Table 16: In-use Stability: How to Develop a Plan for Your Product

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SCOPE:

In-use stability can refer to a number of situations where the disposition of the product has changed between allocation of the product from its commercial source to administration to the patient. This includes products taken from a vial, put into an IV bag and administered over several hours; prefilled syringes dispensed to the patient and taken home or to their physician for storage and/or administration; product prepared in a hospital pharmacy and sent to the patient room; and reconstitution and storage of a lyophilized product. All of these scenarios have unique challenges as it relates to the types of stresses undergone before administration. These include but are not limited to compatibility with the IV bag or administration device, fluctuations in temperature, or exposure to light. Table members will discuss requirements and approaches for ensuring the quality of product during common or extreme conditions prior to administration to the patient.

QUESTIONS FOR DISCUSSION:

1. What types of studies are performed for one or another of the in-use scenarios outlined above? How are these designed?

2. How is the data used from in-use studies? Is this used in combination with data from other stability assessments?

3. What are the typical challenges with performing these studies?

4. What guidance(s) is used, and what kinds of questions have been received from regulatory authorities.

5. Do companies perform in-use studies as stand-alone or in combination with other stability assessments?

NOTES:

- Three major themes
  - Early vs. Late stage activities
  - Extent of testing
  - Small vs. Large company strategies
- Microbial challenge studies
  - Some have performed them, but some have not – focus more late stage
- Time limit on in-use reduces risk of microbial growth (ie. do not administer after 4 hrs)
- Studies should focus on a timecourse approach after vial breech

- **Regulatory precedence**
  - No regulators with experience at the round table
  - Some early phase queries for data requested, but mostly focused on biochemical stability and not microbial
  - Clarity of label is critical for compliance in preparation and dosing
  - Confusion on the same product and label differences between countries (ie. US provides 4 hrs but elsewhere provides 12-24 hrs stability prior to dosing)
  - Negotiation, with appropriate data, stability and safety risk, needed for appropriate, local assignment of in-use stability

- **Biochemical testing**
  - Most focus on concentration, aggregation, appearance
  - Question regarding how to determine the significance of a change at low dose concentrations
  - Some consideration of statistical approaches may be valuable
  - Testing under certain conditions
    - Photostability (ICH Q1B) cannot be translated to in use conditions
    - Lab light vs. sun light (ie. clinical samples near windows)
  - Some use the pre-approved specification
    - Modeling in use changes together with other changes over shelf life

**References Discussed**
2. USP 51 for guidance on microbial challenge studies