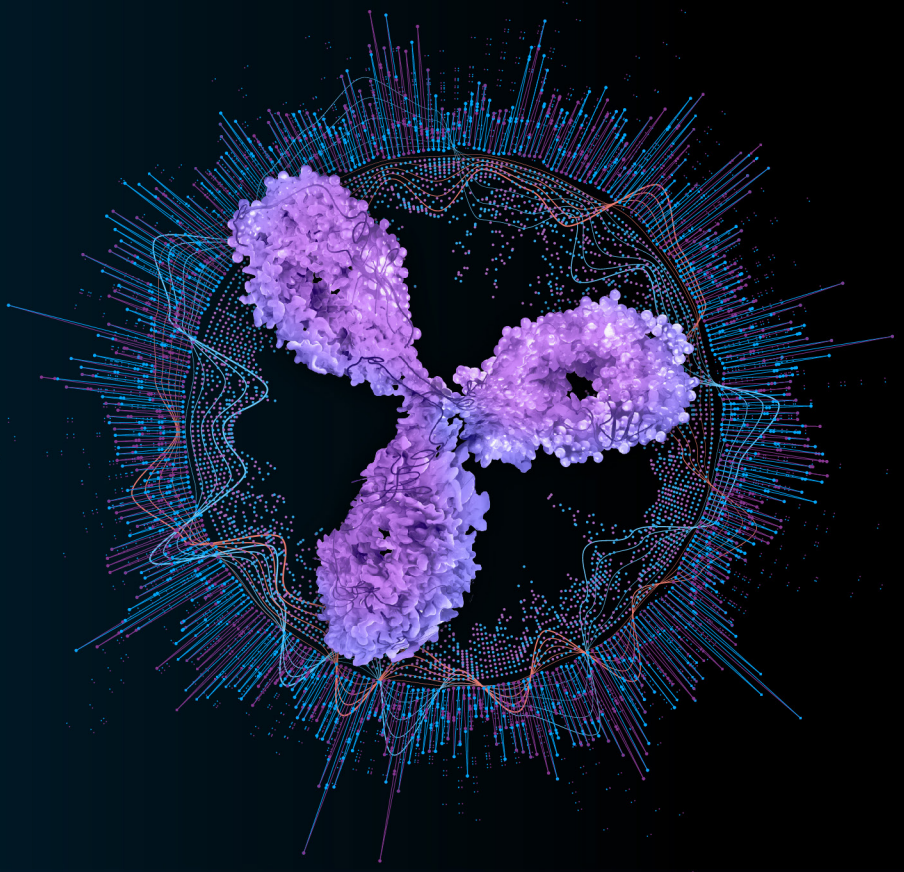
A STRATEGIC APPROACH TO PRE-LICENSE INSPECTIONS



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Pre-License Inspections (PLIs) are performed as part of the Biologics License Application (BLA) approval process to confirm that the biologic drug product is being manufactured and released in alignment with the information filed in the BLA. This article will provide insight into the PLI process from the perspective of a contract development manufacturing organization (CDMO). Based on Avid Bioservices' experiences, we believe that PLI success is determined by two major aspects: (1) great collaboration between sponsor and CDMO and (2) excellent quality track record of the CDMO.

Pre-License Inspection (PLI): Part of the Biologics Licensing Process

The Biologics License Application (BLA) is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2). The BLA is regulated under 21 CFR 600 – 680 (fda.gov), which includes applicant information, product/manufacturing information, preclinical studies, clinical studies, and labeling.

Once the sponsor has filed the BLA, the U.S. FDA (or other regulatory authorities) will conduct a PLI of the facilities/sites that are responsible for the manufacture, testing, and release of the product. The agency uses risk-based Priority Inspection Criteria to determine which sites require a PLI, taking into consideration recent GMP issues and recalls; the nature of the products and the complexity of the manufacturing process; whether the BLA is the first filed for the facility; the target indication; whether it is a candidate with an accelerated approval process

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or if there is a shortage of the drug or similar products; and other factors.

If a sponsor relies on numerous outsourcing partners for manufacturing and analytical support, that is also often a driver for a PLI for multiple sites. In such cases, there is almost always a requirement that the regulatory body visit the sites where products are being produced and tests are being performed.

During a PLI, the FDA evaluates the readiness for commercial manufacturing and the conformance of the formulation, manufacturing operations, and analytical methods. The information will be listed and provided in the CMC section of the BLA. Often, the sponsor will propose a date for the PLI, and the inspection is generally scheduled to align with the timing associated with the BLA review and the manufacturing schedule of the product in review. If there are no major issues found during the PLI, this would fulfill one item on the FDA checklist to recommend BLA approval. If some issues are identified that can be reasonably remedied, the investigators may recommend withholding approval until the issues have been resolved.

While each regulatory authority may have different specific requirements and requests related to a PLI, the frameworks are relatively similar from one regulatory agency to another. In some cases, if one agency has already conducted a PLI and recommended approval, other regulatory authorities may waive their own onsite PLIs.

Focus on Quality and Manufacturing Process

The main objective of the PLI is for the regulatory authority to get a first-hand view of the manufacturing site, its quality systems, and the state of compliance with regulatory requirements and to confirm that what is being done conforms to what is claimed in the BLA. These inspections are generally similar to typical regular inspections of production sites, but with a focus on the product for which the BLA was filed. In addition to auditing the quality systems and practices, they will perform a detailed inspection of the manufacturing area where the product in question is being produced. In some cases, the FDA inspector may also want to be present in the manufacturing area to observe the actual manufacturing operations of the products.

Collaboration is Essential to Ensure a Successful PLI

The foundation of a successful PLI is extensive and transparent collaboration between sponsor and CDMO. In Avid's experience, the client provided the CMC sections of the BLA package to Avid for review, which is an essential activity to ensure that the submission package is accurate. An additional benefit of these activities is to allow the CDMO to prepare for the actual inspection.

The objectives of the PLI are 1) to align roles and responsibilities between the CDMO and the sponsor, 2) to prepare a presentation to begin the inspection, and 3) to strategize the storyboards. A committee is created by comprising technical operations, quality, and project management from both the sponsor and the CDMO. Technical and operations typically include process development, manufacturing science and technology (MSAT), process engineering, and manufacturing; meanwhile, quality consists of analytical development, quality control, and quality assurance. In some cases, a third-party consultant may also be brought onto the committee to serve as an observer.

Finally, the project manager (PM) plays a crucial role in facilitating discussion within the PLI committee, as there are various discussions and preparative work that must be performed before, during, and after the PLI. The PM is responsible for streamlining communication exchange and navigating the timeline and critical milestones of the activities. Having a strong PM will also drive preparation and the success of a PLI.

Avoiding the Main Causes of PLI Failure

Once a BLA has been submitted for review, it is essential that the sponsor company and all outsourcing partners conduct internal audits/mock audits as part of preparation readiness for the PLI. A mock audit will also allow the PLI committee to assess the readi-

ness of the CDMO. This exercise can be very beneficial, as it helps to identify potential quality issues and deficiencies that have occurred. Another benefit of mock audits is on-the-job training, which ensures that all CDMO personnel are always in audit-ready mode.

Failed PLIs generally occur for two main reasons: an inadequate quality system or a lack of / insufficient planning and preparation. A poor quality system will earn a drug manufacturer a 483 citation regardless of whether the inspection is general or for a specific BLA.

Planning and preparation have to do with understanding what questions will be asked and having appropriate responses ready. In particular, it is essential to be able to adequately explain any deviation that has occurred. These are expected for all manufacturing processes. One of the key strategies at Avid Bioservices involves the development of PowerPoint storyboards to visually explain any exceptional conditions that may have occurred during the execution of the process validation activities.

Working with an Experienced CDMO to Prepare for a Successful PLI

Another key to achieving successful PLIs is recognizing that the PLI should be top of mind even before the BLA is submitted. An experienced PM and CDMO would work on an extensive timeline building up to the actual PLI.

For sponsors that outsource development and manufacturing activities, it is essential to work with a CDMO that has experience and values excellent collaboration. Collaborative and strategic planning for tech transfer, process validation, BLA submission, and the PLI are key to passing a PLI.

Quality, Collaboration, and Transparency Drive PLI Success at Avid

Since 2016, Avid Bioservices has successfully passed four PLIs. In total, Avid has had eight successful PLIs (or PAIs (pre-approval inspections)) in our history in support of clients. Avid was issued zero 483s following the last five FDA inspections.

Avid's success derives from the robust quality system, which applies to both clinical and commercial projects. A second differentiator for Avid is our commitment to collaboration – both internally and with external stakeholders. In addition to preparing detailed storyboards, we have extensive checklists that are used to prepare for PLIs. Our quality compliance system includes training on how to effectively interact with regulatory inspectors.

Avid's goal is to provide transparent communication to the sponsors throughout the life cycle of the program. As an example: sponsors are informed and updated on the status of process validation–related and then are also involved in any decisions that are required to be made. We view this as a critical component to the success of the program.

What sets Avid apart is the combination of our quality system, experience, and collaborative philosophy. Combining these three aspects, Avid has been able to be routinely successful at supporting sponsors and patients to produce safe and high-quality products.

The Storyboard Approach

Avid uses the term *storyboard* to refer to a PowerPoint slide deck that is created to outline the manufacturing and testing activities.

Significant effort is made to be unbiased, and the storyboards are developed jointly with Avid's clients. The goal is to help the inspectors understand these activities before they review the actual data, which can be vast. They have to review hundreds or thousands of documents; we try to simplify that effort for them. Having the storyboards means that the inspectors are informed before reviewing all of those documents.

If questions arise during the inspection that are not covered by the prepared storyboards, Avid will work with clients to generate (within a day) additional storyboards to address the inspectors' questions.

ABOUT THE AUTHOR

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William Leonardi currently serves as Director, Late Stage Project Management at Avid Bioservices and oversees client management for late-stage molecule/projects. He is responsible as a single point of contact for Avid's clients' programs ranging from technology transfer, process characterization and validation, to commercial/post-commercial processes. In his role, he works closely with Avid's customers by designing and developing strategic timelines to meet the critical milestones for client projects. In addition, he collaborates with multiple cross-functional teams, which include manufacturing and technical operations, quality, finance, and business development, to ensure the projects that are transferred/developed would meet Avid facility and quality standards. During his time at Avid, he has been involved in multiple strategic projects involving Pre-Licensing Inspections (PLIs), Investigation New Drug (IND) submissions, and various technology transfer activities for early- and late-stage programs. William graduated with a Bachelor in Chemistry from UCLA, a Master of Business and Science (MBS) in business of bioscience and bioprocessing, and a Ph.D. in pharmaceutical discovery and development from Keck Graduate Institute, Claremont, CA.

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