Roundtable Session 1 – Table 4: Regulator Review Preferences and Recent Review Trends:

Questions and Key Issues - Focus on US FDA

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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 the 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:

- Current trends for information requests (IRs)
    - Gross content request on the specification
        - Combine in-process fill weight checks with volume testing on the specification
        - Most common for commercial stage, but some questions noted for clinical programs
    - ADCC effector function
        - Sponsors have been asked to address during clinical development
        - Recommend keeping retain samples and introduce testing at the pivotal stage
    - FDA has been exhibiting scope creep on equipment validation and DP manufacturing controls
        - Not waving inspection following increase in GMP IRs
        - Example: 3 BLAs in one year, inspections performed for each, including the same facility 2x
        - Potential Annex 1 impact
        - For lifecycle products with an extensive history

        - FDA has requested tabulated data in 32R as for a new BLA
    - Example: site transfer, no process change, no potential impact to PK
        - FDA requested CPP data, 90 batches, min-max data
        - FDA had difficulty scheduling the pre-approval inspection (PAI)
    - Example: In the past 6 months, 3 BLA annual reports filed, IRs received for each
        - Received IR for process performance data for different brand of sterile filter
        - Different brand same materials of construction, same pore size, like-for-like
            - Should not be considered a high-risk change

- Requests for tabulated data in 32R in addition to information filed in module 3
    - One explanation is that FDA is using the tabulated data to populate KASA
        - Likely related to FDA's PQ/CMC data standard concept
    - inconsistent questions
    - Is it possible to push-back?
        - One company provided the data and tables in the preferred FDA format in S25
        - FDA still sent an IR asking for the separate table(s) in 32R
        - Consider a meeting request to discuss how limit or eliminate redundant data submission

- Microbial in-use data requested at IND stage, Phase 1
    - Language to restrict microbial in-use hold time in absence of microbial challenge data
    - Requests for information in the pharmacy manual
    - These questions have come in the past in different forms
    - One example of language that is not typical
        - Establish an in-use hold time **less than 4 hours**
        - Because FDA has observed growth in less than 4h at 2-8°C
        - The more common IR or non-hold comment is to establish a hold time **≤ 4h**
    - The IQ consortium working group on in-use stability has published best practices
        - https://journal.pda.org/content/early/2023/10/25/pdajpst.2022.012806
        - FDA/CDER/OPQ/OMPA is publicly aligned with recommendations in the publication
        - FDA/CDER/OPQ/OPQA opinion on the recommendations is pending

- General
    - IRs are coming in very late, with 1 month to go before the action date
    - IRs coming within the last week of the PDUFA date
    - Some questions requested with 24-48 h turnaround time

- Other topics

- Closed system transfer devices (CSTDs)
    - Companies are taking different approaches to providing versus not providing data
    - For some companies testing is performed but not necessarily submitted

- FDA view of EMA post-use post sterilization integrity testing (PUPSIT)
    - Most companies provide this data

- Medical Device submissions
    - Essential performance requirements (EPRs) included on release and stability testing
    - Break-loose, glide force, provided on release