Table 18: Regulator Review Preferences and Recent Review Trends - Questions, Key Issues

Facilitators: Gracie Sheng, *Genentech, a Member of the Roche Group, South San Francisco, CA,* USA and Elizabeth Schmidt, *GlaxoSmithKline, Phoenixville, PA, USA*

Scope:

This roundtable will discuss and share experiences with recent regulatory review trends and questions. After years of hard work to develop and characterize the processes to manufacture a medicine the regulatory approval process is the final step to make the medicine available to patients who need it and lengthy review timelines can delay the approval. To minimize the number of information requests and ensure the required data is provided first time it is important that applicants understand the regulatory review preferences and the recent review trends. Additionally, due to challenges presented by the pandemic, such as raw material shortages, the need for minimal approval timeline is a key to not disrupt the supply chain.

Questions for Discussion:

1. What trends are you observing from health agencies reviewing marketing applications and how are you responding? How are the responses received?
    a. Specification Acceptance Criteria
    b. Reference Standard Strategy
    c. Microbial Control Strategy
    d. Nitrosamine risk assessment
2. Sharing novel/expedited regulatory strategies due to pandemic (raw material shortage).
3. Established condition: sharing experience since FDA's pilot program
4. How often do you include PACMP in the BLA to downgrade reporting category for future change, which process steps do you use this tool often? Examples such as future cell banks qualification, cell culture, purification, reference standard, site change, etc.
5. Manufacturing summary info requests by FDA: is this more common, are companies doing this preemptively in the BLA. Are these requests limited to process parameters & controls, or do they expand to analytical methods and validations?

Discussion Notes:

Nitrosamines:

- Lots of information requested from EMA.
- Lilly is starting to proactively include the risk assessment form, it is not enough to just state that the risk assessment is done and there's no risk.
- This is consistent with what NovoNordisk has seen

- No one could comment on whether anyone has seen anything in their assessments for biologics

Specification Acceptance Criteria:

- NovoNordisk has seen different responses for impurities for the same API material from the US vs. EMA. EMA has been asking to tighten and recalculate, the US did not ask anything. The EU wants them to include all new batches in the assessment, not only clinical relevance.
- FDA asked a bunch of questions about microbiological testing though and the EMA did not ask much.
- FDA considers more of a holistic approach (with maybe wider but justified specs), but EMA has a lot more challenges and batch data into the consideration for the specifications.
    - For global distribution, of course the tightest specs must be met
    - In order to tighten specifications, might have to shorten hold times

Reference Standard Strategy:

- Has putting protocols in place in the regulatory submissions for new batches minimized regulatory reporting when a new batch is made?
- For 'other' markets without a routine reporting plan or defined plan for new RS's, this has been helpful.
- FDA has wanted to see actual protocols for requalification testing, but it doesn't reduce the reporting category (FDA has made that clear in their documentation)
- Lilly has had the same experience

Microbial:

- UMA: US FDA has been very particular about bioburden method qualification
- Also, asking about accuracy and intermediate precision for site-to-site comparisons for the same test methods
- Wanting to be sure that there are good controls for microbial strategy
- Look at the presentations from the FDA, and have the manufacturing tech ops persons to learn what the presentations have been (Patricia Hughes) to be prepared

Raw Material Shortages:

- Results in lots of post-approval changes and communication to the health authority on shortages during the review period.

Container Closure Integrity Testing (CCIT):

- A recent submission did not have annual CCIT as a commitment for an IND, but it was requested to do that (and separating this out from sterility).

- For BLAs, there has also been discussion about all methods are validated and providing the methods in the process validation section

Pandemic Regulatory Strategy:

- New IND provided compendial excipients and raw materials that were to be used
- Pandemic Year 2, can't get those materials that covers all the compendia expectations
- Materials that can be procured meets some of the compendia, but not all (maybe just conforms to USP)
- There have been delays in routine reviews and variations due to COVID, pandemic
- e.g., 6 month timing is planned, but it took a year
- There have also been delays in site additions to regulatory submissions during this period of time

Established Conditions: Sharing experience since FDA's pilot program

- By a site that was a part of the pilot program, it has been very helpful and was overall a positive experience

How often do you include PACMP in the BLA to downgrade reporting category

- It has been submitted and approved by the FDA and EMA, but sometimes the sites don't actually follow it all, so it didn't reduce any reportability
- The back and forth and level of detail boxes you in, and if the change wasn't EXACTLY what you communicated, it doesn't buy any benefit in reporting category
- For Site Changes, it has to have a PAI, but if there is upfront agreement in the comparability strategy, it could be beneficial to including these
- No one commented on having any denial of the agency to review this
- An example is that for the cell bank qualification has had a lot interactions for a long history, and for a breakthrough therapy, there was an agreement to make some commitments (such as PMC), for when the next cell bank is made and ensure that you have materials put on stability
- Very pricey to have to do all of this for lifecycle management in the future

Manufacturing Summary Info Requests by FDA

- Two years ago at the WCBP, there was discussions for mapping CQAs in Module 3 and after the meeting there were comments that there have been FDA requests to ask for manufacturing summary documentation during RtQ
- Some companies now just treat it is default in the beginning for the submission for the BLA
- Another company provide 2 examples for where it was clear that the CQAs and CPP are a clear expectation as part of the submission

- Another company was told in a Type C meeting to provide this meeting upfront in the BLA
- Another company has been asked now in advance about method specification, CQA summary, and process parameter information in table format in regional section
- For methods, in table format, what did that look like?
- Summarizing method validation and ranges, that you would have in Module 3, but in table format in Regional Submissions
- Maybe the session on Thursday afternoon might clarify if the request is related to maybe a pilot of something very specific that will be expected going forward
- There's also a recent trend for two programs for one country for control charting for CQAs, so they are starting to make that readily available to support process parameters
- There's also an example that one project asked for analytical, but a second one at the same time, they haven't asked for the analytical information
- Would be nice to know expectations vs. it being individual reviewer specific

Inquiries LEAR (spelling) Effect from the FDA: No one had comments.