

Table 2: Stability

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Questions for Discussion:

1. Stability indicating methods - the chicken or the egg?
 - demonstration of stability indicating ability of a method - when to do it in the development lifecycle?
 - Distinguishing between instability and analytical method variability - what if you see a trend that is within the intermediate precision of the method?
2. Using platform data to support setting a shelf life
 - When, and under what conditions is it justified to claim platform prior knowledge?
 - How is the platform knowledge shared in the IND/IMPDP?
3. Attributes and analytical methods in a stability program
 - Do you only test by methods that are also in release, or also include characterization studies?
 - If using characterization: would you report the results in the IND/IMPDP? If yes, where?
4. Stress conditions, forced degradation, and modeling
 - Using results from stability under accelerated conditions to model stability at the intended temperature - does the Arrhenius model apply in all cases?
 - When, how and under what conditions can stability results be extrapolated, to allow making predictions and accelerating early development?
 - Role of forced degradation studies in understanding stability and the critical quality attributes

Discussion Notes:

1. Stability indicating methods - the chicken or the egg?
 - Both product and analytical method knowledge increase throughout the development lifecycle
 - In early development, method knowledge may not be sufficient to determine if the method is stability indicating
 - A stability indicating method should pick up differences between release and end of shelf life limits
 - Forced degradation studies - to understand routes of degradation and the methods' stability indicating ability - are done as early as possible in the product development timeline, as they inform important decisions
 - Certain methods that have not been shown to be stability indicating may remain in the stability program in early development, while further method and product knowledge are being built

- Although the potency assay should be stability-indicating, it often has a very broad variability that does not allow to pick up differences in critical quality attributes with sufficient sensitivity
- Methods more sensitive than potency - e.g., chromatography or physicochemical methods - typically pick up small changes in the product that the potency assay may not pick up
- If a trend is seen in the potency data, but the results are still within the method's intermediate precision, then the results of physicochemical or chromatography assays can be useful to confirm or disprove a product quality change
- In early development, the formal stability studies may be limited to the methods that are regulatory recommendations, and other potential critical quality attributes be monitored in characterization studies
- As method and product knowledge increase, characterization methods that are shown to be stability-indicating may be added to the formal stability program
- Trending results for a reference material may be useful to decide if differences in the product are analytical method variability or product degradation

2. Modelling and applying prior knowledge

- Stability data currently needs to be included in regulatory submissions from the beginning, but guidance is under revision and may allow a science and risk based approach in the future
- For example, if a product is under accelerated development it may be accepted to not include stability data for that product in the initial submission
- From a scientific perspective, it can be assumed that if a product is stored well below the formulation buffer's glass transition temperature - these are frozen conditions - then it is stable
- A number of different approaches for modelling stability data are available and/or have been reported in the literature:
 - Arrhenius model for liquid formulations
 - Advanced kinetic analysis - published by Sanofi for vaccines and oligonucleotides; allows good prediction of the impact of temperature excursions
 - Bayesian statistics may be used to build stability models
 - Prior knowledge from similar products may be applied to define a stability model
 - Use of prior knowledge and applicability of a model must be justified appropriately
- Accelerated stress conditions are not consistently predictive of long term stability
- Multi factorial study design may be needed in certain cases, e.g., impact of light and temperature stress; increase of oxidation and high molecular weight species