Table 18: Design of Stability Studies for Accelerated Product Development

Facilitators –

Pam Rood, *Genentech, a Member of the Roche Group*

Kayla Woodlief, *Biogen*

Scope:

While companies are driving for faster development timelines, by its nature, stability data and expiry determinations are typically some of the last information to be dropped into the registration package. Additionally, even with ICH guidance, the requirements between countries are not standardized and need to be considered when developing the stability program strategy. In this roundtable, approaches to collect stability data earlier in product development and strategies to create a stability program that complies to global expectations will be discussed.

Questions for Discussion:

1. How are primary batches defined and justified? At what stage of development are you gathering primary stability data from for expiration setting?
2. In the 2017-2018 timeframe, FDA provided stronger feedback regarding exploring alternatives to the standard approach of monitoring post approval annual commitment batches of drug substance at the recommended storage condition. The goal was to identify alternative study conditions/acceptance criteria/durations to enable early identification of the cumulative effects of minor intended or unintended manufacturing changes on product quality.

    • What is the current experience?

    • Are there standard approaches that have worked well and been acceptable to the Agency?

    • Have any new points been raised by the Agency that companies have found helpful?

3. Have alternative stability packages (prior knowledge, ASAP studies, etc.) been utilized to support initial expiry assignment? Clinical or commercial phase?
4. What is the stability strategy for a program with material constraints (limited inventory)? Have companies been successful with justifying omission of stability studies (DS, accelerated/stressed study arms, photostability, reduced testing, etc.) in light of material constraints?
5. How are changes to stability requirements managed while maintaining timelines?

Discussion Notes:

January 25 and 27 –

1.   How are primary batches defined and justified? At what stage of development are you gathering primary stability data from for expiration setting?

Notes:

- Traditionally, primary stability was only from PPQ batches, but moving to pivotal or earlier batches if no significant changes between pivotal and PPQ manufacturing

- ICH Q1A allows 1 representative pilot scale batch as primary. Looking to use 1 development batch and 2 commercial batches due to limited supply. Scale differences and facility fit considered low risk

- Producing 3 registration batches as early as possible to start stability studies

2.   In the 2017-2018 timeframe, FDA provided stronger feedback regarding exploring alternatives to the standard approach of monitoring post approval annual commitment batches of drug substance at the recommended storage condition. The goal was to identify alternative study conditions/acceptance criteria/durations to enable early identification of the cumulative effects of minor intended or unintended manufacturing changes on product quality.

- What is the current experience?

- Are there standard approaches that have worked well and been acceptable to the Agency?

- Have any new points been raised by the Agency that companies have found helpful?

Notes:

- Continue to monitor at the long term (frozen) storage condition with same historical approach. Addition of either an accelerated (5°C) study arm or one at an appropriate stress condition with following considerations:

  o   reduced selection of methods/attributes

  o   variable time points depending on the product and primary selected attribute chosen for assessment

o   some products have included acceptance criteria when expected degradation is well known (e.g. when studying at 5°C), some products have included a combination of alert/action limits and qualitative evaluation criteria (e.g. when monitoring at stress conditions)

3.   Have alternative stability packages (prior knowledge, ASAP (Accelerated Stability Assessment Program) studies, etc.) been utilized to support initial expiry assignment? Clinical or commercial phase?

Notes:

- For clinical, use development/representative stability data and extrapolate for expiry setting.

- Use real time data for IMA

4.   What is the stability strategy for a program with material constraints (limited inventory)? Have companies been successful with justifying omission of stability studies (DS, accelerated/stressed study arms, photostability, reduced testing, etc.) in light of material constraints?

Notes:

- Little change in stability program

- Reduced time points

- Test CQAs specifically instead of following platform stability program

5.   How are changes to stability requirements managed while maintaining timelines?

Notes:

- Develop strategy/timeline after considering associated risks of not meeting country-specific requirements

- Use pre-filing meetings or Q&A to test the acceptability of deferring certain requirements as commitments either to provide during the IMA review period or post approval

- Delayed or tiered submission timing (i.e., manage the timing of the filing to ensure sufficient data is available for each region)

- Caution against setting precedent in submission content

Other Notes from discussions:

- Use of accelerated or stressed conditions used for comparability studies

- Use of next generation sequencing (NGS) for clonal stability and MCB testing