Table 12: Design of Stability Studies for Biotechnology Product Development and Lifecycle Management – A New USP Chapter

FACILITATOR: Joseph Kutza, A member of the AstraZeneca Group

SCRIBE: Camilla Santos, Amgen Inc.

SCOPE:
Biotechnology derived or biological medicinal products are inherently complex, often requiring specialized technologies and procedures to ensure their quality, safety and efficacy. One of the essential requirements for any medicinal product is that these attributes remain applicable throughout the shelf life of the product until the labeled expiry – namely product stability. In addition, the stability of the product must be assured from the moment it leaves the company until it is administered to the patient.

Regulatory guidance in regards to biotechnology/biological product is available from ICH Q5C and repeated in the USP chapter <1049>. However, whilst the guidance covers regulatory expectations in a broad sense, the complexity of the actual design of expiry setting studies as well as various other stability studies necessary for product characterization and use are not covered. Therefore, the intention of the new companion chapter is to provide further detail regarding the design of stability studies from the earliest stages of the product development lifecycle, through product licensure and then post approval. This chapter will consider both drug substance and drug product, including drug/device combinations, noting that there are differences between each that influences the content of their respective stability studies (e.g. bulk thaw and fill, combination product/device functionality).

Additional stability studies, such as those used for temperature excursions, time-out-of-temperature prior to use (i.e. for patients with home use), comparability, combination product/device and in-use studies will be discussed. This chapter will therefore provide a holistic approach as to which studies to perform at relevant stages of product development and best practices around their design and execution.

It is important to recognize the need for stability studies that result in a comprehensive understanding of the degradation pathways of the product (both drug substance and drug product) and those attributes that are stability indicating versus those that are not. From from a risk based approach and using Quality by Design principles it can be valuable to understand how to determine which attributes that change over time might impact safety and/or efficacy (for example, looking at patient serum samples for in vivo interactions with product).

The scope of this particular chapter will focus on biotechnology derived protein products as well as vaccines and combination products. Other biotechnology/biological products such as cell and gene therapies and protein products such as drug-conjugated monoclonal antibodies have unique stability requirements of their own. However, in general, many of the concepts described in this chapter will broadly apply.
QUESTIONS FOR DISCUSSION:
1. Developing stability specifications – within lot release or separate?
2. Stability studies for comparability – best practices and challenges
3. Changing expectations for studies on DS attributes that don’t change at recommended storage (e.g. frozen DS)
4. Determining the criticality of attributes that change over time
5. Expectations around product in secondary packaging and stability approaches
6. Statistical approaches for trending and reactions of the quality system to signals
7. Time out of temperature for patient use products – designing end to end studies
8. Optimizing stability studies based on accrued knowledge (critical CQAs, change over time, testing frequency, etc.)
9. Are there any other subjects that should be in the chapter?

DISCUSSION NOTES:
Discussion opened with an introduction by Facilitator as to the scope of the new USP chapter
- Focus is US, guidance to expand the existing ICH and FDA guidances (fill in the gaps)
- USP chapter is guidance only and will a be chapter above 1000
- Will focus on lifecycle stages starting with toxicology through post-market approval lifecycle management
- Chapter is open to all biologics, including vaccines and cell & gene therapies

Roundtable discussion questions and notes:
- Will the chapter be proscriptive with respect to temperatures and/or methods (such as bioassay)?
  - The USP chapter will refer to ICH, which covers the basics
  - Points to consider and best practices are likely to be discussed, yet the USP chapter is not intended to be proscriptive about stability temperatures or methods
- Will there be any new requirements about stability of product in devices?
  - The USP chapter is guidance only and will not place any requirements on industry
  - The chapter will provide points to consider and guidance with respect to stability of product in devices, allowing for the numerous types of devices in the clinic and market (from autoinjectors to on-body devices)
- Will there be additional guidance for highly concentrated products with glass transitions in the subzero ranges (Tg between -20°C, -30°C, or -70°C)?
  - This is not a current focus of the chapter, although there may be discussion regarding stability of stable, frozen products such as monoclonal antibody drug substance and what sponsors may consider to justify less stability
- Will the chapter touch upon Room Temp Room Light (RTRL)?
  - There is a section for ‘in use stability’ in the chapter
  - Attendees asked for additional guidance on this topic as there is a gap in ICH
- The topic of photostability followed next, with reference to ICH Q1B
  - There is no change to Q1B
  - Manufacturers still need to understand the manufacturing process, time out of refrigeration, light exposure during manufacturing steps, and impact of changes such as changing from stainless steel tanks to biobags
- Facilitator asked if other stress conditions relevant to biologics were a concern
  - One participant highlighted concerns related to metal ions
• Metal ion stress will not be covered in this chapter
  o Existing USP chapter and ICH Q3 alignment may be in the works

• Participants were asked if their companies have the same or different specifications for lot release and stability
  o Responses were mixed, about half have a single specification and the other half have a lot release specification and a stability specification
  o One participant discussed the use of characterization methods on the stability specification to gain knowledge of product trends and degradation (applicable more to gene therapy products than mAbs)
  o Most companies utilize a similar set of methods on stability as lot release (but not all do so)
  o Thoughts for separate specifications implies prediction of degradation pathways and allowance for safe/efficacious product at expiry
    ▪ Many mentioned the hurdles in collecting enough data to do so

• Facilitator asked how many participants use stability in comparability evaluation?
  o A few offered responses relating to risk assessments
    ▪ A new drug substance site with a process scale up will most likely include stability as part of the comparability evaluation
    ▪ A new drug product fill line with no other process changes may leave stability out of the comparability assessment and include only as part of the validation package

• Will the USP chapter cover tech transfer?
  o How much time of stability data is needed to support a tech transfer (3 months, 6 months, or more)?
    ▪ Risk dependent and region dependent; in some cases, a file can be supplemented with stability data collected during the review time
    ▪ Some regions may want as much as ½ the shelf life at time of file
  o Many participants discussed the ‘timeline crunch’ encountered when waiting for stability data
    ▪ Results at accelerated/stress conditions are often difficult because a product at 40°C for one week may show comparable results yet at one month is vastly different in its degradation profile, and companies struggle with whether to include such data in the submission package

• Participants were asked how their companies address DS attributes that do not change on recommended storage conditions (RSC) but may change at accelerated/stress conditions?
  o Example discussed was charge variants
  o One participant discussed a regulator request to monitor bioburden on frozen DS stability
    ▪ Others offered suggestions to push back and have had success in doing so
    ▪ Consideration should include the storage container used for stability
      ▪ A large container stored at 5°C that is opened at each time point to extract material and then returned to chamber is likely to need bioburden testing, whereas a single container removed for testing at each time point is not

• Participants were asked if they had products with frozen DP?
A couple have frozen DP and noted the particular challenges this presents on stability, especially if the product cannot withstand multiple freeze/thaws

### Time out of temperature for patient use – how are the studies designed?
- Participants offered varied responses
- Most found supporting freeze/thaw studies helpful
- Others use accelerated studies and/or bracketing to support time out of temp
- Temperature cycling studies are often useful
- Some store product at higher temp for 2 to 5 days before placing on stability with the specific intent that the higher temp time is to support excursions
- Some expose the product to higher temps and then store at RSC and monitor for 3 months or 6 months to evaluate stability indicating attributes (such as size exclusion)
- The length of time stored post exposure is variable
- Many start such studies well before the file, and often well before the Phase III clinical studies to support temperature excursion during shipping or patient use
- One company starts such studies to support Phase I clinical trials
- One company routinely stores product at room temp for 1-2 weeks prior to placing on stability at RSC (mostly for mAb which are somewhat stable at room temp)
- Questions were asked related to setting product specifications to allow time of out temp
- Most do not include such data in the market application because the time out of temp is not part of the label claim
- Most execute time out of temp studies on DP in the final container
- Participants asked for more guidance on this topic, including the length of time to be considered for supporting temperature excursion studies (2 weeks out of temp, 4 weeks, etc)
  - Can USP chapter look at common excursion times and offer suggestions

### Topic of what is considered ‘time zero’ drew a lot of interest
- A few companies define the test window as 30 days
- One company defines time zero as the date of manufacture, and struggles to complete testing within a 30 day window, particularly for product made at CMO
- Many define ‘time zero’ as the date in the stability chamber and will re-test if the product is placed in the chamber more than 30 days post release
- A question was asked about changes in the degradation rate at accelerated/stress conditions if young versus aged product is used (little response was offered)
- Some spoke of being asked to perform end-to-end studies, where DS at expiry is filled into DP and monitored through expiry
  - Several have encountered the question, one company does a small scale DP fill with aged DS to support such inquiry
  - Can be done with development lots, no strong driver to do on process qualification lots

### Participants were asked what they would like to see included in the USP chapter
- Responses included additional guidance on shipping validation
  - What to test, what to consider
One participant spoke of the PFS shipped via air with the pressure differences and the resulting impact to the product/syringe

- Additional guidance on post-marketing stability and process changes
- Additional guidance on evaluating comparability – stability
  - Stats for trending, visual observation
  - Shelf life extrapolation for clinical (more than what exists in ICH)
- Additional guidance on the orientation of vials
  - Inverted for worst case leachable/extractable or upright?

Facilitator closed the discussion with a friendly reminder that the USP chapter is still in draft and will necessarily go through FDA review prior to public comment.