Roundtable Discussions Session 1 - Table 12: Bridges Strategies for Manufacturing and CQA Assay Changes Moving Phase 1 to Phase 2 Focus – from Phase 1/2 to Pivotal

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Abstract:

The manufacturing and control strategy principles for C&GT products pose unique challenges given the evolving global regulatory guidance in this space and the relatively rapid clinical development into pivotal phase typically associated with the indications these products are intended to treat. Well-defined control strategies may not be possible prior to pivotal studies given that there is usually limited manufacturing experience with few batches required to supply early phase clinical studies. In this roundtable, we will discuss the various bridging strategies for manufacturing and CQA assay changes moving from Phase 1/2 to pivotal phase.

Discussion Notes:

- Front load CMC development so you can be ready at any point for an accelerated pathway
- Agency is giving more detailed CMC comments to sponsors at EOPII to help them minimize mistakes for fast Ph III (eg method validation deep dives)
- OK to make non-GMP batches for purposes of process development and method validation, so long as they reflect the characteristics of the GMP material
- If sponsors make 5 non-GMP engineering batches just like the GMP process, and 5 GMP preclin/clin batches, they might be able to use n = 10 batches for spec setting
- changes in raw materials can have a disproportional impact on these processes, so try to include multiple lots of raw materials in the engineering runs to assess impact on product
- But realize there could be a string of good or bad lots of RM at a given vendor, so different lot #s does not guarantee maximum variability
- Can do an in-use test for some RM (eg cells, vectors, media) before accepting the lot for use, but cant always determine critical characteristics from an in-use test
- You don’t know what you don’t know because you can only respond retrospectively to problems; hard to prevent problems before you know they are even possible
- Try to leverage your own prior knowledge, but there is even greater value in attending CASSS meetings, to see problems faced by others (THEIR prior knowledge becomes YOURS)
- Vendors favor wide control ranges for their materials to reduce scrap and support diverse applications, so it is up to the user to determine how narrow they should be for their applications
- Health agencies advise RM vendors to totally segregate their RM production processes to prevent possibility of cross-contamination
- Industry feedback to vendors is very powerful in convincing vendors to change practices to meet high user quality needs
- Increased vendor quality controls could lead to increased scrap and increased prices, but it would be worth it to avoid contaminating a user process
- Emerging consortia for critical materials in CGT products; eg BioPhorum

- Vendors may segregate production space but share purification or packaging space, still a risk to product quality
- Recommendations to support CMC package for CGT:
- Leverage platform processes, methods (see SCB and ARM publications)
- Use product reference standards to link process/method changes (set aside the discussion on challenges with CGT RS!)
- Use product retains for comparability studies and method bridging studies
- Generate non-GMP runs if needed to increase data on process variability
- Don't confuse something CRITICAL with something CONTROLLABLE. Just because you can control it doesn't make it less critical
- Leverage R&D data but be aware of data integrity concerns (FDA letter re Zolgensma fabricated R&D potency data in BLA)