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

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Abstract:

Global health authorities are increasingly focused on scientific rigor, lifecycle management, and risk-based approaches, resulting in more nuanced and challenging questions during development and approval. This roundtable will dive into the latest trends shaping regulatory interactions— covering comparability, control strategies, advanced analytics, and expectations for novel modalities. As agencies sharpen their focus on innovation and patient safety, understanding these trends is critical for accelerating approvals and avoiding costly delays.

Discussion Questions:

1. What emerging themes are you seeing in agency questions during IND/BLA/MAA reviews?

2. How have expectations for control strategies and lifecycle management evolved?

3. Are there notable differences in queries from FDA, EMA, PMDA, and NMPA? How do you harmonize responses globally?

4. What unique challenges arise for advanced therapies (e.g., CGTs, mRNA)?

5. How can industry anticipate regulatory expectations to reduce uncertainty and improve readiness?

Summary of Notes from Roundtable Session 1 – Table 1

Attendees of the roundtable have experience supporting ADCs, cell and gene therapy, biologics, peptides, bispecifics, trispecifics, and vaccines.

Topics of interest include the following

- How AI is changing the queries the industry is receiving; is there anything we can do to
- Expectations for tightening expectations
- If other companies are getting BLA registration type queries earlier in the submission process
- Learn recent trends in Qs from HAs and experiences
- If we are seeing a change in the questions and level of details being requested
- Promote what is being done in IQ consortium
- AI implementation questions regarding how we validate
- Trying to get ahead of questions that might be received as part of BLA submission
- Questions around contamination strategies

1. Impact of Artificial Intelligence (AI) on Regulatory Queries

- **Agency Use and Speculation:** There is industry speculation that the FDA may be using AI, triggered by receiving unusually quick questions (e.g., within 30 days) on minor changes in annual reports. However, there is no official evidence to confirm this.
- **Industry Transparency:** Participants felt that agencies should be more transparent if they use AI (e.g., providing a disclaimer), as this would allow the industry to adjust submission strategies (e.g., by ensuring key search words are included).
- **Internal AI Efforts:** Companies are evaluating or building internal AI capacity for tasks like checking submission consistency, categorizing information, and drafting. They are concerned about the quality and validation of AI software used for submissions.
- **Risk of Bias:** A concern was raised that if the FDA releases its AI code for transparency, it could be biased, and relying on it could make AI the de facto regulator.

2. Evolving Expectations for In-Use/Stability Studies and Patient Safety

- **Beyond ICH Requirements:** The FDA is increasingly asking for higher-than-ICH-required data for in-use studies to support the label claim for BLAs, specifically looking for data to support the real-life patient handling excursions (e.g., higher temperatures outside the specified range).
- **Pharmaceutical Manuals and Drug Preparation:** FDA (CBER) is showing extra vigilance, often asking questions about drug preparation information (pharmacy manual) and in-use studies (e.g., for ADCs).
- **Global Harmonization:** Canada and China also consistently ask questions about the pharmaceutical manual and overdose concerns, respectively. Issues related to IV bag material are also a common, regional experience.
- **Pushback:** One company mentioned they are trying to push back on the FDA's request for additional in-use data outside the label claim. The group confirmed that pushing back is sometimes successful, depending on the topic.

3. Earlier BLA-Type Questions in Drug Development (Pre-Phase 3)

- **Derisking Programs:** Companies are increasingly seeing BLA-level questions earlier in the drug development process, often before Phase 3. It is speculated that this is the FDA (CBER) attempting to derisk the program by reviewing data earlier.
- **Excipient Control:** For excipients (e.g., polysorbate), the FDA has recently requested specific specs and testing where previously process control and FIO measurements were acceptable.
- **Regulatory Approach:** Agencies are using language like "we advise" instead of an explicit requirement. While higher-level document responses have been mostly accepted for permission to proceed, they often include feedback requesting a review of specific things (like protocols).
- **Data Requests:** Agencies have been frequently requesting Excel spreadsheets of company data to run their own statistical analysis. HAs are also expecting companies to submit analytical data upfront to support future changes to analytical procedures.

4. ICH Q12 and Accelerated Pathways

- **Implementation:** One company successfully submitted a PACMP (Post-Approval Change Management Protocol) to reduce the reporting category for a common process change, securing approval with minor queries, demonstrating the value of ICH Q12 elements.

5. Other Noteworthy Regulatory Focus Areas

- **EMA Protein Specifications:** The EMA is expecting protein concentration and protein content specifications of +/- 5%. This information has also been published on the EMA Q&A website under the biologics working party.
- **Internal Agency Changes:** Questions can sometimes be related to management changes within the HA (e.g., Micro group at CDER) and internal performance metrics that incentivize groups to generate a certain number of questions or focus on specific topics to ask those questions on.
- **Widening CQAs:** The question regarding changes for widening Critical Quality Attributes (CQAs) did not resonate widely with the group. No one responded with experience with questions around this topic.