Roundtable Session 2 – Table 1 – Recent Trends in Questions from Health Authorities

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Abstract:

In the current regulatory environment, global health authorities have shifted their focus to a demand for deep scientific assurance. We are seeing a new wave of health authority questions that probe the underlying logic of our risk assessments—moving beyond what the data says to how we have mitigated risk throughout the product lifecycle. The "burden of proof" has evolved.

Discussion Questions:

This roundtable will explore recent trends in HA queries with a focus on how industry is using intensified risk-based justifications to defend CMC strategies. By crowdsourcing these experiences, we will identify where authorities are seeking higher levels of assurance and how we can better harmonize our scientific narratives to reduce regulatory uncertainty and accelerate patient access.If you had to pick one 'trending' topic that resulted in a surprise Request for Information recently, what would it be? Are there specific areas where the 'bar' is being raised globally?"

With the push for accelerated pathways, we often launch with leaner data sets. What trends are we seeing in terms of 'Post-Approval Commitments' versus 'Pre-Approval Requirements'?

Has anyone been successful in recently justified wider ranges for CQAs: How was ‘assurance' gained that these wider ranges wouldn't impact the patient?

Has anyone recently received a question that pushed you to provide much deeper 'worst-case' data or a more granular risk assessment than in previous filings?

Despite ICH Q12 progress, standardized queries that vary by geography on the same data set continue to occur. Has the use of a 'Master Global CMC Rationale' to preempt these differences been successful, or is today’s reality still one of highly customized regional dossiers?

Notes:

Questions around polysorbate 80 (global) – quantitation, degradation – demands to add PS80 testing as a routine release test starting at phase 3 clinical supply, conversations around difficulty of establishing a validated test method, conversations around inclusion in the specification for DP versus acceptability of FIO/characterization for DS (report results). Also questions about stability. Conversation around the quality of the polysorbate raw material as an incoming excipient. Conversation around impact of certain host cell proteins on degradation of

polysorbate (especially for high concentration proteins). Some firms then do studies to demonstrate impact of varying levels of PS on product quality after stress such as agitation. Understanding impact on product quality like aggregation, visible or subvisible particles, role of PS in stabilization. Also understanding the stability of the PS itself and free fatty acids.

CBER vaccines asking for detail on methods and for method validation already during clinical development. Also for cell and gene therapy - - issues of quality of methods during development and that analytical methods were not “good enough” at time of commercialization. Therefore pushing for analytical methods development, qualification and validation.

Questions on specs – always to tighten. Question to add spec for HMW/HMMS independent of spec on monomer even at phase 1. Several are mentioning that in particular for bispecifics/ trispecifics etc there is a push for HMW/HMMS acceptance criteria early in development. This attribute is relevant for understanding of product quality from early development. Recommendation to add this spec at Phase 1 even if the method is not ‘GMP validated’ at this time.

Increasing demands from US FDA to move detail on the equipment sterilization conditions and equipment into the P.3.3 even after the sterilization validation information has been included into the P.3.5. (versus inclusion into A.1) This gets problematic for reliance if the US is the reference authority. Even if changes to A.1 are reportable, it seems that P.3.3 is more “enforceable”.

Insistence from US FDA on detail on the sterilizing filter information into the P.3.3, even to the level of the vendor part number. Issue is “like for like” changes and visibility to changes that would otherwise be managed only under the pharmaceutical quality system.

Feeling like the FDA has been moving to a more conservative position over the last two years, less science based risk assessment. This is a problem when trying to leverage a reliance procedure especially for a post-approval / authorisation change assessment.

Sterile assurance information (OPMA)

Shipping validation (OPMA)

Bridging / transfer of an established shelf-life (drug substance container closure change, push back on the basis of data at 40 degree C even though the DS is stored frozen - - moving from bottle to bags, evaporation causing increase in protein concentration in bags at 40 C)

Discussion about the pragmatism of how to respond given the timing of a question and the urgency of the response.

Discussion about the reputation of the firm, the history, and how that does or does not impact the review and questions that may be sent. Reviewers aim for consistency, to approach each review with consistent approach.

Discussion on strategy of the firm about how to “push back”, do you adapt for every submission or how many times do you try to push back. How to give feedback to FDA and facilitate conversation without the urgency of a file under review.

Focus on common interest of supply, and making sure patients have assurance of continuity of supply. How can we communicate risk of drug shortage for PAC assessments?

Getting questions about process related impurities, leachables even early in development (phase 1)

Even though they have an ELISA binding assay in the specification, there was an insistence to include a cell-based potency assay available as a characterization assay into the specification with acceptance criteria (even though it is not yet GMP assay).

This push is to incentivize the firms to improve their assays and think about assay development earlier in product development.