Table 23: Modernizing Stability ICH Guidance, Including Science and Risk-Based Approaches to Encompass Biologics and New Modalities

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Scope:

ICH Q1A was the first quality guideline to be developed after the ICH organization was formed and harmonized the core stability package for new drug substance and drug product registrations. Additional specific stability topic guidelines were released to form a Q1 series, with a separate Q5C guideline dedicated to biologics stability. Later, ICH Q8-Q12 ushered in the important concept of "science- and risk-based- approaches" to pharmaceutical development, manufacturing, and product lifecycle management. The ICH Quality Discussion Group (QDG) proposes revision to the ICH series of stability guidelines to modernize and align the stability guidance with such science- and risk-based approaches.

Where should the guidelines be clarified, and where should they be updated and amended to enhance their usefulness to both industry and regulatory agencies?

Let us discuss how modernization of the stability guidance could encourage demonstration of enhanced stability and product understanding and reduce or replace portions of the conventional stability data package to support initial marketing applications and lifecycle changes.

Questions for Discussion:

1. How could risk assessments be constructed to:
    a. identify shelf-life limiting attributes
    b. inform stability testing strategies
    c. justify design of special studies (in-use stability, temperature cycling, etc)
2. How are alternative stability tools (including accelerated stability modelling, applying prior stability knowledge, and advanced kinetic analysis) used to:
    d. predict the stability profile
    e. support or establish retest period/shelf-life (clinical or commercial)
    f. facilitate post-approval changes
3. How are science- and risk- based approaches incorporated into current regulatory filing strategies and dossiers? What changes to Q1/Q5C could facilitate global registrations?
4. How have accelerated and early access programs (e.g., EMA PRIME, FDA BTD, emergency use authorization) furthered the innovation of scientific tools related to stability? Will these alternatives to the conventional stability program become standard?
5. How can ICH Q1/Q5C be adapted to accommodate new modalities?

Discussion Notes:

- In 2022 it is anticipated that ICH will initiate a revision to the disparate Stability guidelines, the Q1 series and Q5C. The roundtable discussion began with some considerations on how stability risks are captured in a BLA/MAA and how they may be reflected in a revised ICH Stability guideline. The responding companies currently capture product quality attribute stability risks as part of their current control strategy processes that evaluate the severity of impact for individual attributes. Therefore, a stability risk assessment does not need to be a specific separate document but can be integrated into the overall control strategy. However, when a science & risk-based predictive stability approach is being employed then additional risk assessment would be expected by agencies that is directed towards the risks associated by the approach used.
- It is suggested by the table that high-level expectations for stability risk assessment would be described in the ICH stability guideline revision.
- How to identify shelf-life limiting attributes was briefly discussed in the context of science & risk-based stability testing. This is a problematic area when different regions may require a different specification that may change the attributes that become shelf-life limiting. As a related topic, the concept of 'smart' stability testing was introduced to the table, the biologic equivalent of 'lean' stability testing. It was suggested that the frequency of testing for an attribute could be proportionate to risk (criticality of the attribute, impact on the stability profile, shelf-life limiting intersections with specification).
- A more science & risk-based approach to stability testing frequency is being recommended for the ICH stability guidance revision.
- It was noted that stability risk assessment and any justified reduction in testing could be more applicable at BLA/MAA once supporting development data have been obtained since criticality of attributes is not typically determined until the commercial phase. During development, general risks pertaining to a predictive stability approach could be addressed through commitments. Currently ICH Q1A/Q5C have little direct guidance on stability risk assessment though has some elements of risk-based flexibility.
- The table recommends that the ICH revision includes specific, high-level guidance on stability risk assessment concepts.
- The identification of attribute interactions was raised e.g., a chemical modification such as oxidation or deamidation impacting the kinetics for another attribute such as dimerization. It was suggested that any such interactions may be reflected in the degradation kinetics (e.g., biphasic, 2-step kinetics). Although scientifically interesting these interactions were not thought to be a critical aspect to defining the stability profile unless a mechanistic approach was being employed. The current kinetic approaches are empirical, and the prior knowledge approach is comparative.
- A discussion on front-loading CMC-analytical activities and how to make the choice between making manufacturing or other changes before or after approval lead to a discussion on what is experience for when a process or method is now "platform" (for example, as applied to how many molecules?) or "prior knowledge".
- Regulatory acceptance, in the clinical phase, for predictive stability approaches based on mAb product knowledge was varied and case by case between products. Examples given

– product entry to clinic delayed due to inadequate in-use stability data (patient safety could not be assured), Applicant not performed sufficient 'due diligence' on the stability program and insufficient information on the stability models used. For both clinical phase and registration, cautions from and to participants - if want to use supporting data from development, data from other products (prior knowledge), or models need to show the relevance, the applicability, and the limitations.

- In another example discussed, an Applicant was unable to use stability knowledge that differed in container closure system e.g., vial to PFS. The agency would not accept the stability data from the vial product for the PFS product, thereby severely restricting the shelf-life. Current ICH guidelines are clear in requiring primary stability data to be from product in the same container closure system as the intended commercial product. The revised ICH guideline should allow analytical comparability data to justify a switch from vial to PFS when data show no impact on stability at the recommended storage condition by the differences such as silicone oil (potential to increase risk of particle formation).
- The table was asked for their 'wish-list for the anticipated ICH Stability guideline revision:
    - Use of analytical comparability data to bridge changes through development that can justify use of development data to determine the product stability profile and shelf-life.
    - Use of 6 months stability data to model the stability profile using Science & Risk-based Predictive Stability Modelling. It was pointed out that we should not describe minimum stability data in terms of time since it is the number of data points balanced with assay variability that is important for accurate statistical prediction or inference. A biostatistician should advise on the minimum data for the predictive stability model being used.
    - Ability to use science and risk-based predictive stability modelling to claim shelf-life greater than the available long-term stability data from primary stability lots.
    - Guidance addressing stability expectations for products of unmet medical need and Orphan designation products, where CMC product development is greatly accelerated, and few lots manufactured and less product-specific manufacturing experience.
    - Flexibility in stability expectations for drug substance (and drug product) that is extremely stable e.g., frozen drug substance (or lyophilised drug product).
    - A risk-based approach to the number of lots on stability in the initial submission after a change in product/process versus commitments for additional lots
    - Post-approval change stability expectations and considerations around products with a major drug substance change not requiring drug product stability data post-change.