Roundtable Session 2 – Table 4: Regulator Review Preferences and Recent Review Trends: Questions and Key Issues (Focus on Ex-US Regions)

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Abstract:

This roundtable discussion aims to delve into recent US FDA regulatory review preferences and highlight emerging trends in the regulatory review process, and the implications of recent trends on the submission and approval processes. Participants will share insights and experiences that facilitate successful submissions and provide valuable perspectives on navigating the dynamic regulatory environment.

Discussion Questions:

1. How has the use of automation impacted submissions?

2. What are strategies for responding to requests for redundant tabulation of information?

3. How does industry view the impact of implementation of KASA at FDA?

4. How might a global data standard for CMC submissions affect mutual reliance?

5. Has the promotion of QbD principles, like attribute-focused justifications to support specifications, been generally successful?

Notes:

- EU Clinical Trial Regulation (CTR)
    - Receiving questions more appropriate for licensure (e.g., approach to setting specs) early in development.
    - Increase in volume of questions for Ph1 CTA (60+), highly dependent on lead country HA.
    - Observing more conservative positions being shared across multiple of the HAs (e.g., France and Germany expectations for virus clearance in clinical phase).

    - Shelf life considerations - It is difficult to navigate country-specific requirements (e.g., PEI requires stability from the GMP clinical facility). Recommendation from one sponsor to initiate clinical studies in countries that allow silent SLE and add countries with more strict shelf life requirements later once stability data is available (e.g., 6 months real time stability data to support 12 month shelf life claim).
    - CTR transition for ongoing clinical studies - recommendation to submit baselining CTA amendment to align the IMPD across all countries in scope of the clinical study prior to transition, including as many prospective changes as possible.
    - Recent Q&A trends
        - For MAbs, requests for measuring glycosylation as either release or characterization even if Fc effector function is not a part of MOA. Need significant data (e.g., "substantiate with data") to justify not part of MOA, well controlled, and not needed on release.
        - Polysorbate questions - need to submit data to show no degrading to justify not testing on stability.
        - Low Endotoxin recovery requests for clinical programs
- China
    - Cannot file a CTA if your supply chain is mixed within and outside China. Manufacturing is either all in China or all outside. Mixed success with listing local China affiliate as study sponsor instead of global organization. Not a new requirement, just focused on enforcement.
    - Registration of multiple DS or DP sites are permitted in the same license; however, License Holders need to manage sample requirements for in-country testing.
- "Upgrading" reduced content dossier IMA countries to EMA/FDA standards
    - Not seeing exceptionally high numbers of questions and questions received are reasonable.
    - For companies not providing EMA MAA level content proactively to newer ICH countries with country specific requirements (e.g., Brazil, Mexico), these HAs are asking for MAA equivalent content even if this content is not required per national regulations.
    - Sharing of EMA MAA assessment reports - share with HAs upon request, no experience with EMA denying the sharing of their report
    - Does submitting a single dossier worldwide provide efficiency in post approval lifecycle management? Too soon to tell.
- International Post Approval Changes
    - Review times in international markets remain a challenge, especially South Africa and Brazil.
    - Large number of manufacturing site driven changes leading to increase in Post Approval Changes across industry. Many recent Breakthrough or PRIME designated products were expedited to the market with non-optimized process yield/capacity and needed to optimize/scale-up/transfer post approval. Fragmented supply chains due to varying regulatory requirements/divergence and longer review times are a risk. Try to bundle as many changes as possible for international markets to manage workload - creates complex matrix to navigate.