

Table 15: Method Selection and Acceptance Criteria to Support In-Use Stability and Compatibility Studies

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Scope:

Pharmaceutical products that necessitate some level of processing such as dilution, reconstitution or mixing with other components prior to dosing require in-use stability studies. The purpose of in-use stability and compatibility studies is to demonstrate the pharmaceutical product remains within its physical, chemical, and biological specifications and retains its safety, efficacy, and performance. The current guidance for pharmaceutical development suggests that the contents for section 3.2.P.2 of regulatory submissions address the compatibility of the drug product to provide the appropriate and supporting information for the labeling. This information should cover not only the in-use stability at the recommended storage temperature but also the admixture or dilution of the products in appropriate container or device prior to administration (e.g. product added to large volume infusion containers).

Even though guidelines are available to construct the framework of these studies, specific information such as the selection of methods and their acceptance criteria can be different for each product.

Questions for Discussion:

1. Are there specific methods typically used for in-use-stability and compatibility studies?
2. How are acceptance criteria selected and justified?
3. What is the typical duration of in-use stability and compatibility studies?
4. What is the number of batches used for these studies especially at early stage of product development?

Discussion Notes:

1. Are there specific methods typically used for in-use-stability and compatibility studies?
 - Typically those for DP release and stability applicable to compatibility studies.
 - Typical methods are SE-HPLC, CE-SDS, CEX-HPLC, HIAC/MFI, A280 and potency
 - Use icIEF when low dose is used, Buffer exchange is performed before icIEF analysis
 - Different methods were used compared to release. For example, for compatibility, CEX method was used whereas for release icIEF was used for charge variants
 - Visual inspection: typically enhanced inspection (amplified light) is added. Sub vis particles are typically by HIAC, flow-cam is also used
 - Release methods are modified if matrix interference is observed

- Choice of methods are phase dependent. Potency- not used in Phase I, but only in late phase
- At early stage of development (IND) some are very vague/general then evolve over course of product development & applied to compatibility studies.
- For co-formulated/co-administered products-basic method is typically available, Needs to optimize for co-admin/co-form CIU studies which is relatively easy

2. Do you do qualification/validation of methods for in-use?

- Phase appropriate
- For early stage, include system suitability, no method qualification
- If the attributes are within the validated ranges, additional validation is not needed. If they are not some fit for use studies needed.
- If dose is outside typical qualification range of the method then authorities have asked qualification at even early stage and validation for late stage and commercial

3. Is there an appropriate time to conduct in-use/stability studies?

- Post-approval reasons differ from pre-approval reasons. Pre-approval need basic information to establish safety. Post-approval reasons can be for competitive reasons.

4. How are acceptance criteria selected and justified?

- Tend to use acceptance criteria for DP shelf life. Some quality attributes might be appropriate to be reported at % change in compatibility studies (as opposed to DP shelf life criteria).
- Sometimes confusion between compatibility and ICH Q1

5. What is the typical duration of in-use stability and compatibility studies?

- 4hr is typically considered as immediate use
- Typically limited by microbial growth / contamination.
 - Is microbial hold required
- Questions received from the agency. Likely prior knowledge is driving agency questions
- Historical data can be leveraged for similar matrices. It has been accepted by the agency for early stages. If not, additional studies are required

6. What is the number of batches used for these studies especially at early stage of product development?

- Depends on stage of development. In early phase (IND), choices are limited in #of DP lots available (e.g. could even be forced to use tox. Lot). Post-approval more choice of DP lots to use as well as age (e.g. at expiry).
 - Light & temperature conditions for the study
- Keep the room light on during the study to mimic the actual clinical set up
- Higher temperature such (30 or 37C) is preferred as worst case

7. Material compatibility

- Used different infusion speed to increase the contact time with bags
- Seen different levels of aggregates in bags from different vendor even with same material
- We never indicate which vendor to use for IV bags, only MOC is stated
- E&L work for IV bag or use vendor data?
- Perform mock infusion to understand interfacial stress?

8. Have any one used transportation studies as a part of CIU?

- Performed some studies due to protein recovery issues; used additional PS-80

9. Other: metadata / capturing results

- Picking right statistical methods