Table 2 and Table 20: Setting Commercial Specifications Beyond Clinical Experience

Facilitators: Katrina Kearns, *Pfizer, Inc.* (Session 1)
Richard Seipert, *Genentech, a Member of the Roche Group* (Session 2)

Scribes: Valerie Tsang, *Biogen* (Session 1)
George Bou-Assaf, *Biogen* (Session 2)

Key Words:

Specifications, patient-centric

Scope:

Specification-setting continues to be a challenging topic because many products are now developed using an expedited and lean approach, resulting in limited available batch data at the time of filing. Limited batch numbers and short development times result in narrow clinical experience ranges for many CQAs. Additionally, global regulatory expectations vary from market to market, creating complicated global specifications. As such, defensible rationales for patient-centric, risk-based specification strategies are more and more important. This roundtable is designed for discussion of these challenges and will delve into potential strategies for dealing with them.

Roundtable Session 1 (Table 2) Notes:

Introductions around the table -- Representation from many companies and FDA CBER

1. *How would you address specifications with limited batch numbers?*
    - Start with statistical analysis to see where you are, even with limited batches. Often will end up with a narrow range because limited variability with few batches. Then pull in different types of data to see what kind of justifications can be made. Stability data, characterization data (relevant variants and impact), interface with clinical teams to understand what adverse reactions are observed and whether correlated to variants, literature. All coming together.
        - Collaboration with clinical: They have started to trace specific lots to specific patients. Can also use dose finding studies to perform calculations (e.g., HMW)
        - Connection to specific patients is very important for cell therapy
    - Depends on the spec. For some attributes there are safety considerations that can't just be based on stats.
    - Example for ADCs -- range of DAR that still shows efficacy, can calculate back to get range
    - Aged material studies -- helpful to use material that is close to intended shelf life in your clinical studies
    - Connection with toxicologists (important to connect with colleagues outside of CMC), tie to dose finding studies, etc. Working closely with clinical, safety teams to understand if there is anything observed beyond what is expected and use the info the justify safety. Overall need to look at risk assessment, prior knowledge.

- Challenges with turnover of people or gaps in time and needing to re-educate colleagues outside of CMC. What kind of tools can be built? CMC people speak a different language than clinical people.
- Challenges with understanding potential impact on immunogenicity. Use of prior knowledge -- E.g., there may be known specific HCPs that are higher risk. If you build clinical data over time then you can leverage it.

2. *How does limited product understanding of quality attribute criticality impact your specification setting process?*
    - For cell therapy, every patient is a batch. Therefore when you file for commercial you have many batches and a lot of heterogeneity. Tolerance Interval as a start and need to go in with a wider range and then it is a negotiation with agency. Need to justify with clinical experience.
    - Sometimes agency will agree to post-approval commitment to evaluate after more batch data available. With initial BLA -- FDA will consider and may accept provisional specification, but it depends -- e.g., unmet patient need, etc. There will also be CPV of course and will confirm or change, and FDA is willing to work with sponsors.
    - Experience widening specs after commercialization? Yes, but it is very challenging and takes years and if one agency disagrees then it can't happen unless you divide your supply.
    - Agency comments: Link and cooperation between CMC and Clinical colleagues is what the agency is looking for. Ideally specification is even narrower than what was tested in clinical trials. Statistical analysis should be done when sufficient # of batches during commercial production. Need to justify the statistical methods that are used. Need to be very careful about CQAs, as requirements are higher (e.g., Mean +/- 4SD is not acceptable for CQAs). Sometimes specs are set too tight and there can be requests for widening -- it is not easy and depends on the agency. For FDA if it is a single outlier for a batch and just one attribute, can submit a PAS for a one time exemption to use the lot which will be assessed case by case. If it happens continuously, then need to collect sufficient data package to show that product will still be safe with a wider specification.

3. *How do we move to patient-centric specifications that include allowance for impact to patients as opposed to being limited to batch data?*
    - "patient-centric" versus "clinically relevant"? PC is what matters to the patient, while CR is what was used in clinical studies? Can use prior knowledge, literature, etc., to understand what matters to patients. Totality of info and risk based approach. PC and CR were intended to be the same, but eventually CR has been interpreted as clinical experience. So now moving to PC terminology to refer to what matters to patients even if not used in clinic before. Leveraging prior knowledge (even if it's not clinical experience with your own product) to apply to your product can apply for certain attributes. Also look at patient population (e.g. for oncology patients whose immune systems are shot, could potentially set different specs because immunogenicity is lower risk).
    - It's about how to justify in the JOS
    - At company specs are set with input from toxicologists, clinical, CMC, etc. At FDA for BLA there are different teams (CMC, pharm tox, clinical). CMC consults with clinical for specifications. If referencing clinical information in M3, adding comments to link to clinical studies can help the reviewers.

- If clinical range is wider but process capability allows for tighter, agency prefers tighter limits. But if few batches available, may not be appropriate yet to understand the true process capability. Also will add or change manufacturing sites during commercial, so there is high risk if limits are set too tight. Industry perspective: If can justify wider specifications without impacting safety/efficacy, could still have tighter process controls within specs to reflect process capability. Allows process improvements, etc and enables supply globally for the long term.
- Challenge for impurity if analytical method is not sensitive enough to detect such low levels, but hard to determine what level is safe if not much known