

Table 4: The Balance Between "Phase Appropriate Specifications" and Preparation for Marketing Authorization in Accelerated Development - Lessons Learned

Facilitator: Alexandra Beumer Sassi, *Voisin Consulting Life Sciences*

Scribe: John R Dobbins, *Eli Lilly and Company*

Scope:

In recent years, regulatory procedures became available that aimed to expedite drug approval. Positive clinical outcomes are driving expedited development of cell and gene therapy products (CGTP). However, the CMC development continues to be a challenge with respect to meeting the highly accelerated timelines and global regulatory expectations. One of the challenges in this accelerated development is identifying the right balance for phase appropriate specifications and the evolution from early phase specifications to commercial specifications with a full product understating.

In principle, the specification for CGTP should ensure the safety and efficacy of the product before use, following the principles outlined in ICHQ6B. However, setting specifications for these products is not straightforward when the clinical development timelines are compressed. Developers face challenges including the lack of adequate analytical methods, limited understanding of the critical quality attributes, and limited number of batches to establish meaningful acceptance criteria.

More specifically, these products are intrinsically complex and regulatory guidance are not readily available to provide detailed requirements for each clinical development phase and each product type. Attributes such as empty/full ratio, replication competency, residual impurities, and potency assays present challenges in establishing specifications that ensure safety, are clinically relevant, and based on manufacturing history.

In this roundtable, we will discuss some of the critical aspects about setting specifications and look forward to hearing from your experiences on specifications setting strategies.

Questions for Discussion:

1. Examples and challenges when establishing acceptance criteria with limited number of batches.
2. Do all specifications tests need numerical acceptance criteria in early development?
3. How do acceptance criteria evolve in an accelerated development program?
4. Have you been successful in using a combination of release and routine characterization testing?
5. As methods change through development, what strategies have been employed to "bridge" for optimized methods?

Discussion Notes:

1. Examples and challenges when establishing acceptance criteria with limited number of batches.
 - a. Table Discussion
 - i. Typically, not able to leverage statistics with limited batches / during early-stage development
 - ii. Assess data from pre-clinical and clinical batch(es) and set reasonable / preliminary criteria. Example discussed – if a batch was determined to be 20% potent would that be suitable for use? What value would start to give concern or indicate a potential product quality issue?
2. Do all specifications tests need numerical acceptance criteria in early development?
 - a. Table Discussion:
 - i. Safety related tests (e.g. sterility, endotoxin) must have criteria established. For other product quality / potency tests generally a Health Authority expectation to establish criteria even if wide in the early-stage development. Some have had success with report results for a subset of the specification tests – however, others have been challenged on this by various Health Authorities.
3. How do acceptance criteria evolve in an accelerated development program?
 - a. Table Discussion
 - i. Leverage specification tests and characterization, as development proceeds, some characterization tests might get elevated to specification tests or get dropped if not informative
 - ii. Continually re- assess acceptance criteria as get more process / batch experience
 - iii. Leverage patient centric approach to focus tests and criteria on risk / benefit and what matters to the patient. Key point of emphasis was to make sure to involve nonclinical and clinical team members in the specification setting process.
 - iv. As move toward the commercial control strategy, some tests can be removed from routine specification testing (e.g. process impurities / media components) if validate removal.
 - v. While dependent on the MOA and product type, in general multiple potency assays with acceptance criteria will be needed to support a BLA (e.g. assess infection, expression and activity)
4. Have you been successful in using a combination of release and routine characterization testing?
 - a. Table Discussion:
 - i. Most employ a two-pronged approach. Specification tests required for product release and then typically conduct a set of characterization test on

clinical batches. The characterization testing allows to conduct additional data that is not required for product release, but used to further characterize the product and inform / optimize the control strategy as development proceeds

- ii. Example was noted that for CAR-T products, the specification tests are typically only a subset of the overall testing done on each batch – multiple characterization tests are also conducted in development.
 - iii. Based on presentations / discussions during the CGT conference, table briefly discussed the characterization of the capsid proteins and identified this as a topic to continue to monitor with respect to the evolving expectations. What is the impact of post translational modifications? If targeted engineering on the capsid proteins – what will the expectations be for characterization / control?
5. As methods change through development, what strategies have been employed to "bridge" for optimized methods?
- a. Table Discussion:
 - i. Limited time for discussion on this topic
 - ii. Key point of emphasis was to ensure have sample retains to facilitate the bridging of methods – especially for potency focused assays.