Roundtable Session 1 – Table 1 – Setting Specifications on Limited Data, Clinically Relevant Specs/ Next Generation Control Strategies: Looking Ahead to Revision of ICH Q6B

Facilitator: Somayeh Tarighat, *Genentech, A Member of the Roche Group*

Scribe: Rebekah Ward, *Pfizer, Inc*

Abstract:

According to ICH Q6B "the setting of specifications for drug substance and drug product is part of an overall control strategy" and specifications should "focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product." Critical quality attributes (CQAs) are typically defined using a combination of prior/platform knowledge, structure-function information, and process and stability data. Therefore, defining CQAs is a key component in the development of an integrated control strategy and the setting of specifications.

Traditional approaches to setting specifications have relied on both clinical exposure of CQAs and manufacturing history. However, improvements in bioreactor productivity, next generation manufacturing, and acceleration of approval pathways has resulted in minimizing the number of batches being manufactured and used in the clinic, limiting the variability of quality attributes, and reducing the available stability data. Thus, establishing clinically meaningful specifications and control strategies for quality attributes which have been deemed necessary to ensure safety and efficacy of the product has become challenging.

The focus of this roundtable is to discuss various approaches for setting clinically-relevant specifications with limited data and the application of next generation control strategies, the advantages and constraints, and feedback from regulators, as we look ahead to the revision of ICH Q6B.

Discussion Questions:

1. What approach does your company take to develop control strategies (e.g. - focused primarily on CQAs and acceptable ranges)?

2. How is clinical information shared with CMC teams at your company? How is this information used when setting specifications? Is a link between specific attributes and clinical safety and efficacy established?

3. How do you leverage prior knowledge or knowledge from other products when setting specifications?

4. What strategies have been successful to widen specifications (e.g. - more data)? What was the feedback from regulators?

5. When limited stability data at recommended storage conditions is available, how do you incorporate stability budgeting for release specifications (e.g. - accelerated stability modeling)?

6. How can the control strategy be adapted for next generation manufacturing? What technologies and strategies can be implemented to ensure product and process consistency throughout manufacturing?

Notes:

1. **Unique Manufacturing**:
    - No template for cell and gene therapies like we do for protein products.
    - Each product has unique manufacturing, making it product-specific.
2. **Phase Appropriate Approach**:
    - Dealing with cell/gene therapies, they are often first in class. Once a product is approved, physicians will preferentially prescribe it to the sickest patients. So, the clinical phase 3 data set may not be representative of what you may see in the real world because of preferential prescribing.
    - Donor variability controls the quality of cell therapies.
3. **FDA Guidelines**:
    - FDA says the process is the product, but there is disagreement that the patient is the product in autologous therapy.
    - Specifications for cell and gene therapies are on a sliding scale and need to be considered when designing specifications.
    - Example: vector copy number, potency. The worst case is probably going to become your typical case.
4. **Donors**:
    - Before clinical trials, working with healthy donors is different from the patients you will see in clinical trials.
    - FDA has said that your healthy donors need to be representative of the patient population. You need to demonstrate that healthy donors are reflective of the patient population.
5. **Allogeneic Cell Therapies**:
    - Donor material is from healthy donors. Set specifications in a phase-appropriate manner per the guidance. For phase 1, you will do a surrogate potency. As the product develops, you will do a functional potency (which may be multiple) before pivotal trials and use that to set commercial specifications.

- Multiple attributes are used to form the potency strategy (e.g., concentration, functional assay, etc.).
- There is a desire to set quantitative specifications. Phase 1 typically involves reporting results or potentially setting a very wide specification.
- You need a statistically relevant number of batches to set quantitative specifications and need to provide a plan to agencies for when to set the quantitative specification.

6. **Variability and Acceptance Criteria**:
    - Traditional approach by ICHQ6B: Does that apply to autologous or allogeneic products?
    - There is a lot of variability in CQA output in the patient populations (depends on age of patients, prior treatment, etc.).
    - The traditional way of setting acceptance criteria is taking analytical variability and manufacturing variability into consideration and setting an acceptance range. In autologous products, the variability cannot only be due to process and analytical variability but also patient donor variability. If you use the traditional way to set the acceptance criteria, how many donors need to be considered to give you a reasonable range? Can you have too many donors and set a "too wide" range?
    - There are three causes of variability: process, analytical, and patient. Patient variability is approximately 75%.
    - Patient-centric quality standards are the best way to go. How to relate that to clinical safety and efficacy?
    - Many batches failed due to acceptance criteria not being set in a way that ensures safety and efficacy.
    - The number of patients should be in the hundreds, but this is difficult to achieve with rare diseases.
    - Each lot comes from one donor for one participant. The variability can be +/- 50%.
7. **Late Stage Considerations**:
    - For autologous and allogeneic products, can you use phase 1 data to help set specifications?
    - You need to be cautious about how you set comparability when changing lots. You need to collect as much data as possible.
    - For QC release, you want to have an assay with less variability but linkage to the functional assay. You need a demonstration of bridging.
    - Post-approval, the most challenging aspect is setting acceptance criteria. You can get product approval, but 30-40% of your batches will fail. It is proposed to try to push

learning of QA to safety and efficacy post-approval. This is a unique situation to learn more about quality, safety, and efficacy.

- Is it reasonable to set wider acceptance criteria at the beginning to allow you to set a specification based on not variability but the relationship to safety? What tools can we use to build that relationship between safety and acceptance criteria?
- Can we introduce this into the ICH framework? This is seen as a large issue that needs a framework.
- There is so much unpredictable post-approval variability.
- Can we use AI to get and analyze the data? (tie in the pharmacovigilance back to CMC). On top of pharmacovigilance, follow up on the relationship between QA and safety and efficacy.
- Is there a question of access to the data? You need data and enough of a larger size data set to enable AI learning.
- You need to proactively think about building a protocol that will allow you to analyze the data.
- This was done but not rigorously accepted. A failed batch was put in the patient. Although the data set is good, it doesn't follow the prescribed methods for evaluating specifications. It wasn't as accepted as hoped.
- How can we set the specifications without failing batches while ensuring safety and efficacy?

8. **Recent Developments**:
    - There is a recent paper with FDA guidance authored by participants (ISPE, Oct 2024).
    - Moving away from LOQ specifications for autologous products. This worked a few years ago but is not acceptable in today's products.
    - Example: A product was approved in the EU but not in other countries due to assay variability in potency. The potency is used to dose patients. How do you dose patients when the linkage cannot be made? A separate standard was found and solved the problem, but this is still an issue for many.
    - How do you relate the quality attributes to patient outcomes when the analytical variability is so wide?
    - You need to build a relationship between quality attributes and safety and efficacy.
    - For autologous products, what is a numerical value for viability? This cannot be answered.
    - Traditionally for biological protein products, you can go lower than +/- 20%.

- The FDA will challenge you if you are below 70%. You need to be able to show no issue to safety and efficacy.
- Healthy donors and high viability: 90% sounds reasonable for healthy donors. 70% may be reasonable for autologous patients. You need to make the argument that you are comparing appropriately.
- What data set can you use for patient-centric specifications?
- One tool was to use platform technology. Can this be used for CAR-T? Yes, absolutely (opinion at the table).
- Can you utilize the platform from different indications? Yes, likely depending on the dose and cell therapy objective.
- How to define the platform? Same vector, promoter, same manufacturing site, and process.
- Platform designation is so restrictive that it can be useless for autologous and allogeneic therapies.
- If you take the designation away, can you use prior knowledge for setting acceptance criteria for the same class of products?
- Yes, same vector and same basic process, analytics, and cells.
- Is there utility in using dose escalation studies? Can we learn something from that to help set specifications? This needs more thought.

9. **Potency Specifications**:
    - Cytokine assays are tighter than cytotoxicity assays.
    - Can you correlate them and use a single assay for release?
    - Typical variability is +/- 30% in the clinical space. It is likely tighter for the commercial space (FDA guidance has a lower number).
    - How do you show potency is predictive of clinical response?
    - For cell therapies, it is very difficult to make that connection successfully.
    - Your potency should meet certain criteria for phase 2.
    - It is difficult to compare back to a clinical outcome due to cell variability.
10. **Relative Potency**:
    - Is there experience with the use of relative potency? For gene therapy, this is the standard. Acceptance criteria will start broad and narrow as the product progresses through the clinic.

- Functional potency can remain a characterization assay rather than a release test (where expression assays are release).
- Acceptance criteria are broad for phase 1. Very often, the batch number is very small to set specifications early on. The range can vary. Typically, start out with +/- 30% variability for a relative potency assay. This is not always a balanced specification.
- For relative potency, a full dose-response curve is used to determine potency. This depends on the dynamic range of the cell.

11. **Stability and Control Systems**:
    - For cell and gene therapies, do you do forced degradation to show that the assay is stability indicating?
    - This is part of development with freeze/thaw and stability studies. You need to know which are stability indicating before you start the study.
    - It is more difficult for cell therapies. How do you degrade a cell and keep it still functioning?
    - It can be challenging for assays to pick up the degradation.
    - How do we use learning to refine the control system over time?
    - Do you drop or add assays? (You would only add things if asked to).
    - Keep certain things as characterization.
    - For commercial purposes, you drop assays if you have multiple for the same parameter or can modernize an assay. This is part of lifecycle management. You need to generate the data to make the change.