Table 3: Bridging Strategies for Manufacturing and CQA Assay Changes Moving from Phase 1 to Phase 2

Facilitator: Shirley Chan, *Genentech, a Member of the Roche Group*

Scribe: Bryan Silvey, *A2 Biotherapeutics, Inc.*

Scope:

As C&GT products are becoming more common in biotech, the international and national standards and regulations/guidelines are still maturing. While it is understood that the principles of manufacturing and control strategy for C&GT products are the same as other parenteral biological therapies, there are unique challenges and strategies for this modality. In this roundtable, we will discuss various bridging strategies for manufacturing and CQA assay changes moving from Phase 1 to Phase 2 development.

Questions for Discussion:

1. What are some unique challenges you are facing when moving from Phase 1 to Phase 2?
    a. How have you overcome the challenges?
2. How have you assessed and demonstrated comparability?
3. What team of company experts/functions participate in the assessment of the change and the strategy (e.g. comparability) of change from Ph1 to Ph2?
4. As product knowledge is in reality just building in Ph1, how is that knowledge leveraged in strategy for the change? If it is a "platform" manufacturing process (i.e for example autologous cell therapy) or QC assay (i.e. for example qPCR, or a potency assay), does that enable the bridging strategy more clear? Less risk?

Discussion Notes:

Focus – from Phase 1/2 to Pivotal

Challenges - <u>limited amount cells/product.</u> <u>Plan Ahead!</u>

Theme/Common Points to Consider.

1. Retains
    - Engineering runs -retains are important to control bridging studies
    - Retains – comparability side by side is required
    - Allogenic – engineering run retains are important

- Retains key in assay comparability. Retains of Engineering runs are the ‘Gold Standard’ from Phase 1 to Phase 2

2. Common Assay Considerations/Lessons Learned
    - Do bridging of methods before comparability of manufacturing changes
    - Using reference standards as source of comparability in method changes – no GMP sample
    - Do development runs for ddPCR
    - Qualify a platform based assay. Like ddPCR
    - NGS used gRNA purity – (e.g. purity assay.)

3. Common Bridging Strategy Comments/Lessons Learned
    - Apheresis retains and characterization - mobilizing can only occur once in lifetime
    - Best practice – assure comparability protocol has ‘success’ criteria. Not high similar (ICH guidance)
    - Highly recommend risk assessment for comparability protocol
    - Risk assessment include clinical design.
    - Early bridging strategy/design should be thoughtful, with changes
    - Product characterization – start early as possible
    - Statisticians – ‘have them at the table’ when establishing bridging/comparability strategy
    - Remember - Comparability and CQA establishment are separate activities.
    - Incorporate into feasibility approach both infectivity and activity (transgene expression)