Table 26: Preparing for PAI and HA Inspections: Trends and General Guidelines

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SCOPE:

The purpose of the pre-approval inspection (PAI) is to ensure facility compliance with appropriate regulations, including current Good Manufacturing Practices (cGMP), development/validation of the manufacturing process and methods and adherence to the submitted process for the Biologic License Application (BLA) or Marketing Application. Preparing for the PAI can seem overwhelming as it is often performed at the same time as marketing application authoring. Being un-prepared for the PAI, however, can lead to significant impact on submission review and approvability. What strategies can be best employed to help ensure a quick and successful inspection outcome?

QUESTIONS FOR DISCUSSION:

1. What are the best practices for PAI preparation?
   a. Are the use of PAI checklists, mock PAI audits, mock facility tours, and weekly meetings employed?
   b. Do many groups use a consultant for a “fresh pair of eyes” to review PAI readiness?
   c. How are known significant deviations or “Hot Topics” handled during PAI preparation?
   d. How are staffed trained for interacting with inspectors and responding to questions?

2. How do we best learn from others?
   a. Are reviews of current trends and enforcement activities preformed?
   b. Training – always a popular topic, is it up to date for everyone?
   c. Data verification, what are the best ways to ensure the source data can be produced quickly? How secure are the data acquisition systems?
   d. Were all previous violations remedied and all prior commitments met – strategies for assurance?

3. What is the best way to reduce response time for inspection requests?
   a. Strategies for timely communication to impacted site experts providing the requested documents and responses?
   b. Strategies for requested documents – how to provide them quickly?

4. How do companies ensure change control and deviation systems are ready for a moment in spotlight?
   a. How are manufacturing, testing, facility, or equipment changes made after submission but prior to inspection handled?
   b. Can deviation reports be generated quickly for a wide variety of topics and requests?

NOTES:

1. What are the best practices for PAI preparation?
   - There are two common CMC related inspections, cGMP inspection and PLI/PAI inspection. The cGMP inspection occurs every two years and is focused on cGMP compliance of the site. The PLI/PAI inspection is conducted as part of original BLA or PAS review. From the prospective of FDA, The purpose of PLI/PAI inspection is to ensure the sponsor has a good understanding of the manufacturing process for the specified drug substance/drug product to ensure consistent manufacturing of high quality, safe and effective drugs. During the PLI/PAI inspection, FDA inspectors focus more on the aspects of GMP compliance and
product understanding, less on process/product development. However, the development reports may be requested if the inspectors have specific concerns.

- There are generally two approaches taken by the sponsors for inspection preparation: strategy planning or try to cover all possible details. Panel members suggest that the correct approach should be case specific and depend largely on the purpose of inspection and the style of inspectors. It is helpful to 1) review existing interactions with the specific regulatory agencies for possible topics of interest; 2) get a list of all supplements submitted since last inspection; 3) look for possible clues in the IR requests received so far.

- It is important to know which health authorities that you are dealing with: different regulatory authorities (FDA, EMA, Japan, Health Canada Russia, Mexico etc.) have very different organizational structures and different style of inspections. Inspection should be prepared accordingly.

- Mock inspections are commonly used for both cGMP and PLI/PAI inspections. In general, the inspection personnel are from a different site within the company so that they can provide a fair assessment of the site and identify the weakness with a fresh pair of eyes. The mock inspections are generally very useful for the preparation of official inspections. Outside consultants are hired for PAI/PLI inspection by smaller companies, although the practice is less common for large biotech companies. In general the panel members feel that outside consultants are more suitable for situations that need specific problem solving skills. Some consultants can pick up nuance issues and get the sponsor to spend a lot of time and effort to fix them.

- In general, subjected matter experts (SME) are responsible for drafting the technical documents, RA-CMC personnel review all technical documents and are responsible for submission content. SMEs take the lead during the inspection to address technical questions, while regulatory personnel address submission content and strategy.

- Training of SMEs: SME should be very well trained/informed to be ready to answer questions:
  - SME should listen carefully to the inspectors’ questions, only address the questions that are asked and don’t speak on other topics unless he/she is asked to respond.
  - Mock tests are also important to ensure the SMEs are ready for inspection. If SMEs are very nervous and deemed unsuitable to talk directly to the inspectors, backup plan should be developed.
  - SME redundancy should be built into the organizational structure to minimal impact from the departure/sickness/vacation of key SMEs.

- Preparing HA inspections for CMOs requires extra efforts. The sponsors should work with the CMOs ahead of time to prepare for the inspections. During inspection, the sponsors normally work in the shadow with the CMO to facilitate the interaction.

- Manufacturing schedule for PAI/PLI: FDA encourages sponsor to communicate to the agency with your proposed manufacturing schedule to facilitate the preparation of the inspection. Sponsors should communicate to their respective project managers.

2. How do we best learn from others?
• CDER and ORA has undergone or is currently experiencing major reorganization efforts to better align internal structure with current trends. FDA have recently also expressed interest to reward good compliance history, however sponsors have yet to see any regulatory relief/benefits from those proposed changes.

• The needs to conduct a GMP or PAL inspection are assessed using a risk based approach. Prior site inspection history, potential impact on product quality, inspectors’ schedule and other factors are part of the consideration for the assessment.

• From sponsor’s experience, inspection observations are shared by various health authorities: for example, Health Canada sometimes will request inspection reports and IR requests from FDA as part of the application review. In addition, if changes are made to correct the observations at one specific site, such changes should be implemented globally across all relevant sites.

• When observations/citations are raised during the inspection, the sponsor should try their best to correct the issues while the inspection is still ongoing. For FDA, the observations/citations are cleared internally within the inspection team first before communicating to the sponsor. If the sponsor disagrees with the citations, the sponsor should clearly provide detailed scientific justification/explanation on why the observations are not sound. However, sponsor should avoid getting into heated debates/arguments with the inspection team.

• Sponsors feel FDA inspectors are open to share knowledge and PAI/PAL inspections generally help the firm to be better prepared for future inspections. One sponsor has had a FDA PLI inspection recently and is very pleased with the process. All panel members agree that both the sponsors and the regulators have shared interests to bring safe and effective treatments to the public.

3. What is the best way to reduce response time for inspection requests?

• Ensure the proper supporting team is assembled to answer requests from the inspectors. Key personnel should be identified at the very beginning to coordinate all inspection requests and keep track of all activities.

• The sponsors should be anticipating the following key “hot topics” items and have the information available:
  
  o Date integrity: one sponsor mentioned that they have very stringent internal source data review to ensure the integrity of the data.
  
  o Microbial control: always a hot issue.
  
  o Key data for legacy products: some health authorities can request original data for legacy product which can be very challenging. The sponsors are not sure how much information should be provided.
  
  o Deviation reports: always requested.
  
  o Topics mentioned/discussed at different sites by the same health authority: information sharing across sites is important as regulators expect similar issues should be addressed and corrective actions implemented across different sites within a company.

4. How do companies ensure change control and deviation systems are ready for a moment in spotlight?
Prior to inspection, the sponsors should get a list of supplements that have been submitted to the health authorities since last inspection. The sponsors should compare the changes mentioned in the supplements and their internal quality management system to ensure all internal documents are implemented and up to date with regulatory submissions.