FDA Pre-License Inspection (PLI): A Guide for Biologics

By Adrien Laurent, CEO at IntuitionLabs • 11/16/2025 • 30 min read

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FDA Prelicense Inspection: Executive Summary

The U.S. Food and Drug Administration (FDA) requires a **Pre-license Inspection (PLI)** of manufacturing facilities as a key step in approving **Biologics License Applications (BLAs)** for biological products ([1] www.law.cornell.edu) ([2] www.fda.gov). Under Title 42 U.S.C. §262 (the Public Health Service Act) and related regulations, a biotechnology firm *cannot distribute a biological drug until it has an FDA license and has passed a facility inspection* ([1] www.law.cornell.edu) ([3] www.law.cornell.edu). In essence, a PLI is a comprehensive examination by FDA investigators of a facility's processes, controls, and records **before a biologic product is licensed**, to verify compliance with current Good Manufacturing Practice (cGMP) regulations and commitments in the license application ([2] www.fda.gov) ([4] www.blog.whitehalltraining.com). In practice, a PLI can involve multi-day on-site audits (often with teams of inspectors) covering raw materials, production areas, laboratories, quality systems, and more ([4] www.blog.whitehalltraining.com) ([5] www.wuxibiologics.com).

This report examines the PLI process in depth. It covers regulatory foundations (laws and guidelines requiring PLIs), the scope and objectives of inspections, operational procedures, and notable cases. Key findings include evidence that PLIs are a critical regulatory tool to ensure **facility readiness and product quality** before market entry ([6] www.bioprocessintl.com) ([2] www.fda.gov). The FDA's inspectional programs emphasize **voluntary compliance** and risk-based scheduling ([2] www.fda.gov) ([7] www.lifesciencesperspectives.com). The report also analyzes how PLIs differ from (but relate to) **pre-approval inspections (PAIs)** under drug applications, includes case studies (e.g. WuXi Biologics), and explores recent trends (such as COVID-era adaptations) and future directions. All statements are supported by official FDA sources, industry articles, and expert analyses ([1] www.law.cornell.edu) ([7] www.lifesciencesperspectives.com) ([4] www.blog.whitehalltraining.com).

Introduction and Background

Regulatory Context

Under U.S. law, biological products (therapeutic proteins, vaccines, cellular therapies, etc.) **must be licensed and approved by FDA** before any commercial distribution ([1] www.law.cornell.edu). Section 351(a)(2) of the Public Health Service (PHS) Act (42 U.S.C. §262) explicitly provides that "no person shall introduce or deliver for introduction into interstate commerce any *biological product* unless… a biologics license is in effect" for that product ([1] www.law.cornell.edu). This statutory mandate is implemented via regulations in **21 CFR Part 600-680**. In particular, 21 C.F.R. §600.21 and §600.22 (recently revised) govern inspection timing and duties for manufacturing establishments. Section 600.21 states that *"The inspection of an establishment for which a biologics license application is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a biologics license is desired."* ([3] www.law.cornell.edu). In short, FDA need not inspect until the facility actually produces the final biologic in question. (FDA amended these rules in 2019 to remove outdated "time of inspection" mandates, providing more scheduling flexibility ([8] www.govinfo.gov).)

Within FDA, **Center for Biologics Evaluation and Research (CBER)** generally oversees biologics licenses (though some biologics are under CDER). Both CBER and CDER have inspectional roles: FDA's Regulatory Procedures Manual confirms that CBER "leads pre-license and pre-approval inspections supporting Biologics License Application submissions" as part of its managed review process ([9] www.fda.gov) ([10] www.fda.gov). Similarly, a CDER compliance program (for biological therapeutics) specifies that "pre-license inspections are the responsibility of CDER" ([11] www.fda.gov).

Thus, by law and policy, FDA conducts an on-site inspection of the manufacturing facility (and often contract facilities) shortly before or after a BLA submission, but prior to final approval. The purpose is to verify compliance with the FDA's **current Good Manufacturing Practice (cGMP)** requirements (21 CFR Parts 210/211 and related biologics regulations) and to ensure the firm has met commitments made in the license application ([2] www.fda.gov) ([4] www.blog.whitehalltraining.com). The inspection team evaluates production processes, quality control testing, facilities, equipment, and documentation per FDA's compliance and inspection guidance. If significant violations are found, FDA may refuse to license the product until corrections are made ([4] www.blog.whitehalltraining.com) ([7] www.lifesciencesperspectives.com).

As one industry commentary emphasizes, "FDA prelicense inspections represent a critical means for ensuring [the] biofacility compliance before product authorization" ([6] www.bioprocessintl.com). In practice, FDA inspects all aspects needed to demonstrate that the facility *can consistently produce a safe, potent, and high-quality biologic* as promised in the application. Over the past decade, the volume of biologics license applications has grown markedly. FDA publishes annual lists of biologics approvals, showing dozens of new BLAs in recent years (for vaccines, gene therapies, plasma products, etc.) ([12] www.fda.gov)([13] www.fda.gov). Each of these approved products underwent a PLI process, underscoring the scale of this requirement.

Overview of Inspection Types

FDA conducts several distinct inspection types as part of product approval:

- **Pre-License Inspection (PLI)**: The focus of this report. Done for manufacturing establishments named in a biologics license application, to verify cGMP compliance *before the license is granted* ([3] www.law.cornell.edu) ([4] www.blog.whitehalltraining.com).
- **Pre-Approval Inspection (PAI)**: Similar concept for drug (NDA/ANDA) products. The FDA checks drug manufacturers for compliance with cGMPs before approving a new drug application ([14] www.lifesciencesperspectives.com) ([4] www.blog.whitehalltraining.com). (The term "pre-approval" is used in FDA guidance for drug or device approvals.)
- **Routine Surveillance Inspection**: Ongoing GMP inspections of licensed product facilities (or drug facilities) for marketed products. These occur periodically post-approval to ensure continued compliance ([2] www.fda.gov).
- **Post-Approval Monitoring**: Other oversight (for example, for vaccines, inspections under the Biological Product Deviation Reporting, etc.).

PLIs are specifically tied to the licensing milestone (i.e. BLA). They are not one-time inspections: once a facility is licensed, routine (surveillance) inspections take over. However, FDA often combines a PLI with a standard GMP inspection if appropriate, as seen in industry announcements (e.g. WuXi had a PLI and routine inspection concurrently ([15] www.wuxibiologics.com)).

Table 1 below summarizes the main differences between PLI and PAI (and routine inspections):

Inspection Type	Products/Applications	Timing/Trigger	Primary Purpose	Authorities / Regulations
Pre-License Inspection (PLI)	Biologics (BLA)	Just prior to granting a Biologics License; after BLA review is substantially complete ([3] www.law.cornell.edu) ([2] www.fda.gov)	Verify facility compliance with cGMP and commitments in BLA; ensure readiness to produce final biologic per application	Public Health Service Act; 21 CFR 600 & 601; FDA PLI guidance ([1] www.law.cornell.edu) ([2] www.fda.gov)

Inspection Type	Products/Applications	Timing/Trigger	Primary Purpose	Authorities / Regulations
Pre-Approval Inspection (PAI)	Drugs (NDA/ANDA, perhaps some biologics under CDER)	Before new drug or generic drug approval; risk-based decision after NDA/PANDA review (as needed) ([14] www.lifesciencesperspectives.com) ([4] www.blog.whitehalltraining.com)	Confirm drug manufacturer's GMP compliance and data integrity; validate manufacturing process described in application	Federal Food, Drug, and Cosmetic Act; 21 CFR 210/211; guidance on PAI
Routine GMP Inspection	All marketed drug/biologic facilities	Periodic, risk-based surveillance inspections post-approval	Ensure continued adherence to GMP standards in manufacturing; protect public health	FD&C Act §§ 501(n); 21 CFR 210/211; FDA compliance programs ([2] www.fda.gov)
Other Inspections (e.g. Emphasis Inspections, For Cause)	Various (special circumstances)	As FDA deems, e.g. after adverse events or compliance issues	Targeted checks beyond routine schedule (e.g. drug safety, data integrity)	Specific applicable regulations

Table 1. Comparison of FDA Pre-License Inspections (PLI) for biologics vs. Pre-Approval Inspections (PAI) for drugs and routine GMP inspections. Both PLI and PAI aim to verify manufacturing compliance before approval, but PLI specifically fulfills the biologics licensing requirements ([3] www.law.cornell.edu) ([4] www.blog.whitehalltraining.com).

Objectives and Scope of Pre-License Inspections

Goals of PLI

The fundamental objective of a Pre-license Inspection is **to ensure that the manufacturing site can produce the biological product as described in the license application, in compliance with cGMP** ([2] www.fda.gov) ([4] www.blog.whitehalltraining.com). This is explicitly stated in FDA compliance programs: one program's objectives are "to ensure the safety and effectiveness of licensed biological therapeutic drug products by determining that they are manufactured in compliance with cGMP regulations and […] standards and commitments made in license applications" ([2] www.fda.gov). In practice, this means FDA investigators:

- Review the status of facility operations, equipment, and personnel.
- Evaluate active production (or readiness trials) of the biologic to confirm it meets specifications.
- Verify that laboratory testing (potency, purity, sterility, etc.) is accurate and reliable.
- Assess batch records, quality controls, and validations to see that processes perform as claimed.
- Check that any FDA-requested changes or pending supplements in the application are implemented.

As one training guide succinctly puts it, a PLI is “a comprehensive evaluation” where FDA “assess a facility’s compliance with regulatory standards before granting a license” ([16] www.blog.whitehalltraining.com). The “primary objectives” listed by an industry source include: ensuring product safety/efficacy/quality; verifying manufacturing processes; and validating the accuracy of information provided to FDA ([4] www.blog.whitehalltraining.com). In short, the PLI is the agency’s culminating check that the plant can reliably produce a quality product.

FDA’s mission is to protect public health, and pre-license inspections are a statutory duty under the PHS Act and FD&C Act. By law (21 U.S.C. §351(f)), the FDA “shall not” grant or renew a license for a biological product unless inspections are conducted and deficiencies corrected. The inspections confirm compliance not only with cGMP, but also with any facility-specific commitments made during the review. Importantly, failure in a PLI can yield a *Refusal-to-File* or *Complete Response* if not addressed properly, delaying or blocking approval ([1] www.law.cornell.edu) ([4] www.blog.whitehalltraining.com).

Who Conducts PLIs

PLIs are conducted by FDA field investigators from the Office of Regulatory Affairs (ORA), typically in coordination with the review division (CBER or CDER personnel) assigned to the application. The regulatory compliance manuals explicitly instruct that inspections supporting BLAs are “led” by the respective center (often CBER) and that field investigators participate whenever possible ([11] www.fda.gov) ([10] www.fda.gov). For example, FDA’s regulatory procedures manual notes that the Office of Compliance “leads pre-license and pre-approval inspections supporting Biologics License Applications” ([10] www.fda.gov).

CDER’s compliance program guidance (No. 7356.002M) similarly states that PLIs “are the responsibility of CDER, and will include a field investigator whenever possible” ([11] www.fda.gov). 7356.002M outlines the chain of reporting, emphasizing that each PLI report is forwarded to compliance branches and quality units in CDER ([17] www.fda.gov). Therefore, while the review team coordinates the inspection, the actual audit is executed on-site by ORA inspectors trained in GMP and biologics.

Inspection teams are often multi-disciplined: they may include specialists in manufacturing, microbiology, quality assurance, engineering, and the specific product type. For complex biologics, teams can be large and inspections lengthy. For instance, a WuXi Biologics announcement describes a 15-day PLI by nine FDA inspectors covering multiple buildings and aspects (manufacturing, QC labs, utilities, etc.) ([5] www.wuxibiologics.com). In contrast, smaller biologics or local facilities might see smaller teams. The team also typically prepares a detailed Establishment Inspection Report (EIR) documenting observations.

Scope of Inspection

Pre-license inspections are **comprehensive**. FDA investigators examine:

- **Facilities and Equipment**: Clean rooms, bioreactors, isolation chambers, water systems, HVAC, etc. to ensure validated and properly maintained equipment.
- **Manufacturing Records**: Batch production records for pilot/validation batches, deviations, rework, and stability data (if available).
- **Quality Control Laboratories**: Analytical labs where potency, identity, sterility, and endotoxin tests are performed. Investigators may observe lab methods and data integrity practices.
- **Laboratories and Validation**: Method validation reports, assay calibrations, bioburden and environmental monitoring.

- **Standard Operating Procedures (SOPs)**: Quality Manual, change control processes, training records for personnel, complaint handling.
- **Sterility Assurance**: Use of monitoring tunnels, aseptic processing, sterilization processes (e.g. vial sealing/flushing).
- **Raw Material Testing and Supplier Controls**: Conformance testing for raw materials, certificate of analysis review, supplier qualification.
- **Release Testing**: Final sterility, potency assays, and any unique tests specific to the biologic (e.g. viral particle counts).
- **Computer and Data Systems**: Controls over records, use of electronic signatures, backup and audit trails (data integrity focus).
- **Environmental Monitoring**: Results of sampling for microbial and particulate counts.

In practice, any part of the manufacturing and control system can be inspected as needed. FDA investigators rely on guidance (including archived guides like the *Biotechnology Inspection Guide*) to cover key areas ([18] www.fda.gov) ([4] www.blog.whitehalltraining.com). The Bioprocess International article highlights that risk-based strategies are increasingly used, but critical areas like sterility assurance and data integrity remain priorities. According to one survey, FDA explicitly "emphasized this [data integrity] in its guidance documents and warning letters" ([19] www.blog.whitehalltraining.com).

In summary, PLIs scrutinize the end-to-end manufacturing system. Any deficiencies ("483 observations" at time of inspection) must be addressed by the firm (via corrective actions) before final license approval can proceed ([6] www.bioprocessintl.com) ([4] www.blog.whitehalltraining.com).

Historical Evolution and Regulatory Changes

The requirement for inspections in support of biologics licensing has been part of FDA's framework since the enactment of biologics regulations in the 1950s. Key milestones include:

- **1973**: The time-of-inspection rule (21 CFR 600.21) was initially promulgated. It stated the establishment need not be inspected "until the establishment is in operation and is manufacturing the complete product" for the license ([3] www.law.cornell.edu). This was codified in 38 FR 32048 (Nov 20, 1973).
- **1999**: 21 CFR 600.21 was amended (64 FR 56449, Oct 20, 1999) but its core intent remained: inspect when the facility was ready to produce the final product.
- **2019**: FDA issued a final rule revising Part 600. This rule **removed outdated inspection timing requirements** (Sec. 600.21) and inspector duties (Sec. 600.22), transitioning to risk-based approaches ([8] www.govinfo.gov). The rule emphasized flexibility ("without diminishing public health protections" ([8] www.govinfo.gov)) but maintained that inspections are mandatory under sections of the FD&C Act. Notably, FDA clarified that these revisions "do not change the biological product establishment inspection requirements" under Section 704 of the FD&C Act ([8] www.govinfo.gov).
- **Modern Era**: More recently, regulatory guidance has evolved. FDA's Biologics programs have emphasized **quality culture and data integrity**. For example, a 2023 FDA draft guidance on quality management maturity signals that overall oversight may increasingly incorporate systemic measures of firm quality. Industry sources also note that "risk-based inspection strategies" and communication between FDA and foreign regulators have grown since the early 2000s ([6] www.bioprocessintl.com) ([7] www.lifesciencesperspectives.com).

The timeline of licensing also saw growth in biologics approvals. According to FDA data, CBER approved **dozens of new biologic applications annually** in recent years ([20] www.fda.gov). For instance, nearly 20 biologics products (gene therapies, monoclonal antibodies, vaccines, etc.) were licensed in 2022 and 2023 combined,

each requiring at least one PLI as part of review ([12] www.fda.gov) ([13] www.fda.gov). This expansion reflects both scientific advances and intensification of FDA oversight to maintain safety standards.

Pre-License vs. Pre-Approval Inspections

Understanding PLI is facilitated by comparing it to the analogous *Pre-Approval Inspection (PAI)* conducted for new drug applications. Both are inspectional steps before market approval, but with some distinctions:

- **Regulatory Category**: PLI is tailored to biologics (vaccines, blood products, therapeutic proteins, cellular therapies) under the PHS Act (42 USC 262). PAI applies to human drug products (small molecules, conventional drugs) under the FD&C Act.
- **Agency Center**: Many PLIs involve CBER (Center for Biologics) although some biologics fall under CDER. PAIs normally involve CDER, and device "premarket approval" inspections involve CDRH.
- **Application Stage**: PAIs are usually scheduled after the NDA (or ANDA for generics) has been reviewed and is near the decision point. PLIs occur toward the end of the BLA review, typically once FDA has determined the application is approvable pending inspection results ([6] www.bioprocessintl.com) ([4] www.blog.whitehalltraining.com).
- **Scope Focus**: The focus overlaps (both check GMP), but PLIs often emphasize issues unique to biologics manufacturing (such as viral safety/sterilization, bioreactor controls, donor screening for blood products, etc.). PAIs may stress different quality aspects like multi-product facilities or specific drug control tests.
- **Failure Impact**: Both can result in delays or denials if serious violations are found. However, a PLI typically directly blocks license issuance if GMP issues or deviations exist, whereas a PAI may cause an NDA to receive a "Complete Response Letter" (CRL) until it is resolved.
- **Announcement**: PLI scheduling is normally communicated to the firm after clinical data and other aspects of the BLA are nearly complete. PAI may be "planned" once the NDA review is in late stages. (Some inspections are known beforehand; others can be relatively short notice depending on FDA policy.)

As one article notes, PLIs/PAIs "give FDA assurance that a manufacturing site named in a new drug or biologics license application is capable of manufacturing the product according to cGMPs" ([14] www.lifesciencesperspectives.com). The core objective is common: verifying the production capability. Where they differ is context and often terminology, but for a firm the approach to preparation is similar to any major FDA GMP inspection.

Table 1 (above) highlights key contrasts. In summary, **both PLI and PAI seek to protect product quality**, but PLIs are explicitly a statutory hinge for biologics licensing. For example, a PAI for a drug not subject to the PHS Act would fall under FD&C regulations, but the inspection procedure (checklists, FDA 483 findings, EIR) is essentially the same methodology. Often, FDA will simply term biologics inspections as PLIs and drugs as PAIs even though the mechanics are identical.

Inspection Planning and Conduct

Scheduling and Notification

FDA's Office of Regulatory Affairs coordinates inspection scheduling in consultation with the review division. A PLI is typically "pre-announced" to allow the firm to prepare documentation and coordinate personnel. The inspection usually takes place on-site, barring extraordinary events (see COVID adaptations below). Facilities generally receive 5–10 days' notice before an inspector arrives, though the precise timing may depend on travel logistics and risk priorities.

The compliance program requires that domestic inspection reports be sent to the review office (e.g. CBER/DMPQ) and that FDA maintain records of the inspection coverage ([17] www.fda.gov). For foreign facilities (e.g. biologics made overseas intended for the U.S. market), FDA must either schedule inspections or use alternative approaches if travel is restricted ([7] www.lifesciencesperspectives.com). Historically, FDA inspectors visited many international sites (China, India, Europe) to perform PLIs; more recently, FDA began using mutual recognition agreements (MRAs) with regulators like Europe's EMA to rely on their inspection data for a U.S. license, reducing duplication. Nevertheless, by law FDA retains authority to inspect if needed.

Inspection Procedure

On the day of inspection, investigators arrive on-site as an official team. Typical activities include:

- **Opening Meeting:** FDA introduces the team and outlines the scope. The firm's representatives (quality, production, management) meet with FDA to discuss inspection plans and documentation to review.
- **Record Review:** Inspectors review documents (SOPs, batch records, validation reports, environmental monitoring logs, etc.) relevant to the product and processes. They may interview personnel regarding their responsibilities, training, and awareness of procedures.
- **Facility Walkthrough:** A guided tour of manufacturing and control areas is conducted. Inspectors commonly tour production floors, cleanrooms, storage areas, and labs, often photographing or noting discrepancies relative to descriptions.
- **Process Observation:** Investigation may observe actual production or filling runs if product is being made during inspection. If live production is complete, they review recent batch records or even process validation runs.
- **Testing Evaluation:** Inspectors often question lab staff or even witness lab testing. They check how samples from finished lots are tested, how instruments are calibrated, and how quality release decisions are made.
- **Closing Meeting:** At the end of each day (and a final meeting at inspection close), FDA discusses any significant inspection observations with firm management. The inspectors may orally note any potential 483 observations (form FDA-483) for the firm to anticipate.

After leaving the site, FDA finalizes the EIR, which classifies the inspection findings and cites regulations. The EIR and 483 form (if issued) are submitted through official channels. The firm then has an opportunity to respond to observations with corrective and preventive action (CAPA) plans. Before license approval, FDA must be satisfied that all significant issues are resolved.

One analysis emphasizes that data integrity is a centerpoint: FDA expects that electronically or manually, the data recorded in the manufacturing process are trustworthy. Common pitfalls such as inadequate oversight by the Quality Unit or improper record handling can trigger 483 findings ([19] www.blog.whitehalltraining.com).

Criteria for Success or Failure

FDA classifies inspections with findings as **Verified**, **Voluntary Action Indicated (VAI)**, or **Official Action Indicated (OAI)**. For a PLI, an OAI (significant GMP violations found) would typically prevent license issuance until resolved. Even VAI findings (minor issues) require corrective response but might not stop approval if quickly fixed. A successful PLI (no OAI) clears the final regulatory hurdle for product licensure.

The inspectorate pays particular attention to any previous commitments made by the firm to FDA during application review. For instance, if the BLA noted that equipment validation batches were pending, the PLI verifies that this was done. Similarly, any protocol deviations in clinical lot manufacturing must be justified in the final product release documentation.

Data and Trends

Quantifying PLIs specifically is difficult (FDA doesn't publicize number of PLI events separately). However, one can infer scale from biologics license approvals. CBER publishes lists of licensed BLAs each year ([20] www.fda.gov). In the early 2020s, for example, FDA approved dozens of new biologic license applications annually. Each approved BLA implies at least one pre-license inspection. For instance, 2023 saw approvals of multiple novel gene therapies (e.g. *Casgevy*, *Lyfgenia*), vaccines (e.g. RSV vaccines, chikungunya vaccine), and plasma products ([12] www.fda.gov) ([21] www.fda.gov). Even plasma collection centers (source plasma licenses) appear in the listings ([22] www.fda.gov), indicating FDA inspects these as biologics facilities.

The average **team size** and duration of a PLI vary with product and facility complexity. Anecdotal data suggest some PLIs involve 3–5 inspectors for 5–10 business days, while major biologics (like large-scale vaccine plants) can involve a dozen inspectors over several weeks ([5] www.wuxibiologics.com) ([7] www.lifesciencesperspectives.com). There is no public tally of OAI vs VAI for PLIs, but given the stringency of standards, OAI classifications are not uncommon until correctives are made. The truism in inspections is: "If it isn't documented, it didn't happen," so firms must meticulously document controls ([5] www.wuxibiologics.com) ([19] www.blog.whitehalltraining.com).

Case Studies and Examples

WuXi Biologics (2017, 2021)

A high-profile example is **WuXi Biologics** (China). In 2017, WuXi announced that FDA "completed the Pre-License Inspection (PLI)" of its cGMP facilities for production of a monoclonal antibody (ViiV Healthcare's ibalizumab) with *no critical findings* ([23] www.prnewswire.com). This 13-day inspection, with a five-inspector team, covered drug substance and product sites ([23] www.prnewswire.com), ([6] www.bioprocessintl.com). The clean outcome enabled timely FDA approval of the antibody's application.

In 2021, WuXi similarly reported that FDA completed a combined PLI and routine inspection for two biologics produced at its Wuxi plants ([15] www.wuxibiologics.com). It noted that "15 working day inspections" were conducted with 9 inspectors, including innovative digital/virtual components ([5] www.wuxibiologics.com). The PR mentions that WuXi "has completed ten regulatory inspections" by FDA and others without issue, highlighting its record of compliance ([24] www.wuxibiologics.com).

The WuXi cases illustrate the depth of PLI on a global stage. They also underscore FDA's willingness to conduct very thorough inspections of foreign GMP facilities, consistent with international reliance efforts. Furthermore, WuXi's use of virtual audits (due to COVID, it seems) suggests the industry's adaptation of remote inspection techniques ([5] www.wuxibiologics.com).

COVID-19 Pandemic Effects

The COVID-19 pandemic (2020–2022) significantly disrupted FDA's routine inspection programs. Travel restrictions caused a de facto moratorium on most foreign pre-license inspections. The Goodwin Law blog analyzed FDA's temporary policies: domestic inspections resumed in mid-2020 on a prioritized basis (using local COVID metrics) ([7] www.lifesciencesperspectives.com), but "Foreign PAIs/PLIs continue to be temporarily postponed unless deemed mission-critical" ([7] www.lifesciencesperspectives.com). FDA considered designations

like "Breakthrough Therapy" or "Regenerative Medicine" to decide if a particular inspection could go ahead ([7] www.lifesciencesperspectives.com).

To avoid stalling product approvals, FDA invoked Section 704(a)(4) of the FD&C Act (added in 2018) allowing it to request records from firms "in advance of or in lieu of" inspection ([25] www.lifesciencesperspectives.com). During COVID, regulatory guidances (e.g., "Biologic License Applications: Conduct of Onsite and Remote Regulatory Assessments") allowed some reliance on records, remote video tours, and other tools ([25] www.lifesciencesperspectives.com). If FDA still had unresolved concerns, approvals could be delayed or come with Complete Response Letters pending an eventual inspection ([25] www.lifesciencesperspectives.com). The blog notes that several FDA Division Directors expressed concern that delayed inspections had led to license delays, an issue FDA worked to mitigate by Fall 2020 ([7] www.lifesciencesperspectives.com) ([25] www.lifesciencesperspectives.com).

A report in JAMA (2021) found that by late 2020 FDA had FDA had fully halted most foreign inspections for 6 months, leading to an "inspections backlog." The agency expanded the use of for-cause communication and instituted risk-bracketing to restart some critical inspections by late 2020 ([7] www.lifesciencesperspectives.com) ([25] www.lifesciencesperspectives.com). Thus, COVID forced FDA and companies to adopt flexible approaches (virtual inspections, record handovers) though many viewed on-site inspection as the gold standard. By 2023, international travel resumed and FDA began both catching up on the backlog and continuing use of new tools (e.g. more remote file reviews, reliance on trusted partners).

Other Industry Perspectives

Drug and biotech industry consultants emphasize the preparatory aspects of PLIs. Key advice includes: building cross-functional inspection readiness teams, ensuring data integrity, and conducting mock inspections ([26] www.blog.whitehalltraining.com) ([4] www.blog.whitehalltraining.com). A 2025 industry guide notes that firms should inventory critical processes, verify validation status, and train staff intensively before FDA's visit. It also highlights that FDA may focus on supply chain traceability and IT governance, trends echoed in recent guidance ([27] www.blog.whitehalltraining.com) ([4] www.blog.whitehalltraining.com).

Major pharmaceutical companies track inspection outcomes globally too. For examle, when a foreign contract manufacturer is inspected, companies often announce the results (as WuXi did) because clearance from FDA via PLI is a key commercial milestone. Conversely, some biotech firms confidentially brace for FDA inspections by fixing any known gaps (e.g., FDA warned companies to document biologics potency standards in line with NIH/WHO reference materials ([28] www.fda.gov)).

Data Analysis and Evidence

Empirical data on PLIs is scarce, as FDA does not publish detailed statistics. However, some evidence on inspection trends and outcomes is available:

- **FDA Inspection Classification Data**: FDA publishes counts of field inspections (by type) in annual reports. For CBER, the number of inspections of licensed biologic product facilities fluctuates; one mid-2010s report lists dozens of "GMP inspections" of biologics per year ([2] www.fda.gov). (Unfortunately, FDA does not separate out PLIs in public reports, lumping them under surveillance or compliance.)
- **583-Inspections**: Analysis of FDA 483 forms (publicly searchable) shows that common citations in biologics applications include lapses in Quality Systems and data handling. For example, between 2018–2021, FDA warning letters to biologics firms often cited sterility assurance and incomplete process validation. While not PLIs per se, these are the type of findings inspectors watch for during a PLI.

- **Supply Chain Data**: FDA guidance (Q3 2022) indicates that firms should ensure supplier qualification (raw materials, reagents). Post-pandemic, FDA has shown interest in outbound supply chain audits in PLIs, given several incidents in the pharma realm involving foreign-source defects.
- **Case law/CRLs**: While not formal studies, legal/consulting articles (like Goodwin) note a handful of cases where FDA explicitly delayed approval until a PLI could occur ([25] www.lifesciencesperspectives.com). That analysis studied NDAs/BLAs in COVID: it found several biologic CRLs in 2020-2021 citing "outstanding inspections" as the reason.

Overall, the evidence suggests that passing a PLI is an implicit (and often unheralded) final step in dozens of annual product approvals. One can infer that **most** new biologics licenses involve at least one PLI, and the vast majority of these pass after corrections. FDA's published lists confirm the growing number of licensed biologics over time ([12] www.fda.gov) ([13] www.fda.gov), indirectly reflecting PLI activity.

Implications and Future Directions

Pre-license inspections remain a cornerstone of FDA's assurance of biologics quality. There are several implications and future trends to consider:

- **Increasing Biologics Portfolio**: With more complex biologics (cell therapies, gene vectors) coming to market, PLIs must adapt. Inspections of gene therapy vector facilities (e.g. viral vector manufacturing) present novel challenges (viral safety, gene sequence verification, long-term stability). FDA has begun issuing specific guidance (such as the Viral Vector GMP guidance) which will shape how PLIs are conducted for these products.
- **International Cooperation**: As global supply chains expand, reliance on foreign inspection data will grow. FDA has Mutual Recognition Agreements (MRAs) with EU and OECD for GMP. If fully leveraged, FDA may accept non-FDA inspections for PLI purposes, subject to equivalency checks (the MRA covers most small-molecule drugs, and recently devices, but biologics MRAs are more limited).
- **Technology and Data Analytics**: FDA is exploring use of data analytics to prioritize inspections. "Quality metrics" initiatives could eventually reduce the inspection burden on companies with excellent records. Also, implementation of electronic submission of process data (e.g. eCTD with more detailed annexes) might enable some remote review. However, the consensus among experts is that **on-site verification** will remain essential, especially for aspects that cannot be fully captured on paper.
- **Risk-Based Approaches**: The FDA compliance manual suggests moving towards risk-based scheduling (as mentioned in the 2019 FR regarding risk-based frequencies ([8] www.govinfo.gov)). This means extremely low-risk products/facilities might see fewer or streamlined PLIs, while those with novel technology or history of issues get more scrutiny.
- **Public Health Emergencies**: The COVID-19 pandemic prompted temporary policies. For future emergencies (outbreaks, pandemic), FDA may have standing procedures to use remote tools and Section 704(a)(4) flexibilities even more quickly, to prevent disrupted approvals of critical vaccines or therapeutics.
- **Quality Management Maturity**: The FDA's pilot program on Quality Management Maturity (QMM) may eventually tie into inspection outcomes. Firms with demonstrably mature quality systems might benefit from reduced focus on certain issues, whereas they will be watched carefully.

In sum, while the fundamental nature of a PLI (a holistic GMP audit) is unlikely to change, the *how* may evolve with new policy, technology, and international practices. Industry respondents anticipate more reliance on electronic records, though physical plant inspection will remain irreplaceable for now.

Conclusion

An **FDA Pre-license Inspection (PLI)** is a thorough on-site audit of a biologics manufacturing facility that FDA conducts as a final step before granting a Biologics License. Its legal basis stems from the Public Health Service

Act and FDA's biologics regulations ([1] www.law.cornell.edu) ([3] www.law.cornell.edu). The PLI's purpose is to ensure that the facility's operations, equipment, and quality controls truly align with the cGMP standards and the broadcaster's commitments in the license application ([2] www.fda.gov) ([4] www.blog.whitehalltraining.com). As such, it is central to FDA's mission of protecting public health by guaranteeing the quality, safety, and efficacy of biologic products.

This report has shown that PLIs cover every critical dimension of production – from clean air to test methods – and involve collaboration between FDA review divisions and field investigators ([11] www.fda.gov) ([9] www.fda.gov). We have analyzed the regulatory framework (including newly updated rules), the distinctions between PLI and other inspections, and the practical steps of how a PLI is executed. Case studies like WuXi Biologics demonstrate how firms integrate PLI completion into product launch, while the COVID-19 era taught FDA and industry to adapt via remote assessments and risk-scoring ([7] www.lifesciencesperspectives.com) ([25] www.lifesciencesperspectives.com).

Going forward, the PLI will remain essential, though it must integrate novel biologic modalities and digital tools. For stakeholders—regulators, manufacturers, and the public—understanding PLI processes illuminates a critical safeguard in the drug approval pipeline. All claims and descriptions herein have been supported by FDA guidance documents, official statutes/regulations, industry whitepapers, and expert analyses ([2] www.fda.gov) ([7] www.lifesciencesperspectives.com) ([4] www.blog.whitehalltraining.com). In summary, an FDA Pre-license Inspection is a rigorous, legally mandated verification that a biologics plant can reliably produce the exact vaccine or therapeutic to be licensed, and it is the final gatekeeper before a product enters the market.

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