Roundtable Session 2 – Table 17 - In-Use Studies - Compatibility Studies and Defining Label Claim

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Abstract:

In-Use Compatibility and Stability Studies will be discussed with a major focus on biologics. The topics at the roundtable will be centered on key quality attributes and risk factors that impact the in-use stability period, for example, the number of subvisible particles, microbial challenge data, extractable & leachables of off-the-shelf ancillary components (IV bags, IV lines, syringes, etc), and different routes of administration.

Discussion Questions:

1. What is your company's overall approach on these topics?
2. What questions has your company received from Health Authorities (HAs) globally regarding these topics?
3. What are other scientifically-sound approaches that you may use regarding these topics?
4. What country-specific requirements impact your company's in-use study design and filing strategy?
5. For products recommended for "immediate use" where in-use stability period is 4 hours or less, does your company perform the microbial challenge studies and file the microbial challenge data?
6. Are companies generally following the guidance provided in the PDA paper or the FDA guidance, or are they adopting a more conservative approach?

Notes:

What is your company's overall approach on these topics?

The general approach to in-use compatibility involves a panel of analytical tests, including light obscuration methods such as HIAC (liquid particle counter), to ensure compliance with established specifications (some companies look at trends rather than specifications).. The strategy involves evaluating the product at time zero and monitoring trends over the specified time course. While HIAC is the predominant method for assessing changes, MFI (Micro-Flow Imaging) data is also often collected for informational purposes.

A key challenge identified is particle contribution from ancillary components, such as Closed System Transfer Devices (CSTDs) and IV bags, which can introduce high levels of subvisible particles. A more nuanced assessment of particle data is being proposed in an upcoming white

paper from IQ Physicochemical In-Use Stability testing WG, suggesting that a specific particle count (e.g., 6001 particles) may be acceptable based on overall risk.

FDA Feedback Highlights:

- HIAC data is the most typical data submitted, with MFI considered supplemental.
- Data trending is considered essential.
- The CMC reviewer is primarily focused on Module 3 (P.2.6), and requests for the pharmacy manual are inconsistent.

Best Practice for Specifying CSTDs in the Pharmacy Manual:

- Some companies explicitly specify which CSTDs are permitted or prohibited for use with their products.
- A conservative approach, often used for Antibody-Drug Conjugates (ADCs), states that a CSTD cannot be used unless explicitly specified.
- Currently, no Health Authority regulation strictly mandates the use of a CSTD; however, hospital or pharmacy best practices may require it.
- Health Authorities have, in some cases, requested the inclusion of CSTD compatibility data within the P.2.6 section of the submission.
- Similarly, some companies have been asked to provide the pharmacy manual to the HA.
- Some Investigator Brochures (IBs) omit detailed compatibility information, instead referring to the Pharmacy Manual.
- It is generally recommended to submit the pharmacy manual to the FDA to demonstrate that the compatibility data supports the intended clinical practice.

CSTD Testing Strategy:

Testing approaches vary but generally involve evaluating CSTD compatibility for the dose solution preparation phase and/or for the full infusion duration. Some companies use CSTDs for subcutaneous (SC) products. In this context, the difference in hold volume and fill volume are critical considerations. Due to the complexity, companies typically specify a permitted set of devices (e.g., A, B, C) while excluding others (e.g., X, Y, Z)

Country-specific Requirements

- **Japan:** Requests have been made to test specific local materials for compatibility, particularly those components used in the preparation and administration of the product.
- **EMA:** Inquiries frequently concern the use of PVC (Polyvinyl Chloride) with DEHP (Diethylhexyl Phthalate). A published risk assessment on DEHP in PVC is a relevant resource.

How many materials do people test

A common practice is to test approximately five typical polymer materials for compatibility studies. A follow-up white paper is currently in progress to address patient risk and other issues related to materials testing

Microbial Challenge Data Considerations: Support for In-Use Periods < 4 Hours

- Parenteral Drugs: Consistent with this published article, most companies do not submit microbial challenge data for in-use periods of less than 4 hours. This is outlined in the paper: "Best Practices for Microbial Challenge In–use Studies to Evaluate the Microbial Growth Potential of Parenteral Biological Products; Industry and Regulatory Considerations" (PDA Journal of Pharmaceutical Science and Technology, October 2023).
- Parenteral Drugs for Specific Delivery (e.g., intravitreal, intrathecal injections): Even if not strictly required, providing this data is deemed prudent as it effectively highlights the microbial risks associated with the specific mode of administration.
- Investigational New Drug (IND) Applications: In-use stability is generally tested for 4 hours at 25°C and 24 hours at 2–8°C (including infusion time).
- Biologics License Application (BLA) / Marketing Authorization: In-use periods exceeding 4 hours necessitate the submission of both physicochemical and microbiological data.

Definition of Low Dose

Low dose is typically defined by concentrations in the range of:

- < 1 µg/mL
- < 100 µg/mL