Manual (IND)
  - Health Care Provider Fact Sheet (EUA)
  - Package Insert (BLA)
- **Compatibility involves more disciplines than you think**
- **Think about the phase of development, healthcare context, and conditions of use you're trying to support in the labeling when you plan your compatibility studies**

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