Table 5 and Table 23: FDA's Requested Process Control Tables – What, Why, and How?

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Key Words:

Process control, data assessment, table

Background:

- The Office of Biotechnology Products (OBP) has been requesting sponsors to provide information on their critical quality attributes, stability, assays, process data, in-process controls, etc. to be summarized in tables provided by the Agency.
- The request is made during pre-BLA submission meetings for the BLA.
- FDA is requesting assistance from sponsors to help organized the data in order to help facilitate their review and it help put things into perspective and synthesize information.
- The CTD is not organized in a way that would allow the agency to easily access or find the information.
- The review timeline is a concern with priority BLA submissions.
- Not providing the information does not result in a refuse to file, or complete response and the tables are voluntarily.
- This table does not replace anything that has already been submitted and is not requested during post-approval supplements
- Table does not need to be updated or maintained.

Rationale

- Agency wants to understand what was performed, how did sponsors get there.
- What IPC, attributes, and range and what did sponsors do to support those ranges.
- Agency wants to understand that the operation is under control.
- The tables are organized by unit operation.
- FDA concern that only relying on DOE to expand range, it doesn't work out when you go to full scale. Helps FDA think about flexibility when requesting for wider ranges.
- FDA wants min and max not individual values for each process parameter.
    - With min and max still requires sponsors to look at each unit operation for each clinical batch.
    - Huge effort and a lot of work and going back to all the historical batches for all the clinical batches.
- Sponsors who have platform knowledge do not typically provide all the process parameters per unit operation.
- Proposed control strategy and have data to support, then put into the table the ranges that you are supporting and ranges that are acceptable.
- FDA has to decide whether the controls are adequate and it's difficult when information is scattered all over.
- Does not replace reviewing at the other sections.
- If the manufacturing process is not informing you on the control strategy, then sponsors don't need provide in the table

Discussion Points:

- May better inform the Agency on your process development, derived from gaps the Agency has seen with multiple filings. If the parameter is drifting, the Agency needs to understand why it's still acceptable supported by characterization, small scale studies, development data.
- Sponsors struggle with providing the tables that shows the operating range, and fear that the Agency will request sponsors to tighten.
- May cause delay in approval by having to defend limits/range back and forth with the agency.
- More critical when sponsors come in with established conditions (EC); FDA needs to understand what data was used to support these ranges and ECs.
- If sponsors feel that the target/PAR/NOR is acceptable and the min and max is not helpful then you do not need to provide it, however, will have to justify the range.
- FDA requires operating range and acceptable range, if you didn't run to range then put in "ran to target", and change the heading so that it is more appropriate.
- Just because you provide DOE and PC doesn't mean it can support the range sponsors requested
- A pain point for the agency is where the range is coming from PC, DOE, the agency does not have visibility of where it comes and to be able to review in a timely manner.
- Data generated during development that are no longer used to justify the control strategy is not required to include in the table
- FDA does not like sponsors running the process narrow and to target.
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Questions:

- Are tables available for sponsors to see in advance? No, however will be provided at pre-BLA meeting so companies have time to organize the information
- Do the parameters feed into an electronic system? No, however it does feed into the parameters that goes into KASA.
- Column headings are changing, is there going to be consistency? Yes
- How do you intend to run your process with what you know about your process? Agency is asking how you fill that gap and justification can be review the DOE. Large companies typically will have that data and smaller companies may not have that knowledge.
- FDA does want companies to operate at the range they justified and need to know that the ranges you are requesting for at scale is acceptable? What is the risk?
- How do you know that the ranges you proposed are acceptable? do they verify the ranges that you established? Justification of range is requested.
- Are combination product parameters required? No, required for drug substance, drug product and not device. Device reviewed by CDRH which have different requirements.
- Is this table required or maintained after BLA? No have not been requesting this post-approval change/supplement i.e. site change and typically provide the pFMEA, etc.
- How close is the pFMEA to what FDA table requires? A summary of the approach that is used to analyze the process is useful for the agency. Rationale of your control strategy so it is useful for thought process.
- Can we just put in the approved/acceptance criteria range from the commercial batch records or insisting on clinical values in PPQ and development? Development, clinical and PPQ is required.
- Is there a desire to look at all the PC, DOE, or describing/summarizing that information what the agency is looking for?
- What is the value of providing the target data?

- Are you looking at the variability of the target data across numerous clinical batches?
- Moving away from small scale models, how can industry better provide small scale models that would inform PC to share with agency?

Other points to consider:

The CTD is changing and changing drastically and may be more harmonized with the recent changes.
When revisions to ICH M4Q come out, things are going to be structured differently.
Past CTD history is a struggle, and need for some guidance to what information/data needs to be provided