Table 20: Compatibility and Globally Relevant In-Use Stability Testing

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**SCOPE:**
Drug Product Compatibility and Stability studies are performed to demonstrate that quality of a Drug Product and its container is maintained throughout shelf-life.

A Biopharmaceutical Drug Product may be administered to the patient straight from its container (a prefilled syringe for example), but it may also require transfer to a delivery system. In this case, the product contact materials may differ from those seen by the product during long term storage, with potential impact on product stability but also potentially the integrity of the administration device.

The long-term storage conditions of the product may also be very different to those of administration. Finally, the way the product is administered may also differ vastly, depending on whether the product is administered by the patient themselves or a health professional and their respective level of training. This can result in different exposure to microbial contamination for example.

This roundtable aims to discuss both the aspects of assessing compatibility and in-use stability testing that can be standardized and globally applied, but also how the industry may want to progress those aspects that are currently not standardized.

**QUESTIONS FOR DISCUSSION:**
1. What are the current regulatory requirements for in-use stability?

2. What challenges have been encountered around use of Closed System Transfer Devices (CSTDs)?

3. How do biomanufacturers define hold time at ambient conditions from a microbiological point of view?

4. How does the industry cope with the multitude of reconstitution and administration devices to ensure that most of them are compatible with their products?

5. In conclusion, what aspects of in-use compatibility and stability testing can be considered globally relevant?
DISCUSSION NOTES:

1. What are the current regulatory requirements for in-use stability?
   a. Do they diverge in different regions / countries?
      • Some countries require 1-3 batches for in-use studies. LatAm countries require 3 batches.
      • Methods used do not need to be GMP validated, need to be qualified methods.
      • Material of construction for in-use material is a consistent issue. Especially for tubing being used and CSTDs (closed system transfer devices).
      • How to know what tubing is used in different sites? Work with clinician/sites to understand what material is used at sites. Some CROs have information/data about what material is typically used at sites.
      • Material chemistry is propriety manufacturers of in-use material often will not share this information. In label claim, can’t site brand to use/not use in label as material of construction will change over time. Label needs to actual cite material of construction.
      • Try to do worst case for all studies.
      • Close interactions between CMC (typically formulators) and clinicians.
      • Time frame of study is dictated by time required at clinic, worst case room temp is 30C.
      • A CQA change is allowed during in-use stability study but needs to be taken into account overall stability and release acceptance criteria.
      • Have to use material at end of shelf life for in-use study.
      • Leachable extractable studies generally not required for 24hr hold time in bags. Leachable extractable studies only required for much longer time in bags (years).
      • If IV bag prep at centralized lab and then driven to IV site, a shipping study in IV bag is required. Typically shipping studies are usually simulated, shakers etc.
      • Control will be at room temp or at temp of DP storage.
      • Is there a space for consortium of industry group to understand what materials are being used for in-use? Yes, there is.
      • Cell based therapies will require tracking stability in bags.

2. What challenges have been encountered around use of Closed System Transfer Devices (CSTDs)?
   a. How are companies addressing challenges of updated USP <800> and listing of drugs as hazardous with associated requirement to use CSTDs?
      • Some CSTDs have caused issues with in-use studies. This is an ongoing issue. Was further discussed at workshop.

3. How do biomanufacturers define hold time at ambient conditions from a microbiological point of view?
   • Microbial control depends on controls in place in lab in which is-use bags are prepped. (i.e., use of biosafety cabinet). US and S. Korea required microbial study.
   • Microbial hold studies are being performed to support filings in all countries. Not just US.
   • Microbial hold studies are required for IND, but can use a platform approach for IND filing.
4. How does the industry cope with the multitude of reconstitution and administration devices to ensure that most of them are compatible with their products?
   a. How is industry approaching bag shortage issues, how are companies addressing this issue?

5. So, in conclusion, what aspects of in-use compatibility and stability testing can be considered globally relevant?
   a. How could the industry drive further harmonization – components of reconstitution / administration devices, standardization of administration practices, etc.
   b. Is there an industry group looking at this?