

Table 40: Regulator Review Preferences and Recent Review Trends - Questions, Key Issues

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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:

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
 - Seagen has seen a lot of questions for specification evaluations.

- Most companies have been asked to tighten specifications as post approval commitments, where a limited data set was used in setting the initial specs.
- Common for companies to have different specs for different countries. Some companies release batches against different specs and distribute accordingly.
- Some Latin countries just issue a blank statement to tighten specifications.
- Merck uses global dossier

b. Reference Standard Strategy

- Merck: Had an example for a marketed product (vaccine), post approval, where there's a process control lot is used in lieu of RS, and there were a lot of questions re: control lot and ACs.
- Genentech has been recently asked to provide protein concentration information for potency RS, which is observed in other companies as well, including binding capacity.
- Japan typically requests very tight acceptance criteria for reference standard which can result in failure of a reference standard lot.

c. Microbial Control Strategy

- Bioburden: GNE shared high level questions related to limits, microbial control over resin/membrane lifetime (also common for Merck), and questions around microbial control for operations which usually get asked during GMP inspections but not so much during BLA review.
- Endotoxin: GSK sets specs based on safety, but was not accepted by FDA as they were too wide. Questions UOM (EU/mL vs EU/mg) were received as well.

d. Nitrosamine risk assessment

- Merck has seen questions from EMA on this
- GNE: provided risk assessment in module 1
- One company shared that though EMA guidance states vaccine product is out of scope for nitrosamine risk assessment, EMA still asked for it during review.

e. Others

- GNE received a question for IND from Italy: shelf life proposed was based on a development batch confirmed using a GMP batch. The question was

regarding a concern that the shelf life did not consider sterility testing and container closure which were not tested in the development batch.

2. Sharing novel/expedited regulatory strategies due to pandemic (raw material shortage).

- Merck filed a CP for a filter, where the change was reduced from CBE 30 to AR. Supply impact was the driver.
- FDA granted expedited review for raw material shortage related change for a rhumatis product.
- Merck successfully filed a CP for a stopper on the primary container via a CBE-30.

3. Established condition: sharing experience since FDA's pilot program

- Only GNE provided experience with the pilot program, one company said EC was submitted to EMA but was asked to remove it since EMA has not adopted ICH Q12 yet.

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.

- Historically PACMP has been used via comparability protocol (US).
- May use in EU, Canada, would be nice if it is globally accepted.
- One company successfully filed a PACMP for future DS process improvements with EMA to downgrade reporting - Protocol submitted as Type II, data submitted as Type 1b. With the same change in Japan, it took 2 years.
- The success can be improved with upfront communication with the HAs

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?

- Not discussed, running out of time.

6. Other, accelerated stability in the post approval stability protocol

- A company was asked by FDA to include accelerated conditions in the annual GMP stability protocol (S.7.2). Merck had similar questions and agreed to the request. GNE has seen similar questions. Merck and GSK shared no acceptance criteria but only profile comparisons were included in the accelerated stability protocol.
- Another company negotiated with the FDA and successfully got the request removed, rational is that enough knowledge has been accumulated