Pre-Approval Inspection Readiness for Pharma Manufacturers and Sponsors

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Meet the Speaker!

Diana Aberion

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Career

- Over 25 years of experience in Quality Assurance, Regulatory Compliance, and Inspection Readiness
- Senior leader in Audits and Inspection Management at Gilead Sciences for 16+ years
- Previous leadership roles at Amgen and CV Therapeutics
- Deep expertise in global health authority inspections, audit management, and quality systems strategy
- Recognized for a strategic mindset, collaborative leadership, and commitment to building strong quality cultures
- Proven track record in driving inspection readiness and achieving regulatory success in complex environments

Education

- B.S. in Chemistry, University of the Philippines
- M.S. in Analytical Chemistry and MBA, University of Washington

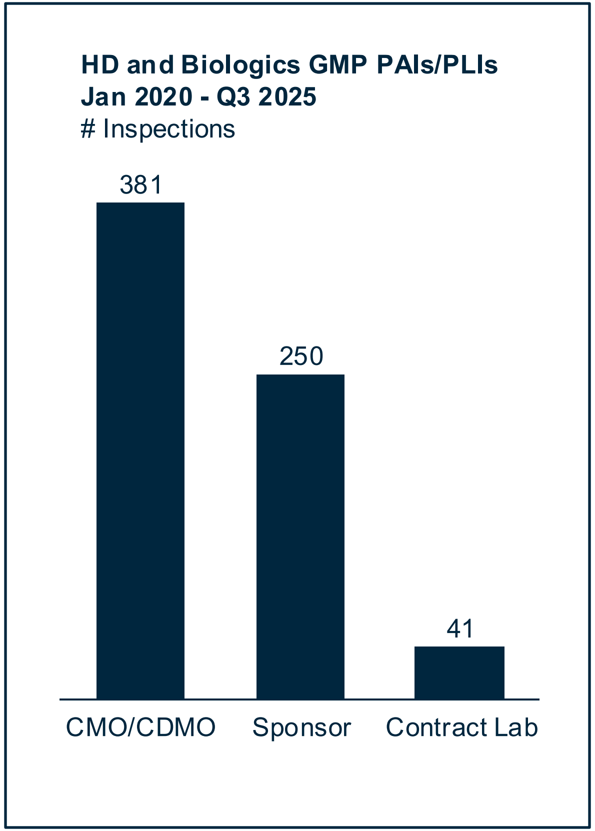
Why Today's Topic Matters to You

- **Contract Manufacturers:** Your operations continues to be FDA's primary focus for demonstrating process control and data integrity, even when oversight is shared with the sponsor.

- **Sponsor Manufacturers:** You remain accountable for ensuring contract partners meet GMP expectations - recent FDA actions emphasize joint responsibility for compliance.

- **Contract Laboratories:** Analytical testing and data traceability are critical to product approval

- **Across the Supply Chain:** Every partner contributes to the product's quality and regulatory outcome - misalignment anywhere can delay approval or trigger enforcement.



Learning Objectives

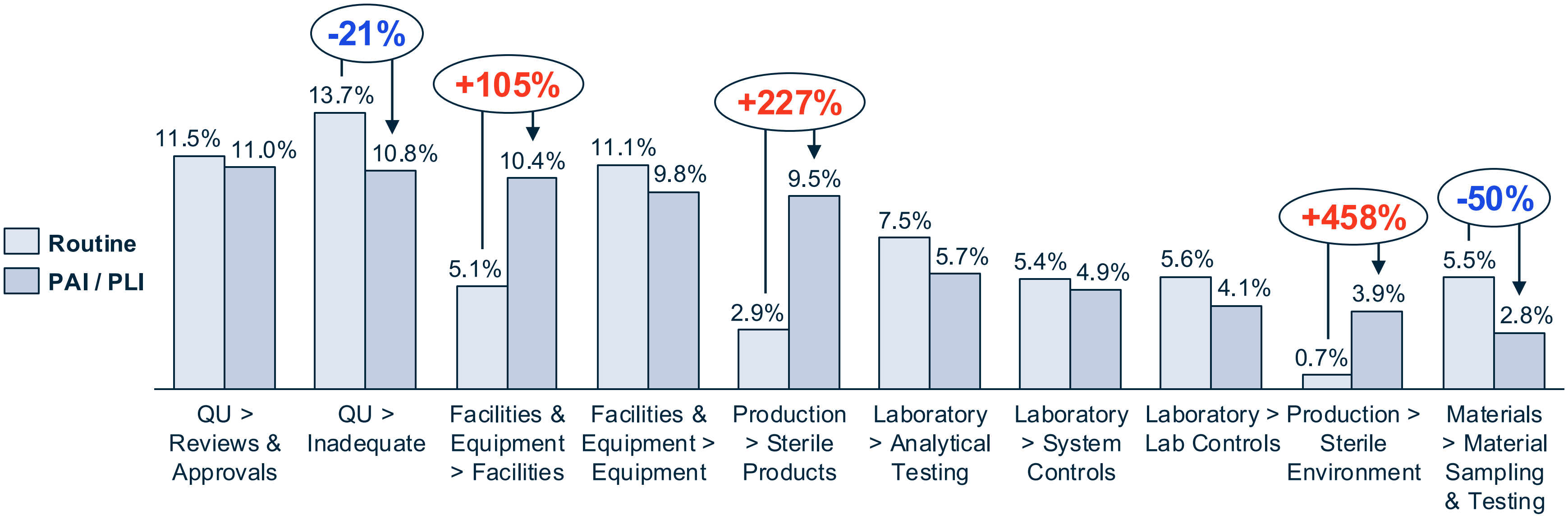
- Distinguish general GMP vs. PAI/PLI
- Anticipate inspection risk with data
  - Discover how to use FDA inspection trends and risk indicators to predict when and where a PAI or PLI is most likely and focus your readiness efforts accordingly
- Build a staged-risk-based readiness plan
  - Learn how leading sponsors and CMOs structure phased inspection readiness across sites and partners to align GMP, commercial, and product milestones for approval success
- Identify the quality system and data integrity pitfalls that derail approvals
  - See what the latest inspection trend data reveal about the most common causes of CRLs and how to benchmark your organization's readiness against top industry performers

General vs PAI Inspections

PAI		General Inspections
Conducted before the approval of a new drug application to verify the facility's readiness for commercial manufacturing and the integrity of submitted data.	**TIMING & PURPOSE**	Performed periodically after a product is on the market to monitor the manufacturing process and the quality of FDA-regulated products, ensuring ongoing compliance with cGMP.
Focuses specifically on the product under review, assessing the facility's capability to produce that particular drug, the accuracy of the data submitted in the application, and the validation of manufacturing processes related to that product	**SCOPE**	Broader in scope, evaluating the facility's overall compliance with regulatory standards across all products and processes.
Emphasizes the validation of manufacturing processes, data integrity, and the facility's readiness to produce the new product at commercial scale.	**FOCUS AREA**	Concentrate on the facility's adherence to cGMP across all operations, including quality control, documentation practices, and overall manufacturing processes.
The outcome directly impacts the approval decision of the new drug application. Deficiencies found during a PAI can lead to delays in product approval.	**OUTCOME**	Findings may result in regulatory actions such as warning letters or enforcement actions but do not directly affect the approval status of a specific product.

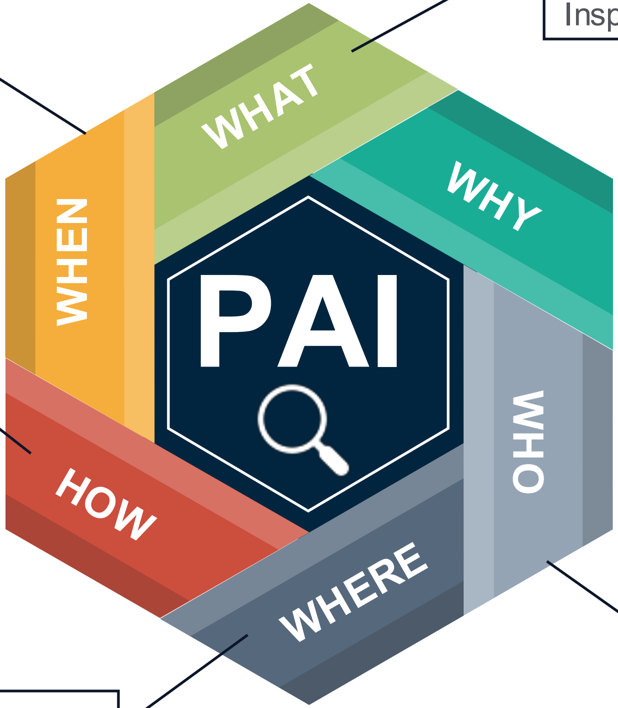
Differences in PAI/PLI vs Routine Inspection Observation Topics

- Routine inspections more commonly cite **inadequate Quality Unit and material testing deficiencies** than PAI/PLI inspections
- Pre-approval inspections more frequently cite **facility, sterile production, and cleanroom environment deficiencies** than routine inspections



Analysis based on top ten 483 observation topics from Human Drug and Biologics GMP inspections, Jan 2020–Q3 2025

Pre-Approval Inspections (PAI)



Definition of Pre-Approval Inspection (PAI)

Objectives of PAI

Supplier Types subjected to PAI/PLI

Countries conducting PAIs

Probability of PAI (How to Predict?)

Triggers for PAI

PAI/PLI Definition

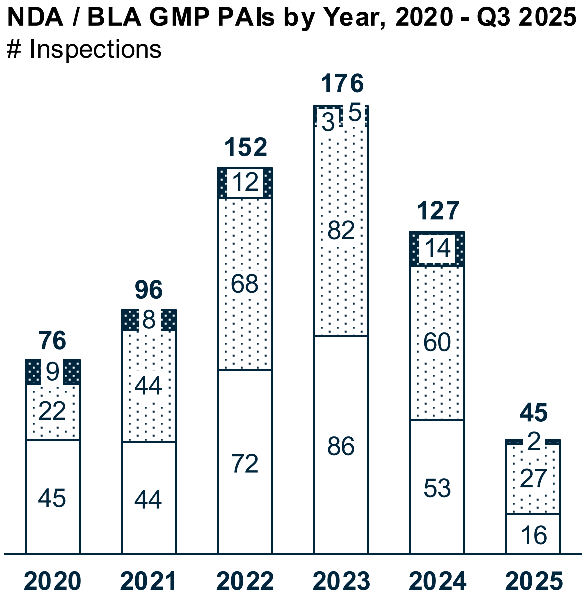
A **Pre-Approval Inspection (PAI) / Pre-License Inspection (PLI)** is a regulatory audit conducted by agencies like the U.S. Food and Drug Administration (FDA) before approving a New Drug Application (NDA) or Biologics License Application (BLA). Its main goal is to ensure that the manufacturing site and processes are compliant and capable of producing the drug at commercial scale with consistent quality.

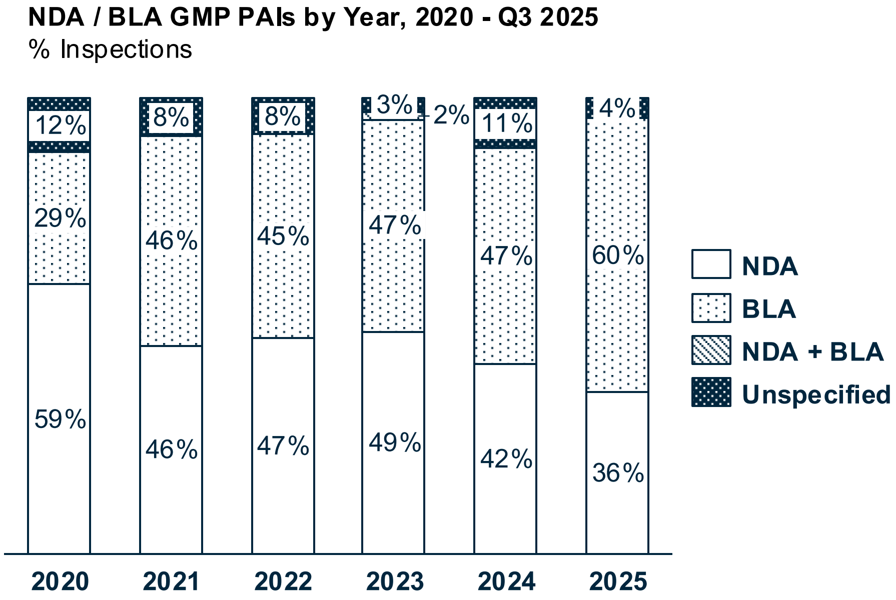
Vendor Types Subjected to a PAI/PLI

*On a case-by-case basis; evaluated only if the intermediate is considered critical to quality of the drug product

Global Regulatory Agencies Conducting PAI / PLI

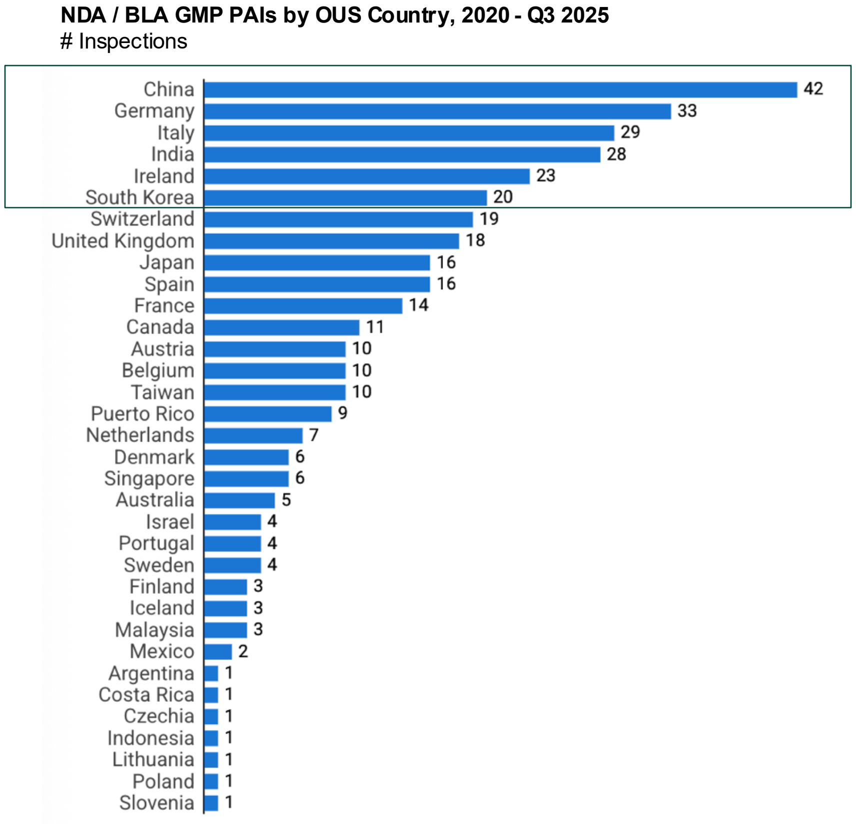
FDA Human Drug and Biologics GMP PAI/PLI (2020-Present)





- Out of 9,832 Human Drugs and Biologics Inspections, 672 inspections (7%) were PAI / PLI
- All inspections represented in the analysis were on-site inspections
- NDA and BLA inspection volumes have fluctuated modestly from 2020 through 2024, peaking in 2023 (176 PAIs/PLIs), with 2025 year-to-date showing lower totals due to partial data and a continued shift toward a higher proportion of BLAs (29% in 2020 to 60% in 2025).

FDA NDA/BLA GMP PAIs/PLIs Outside of U.S. (2020-Present)



- Vast majority of PAIs occur in United States
  - 310 PAIs in USA 2020 – Q3 2025

Triggers to Conducting a PAI/PLI

FDA uses a risk-based priority inspection criteria to make the decision based on the following risks:

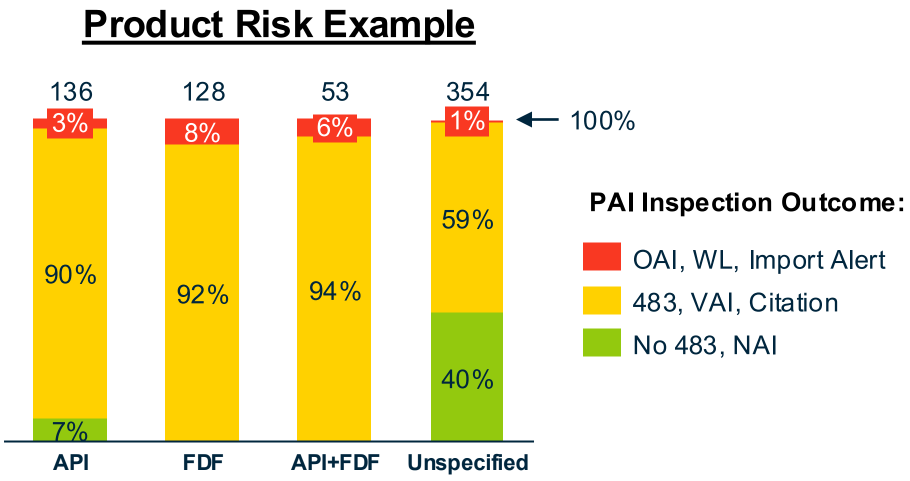
Product Risk
- New molecular entity (NME)
- First application filed by applicant
- First ANDA filed for an approved drug
- Referenced Listed Drug (RLD) has complaints, ADEs, stability issues
- Patient population or for serious condition
- Breakthrough therapy, shortage situation

Facility Risk
- CGMP issues relevant to application product
- Recent FARs relevant to application product
- Recent recalls relevant to application product
- Numerous applications filed at once

Process Risk
- Narrow therapeutic range (95%-105%)
- API derivation is high risk (derived from animal tissue)
- Development data is incomplete
- Batch records non-specific
- Complicated process
- Substantially different process than previously covered at facility
- PAT, NIR, QbD

Reference:
- *FDA Compliance Program 7346.832*

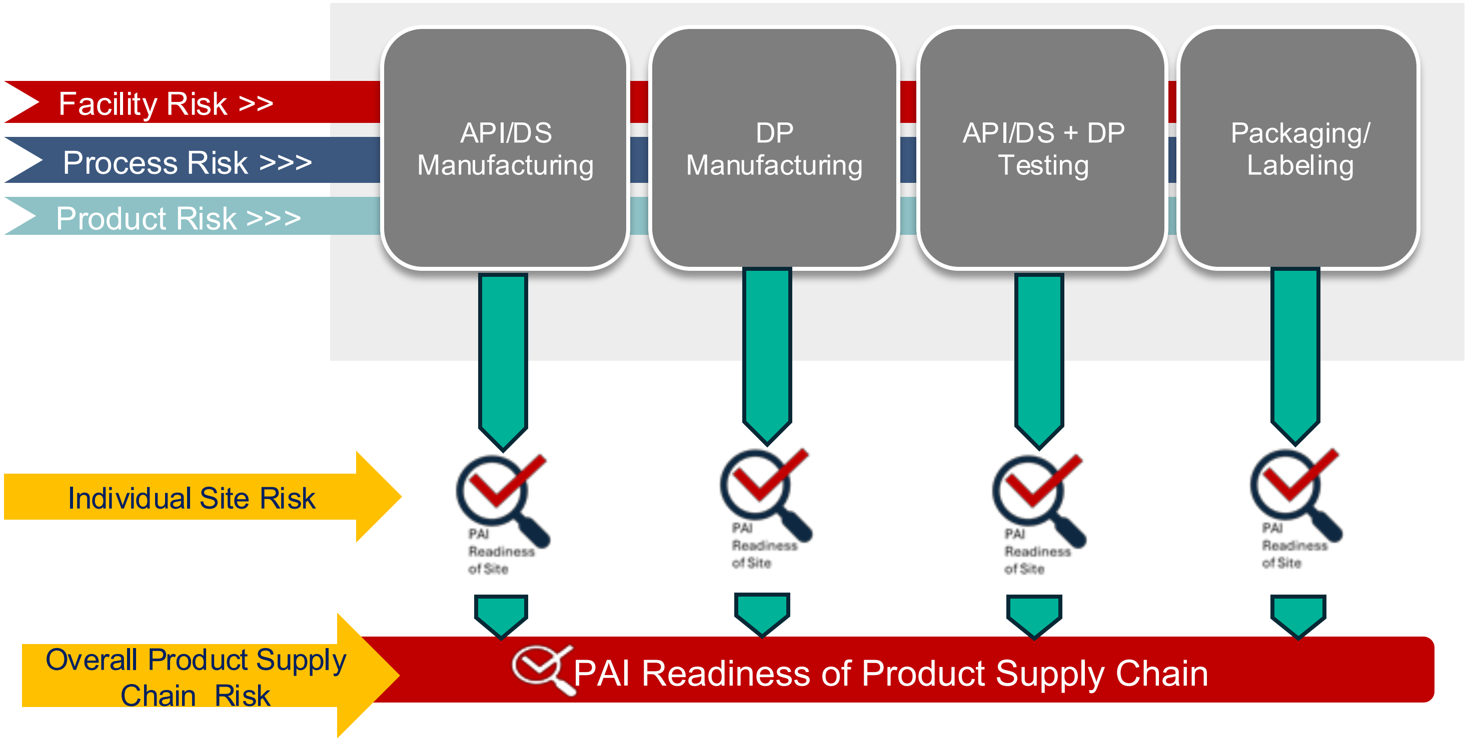
Human Drugs and Biologics GMP PAIs/PLIs, 2020-Q3 2025



- Finished dosage forms sites are more likely to result in a 483, citation or mandatory FDA action than active pharmaceutical ingredient (API) sites.

PAI/PLI Risk Assessment, Identification and Mitigation

PAI Risk Assessment includes both individual site risks and overall product supply chain risk.



How to Predict Probability of a PAI/PLI

- CBE-0, EU Type 1A, Canada Level IV or equivalent changes

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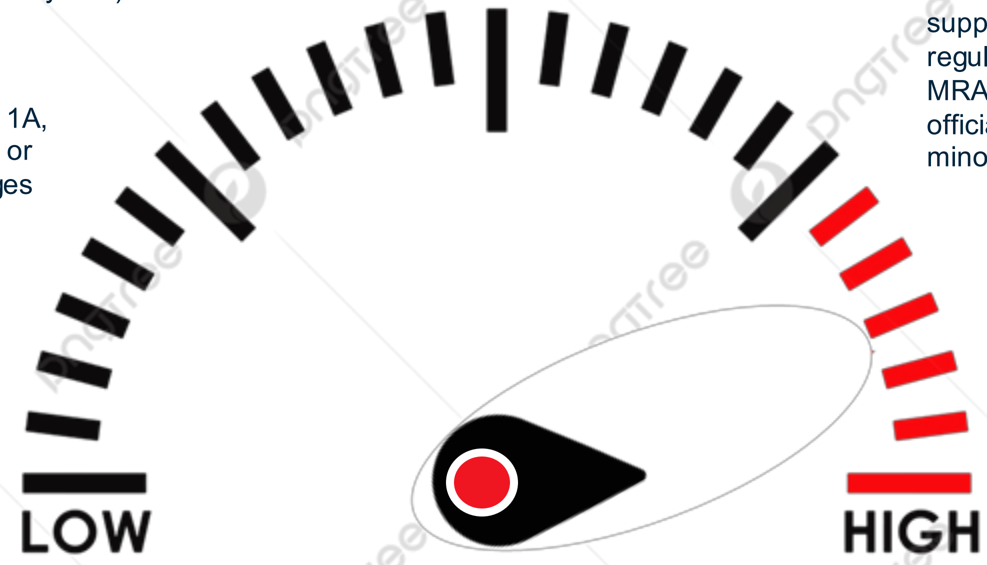
- CBE-0, EU Type 1A, Canada Level IV or equivalent changes
- Recent successful inspection (no deficiencies) by a local regulatory health agency or country with MRA (within the last 2 years)
- New Drug Application (NDA), Biologics License Application (BLA), Prior Approval Supplement (PAS), CBE-30
- Supplier has not been inspected by local regulatory health agency, OR supplier was recently inspected by local regulatory health agency or country with MRA (within the last 2 years) with official action indicated (OAI) or some minor deficiencies noted
- Filing of new supplier/site/new type of operations (not previously inspected by the FDA)
- Filing of new product (especially if new molecular entity, shortage, breakthrough / serious condition, new dosage form to site)
- Multiple filings for multiple products



PAI/PLI Readiness Staged Approach

The 3-Staged PAI Readiness Approach aligns with the timing of relevant documentation as part of NDA/BLA filing

START:
Notification that site is selected to be included in filing (as early as 1 year prior to anticipated filing date)

Product transfer activities are deemed successful and PPQ batches can be started.

Completion of PPQ

END:
Evaluation of Residual Risk for entire Product Supply Chain

STAGE 1: GMP Readiness

- Supplier Qualification (Quality Agreement, Audit)
- Data Integrity Assessment
- Sterility Assurance Assessment
- Availability of key Development Reports

STAGE 2: Commercial Readiness

- Technology Transfer
- Method Transfer and Validation
- Site Prepared PAI Risk Assessment
- General Site Quality Records
- CMO Supplier Qualification; RSM/API/ RM Supplier Verification
- Stability Studies

STAGE 3: Product Readiness

- List of PAI Product Quality Records
- Final Technology Transfer for Product
- Stability Studies

Compliance Risk

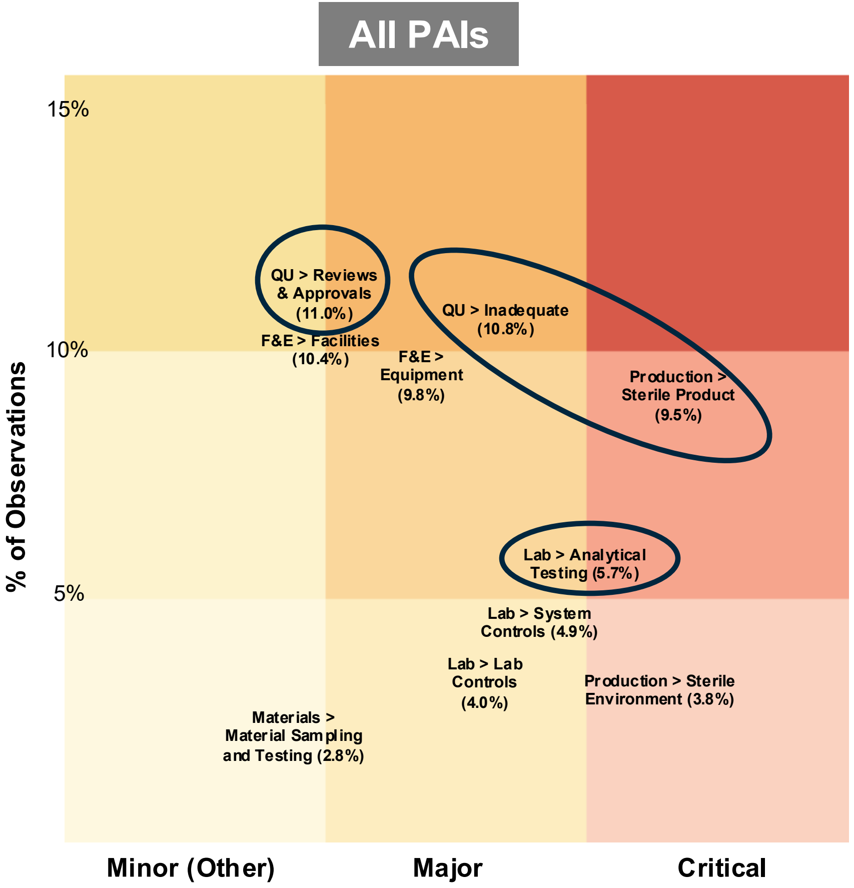
Compliance Risk

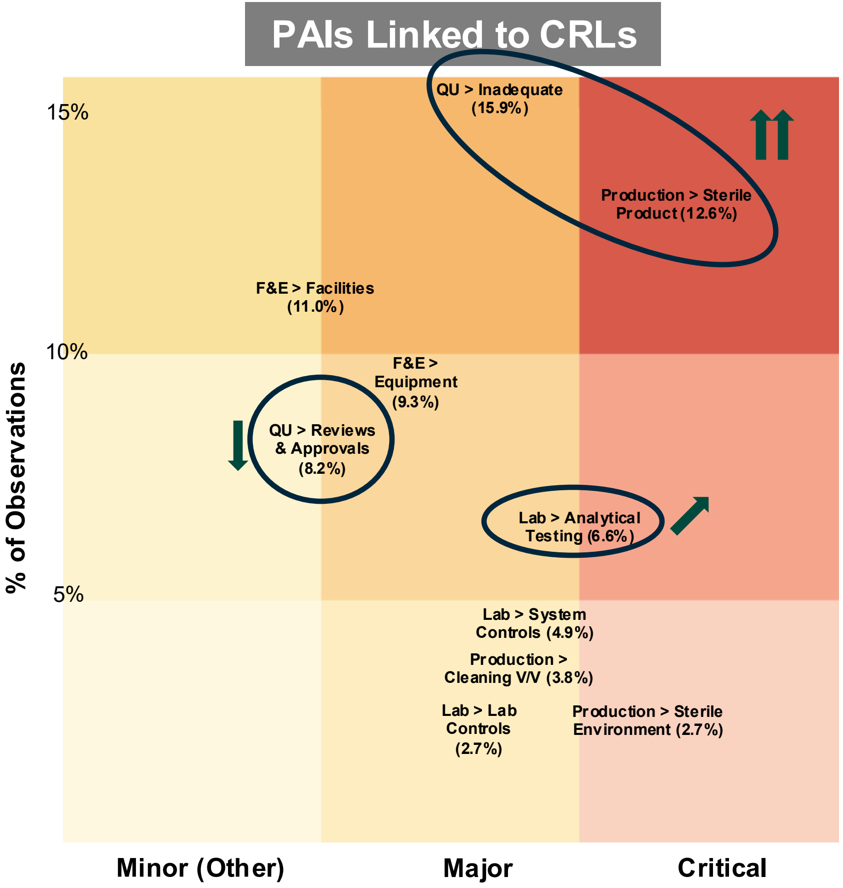
Process/Product Risk

Process/ Product Risk

Risk Identification, Documentation and Mitigation

Top 483 Observation Topics for All PAIs/PLIs vs Those Linked to CRL

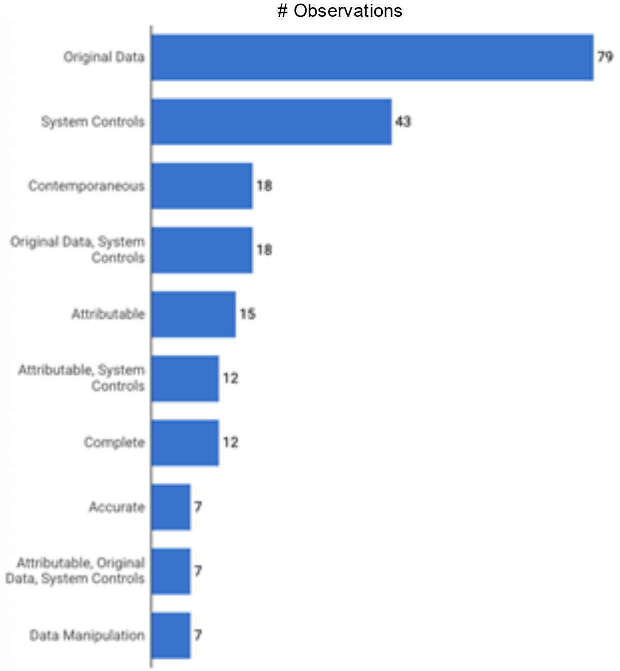




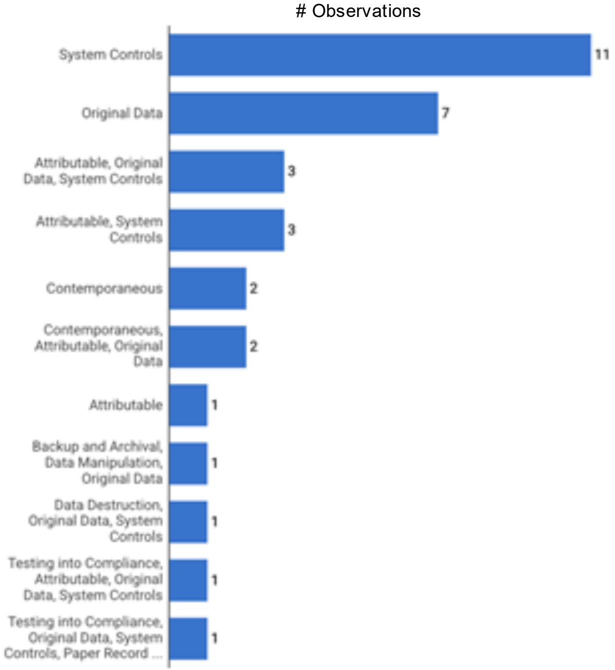
Analysis based on 1,690 Form-483 observations from PAIs/PLIs, 182 of which were linked to CRLs

Data Integrity Topic Differences in PAIs/PLIs

All PAIs



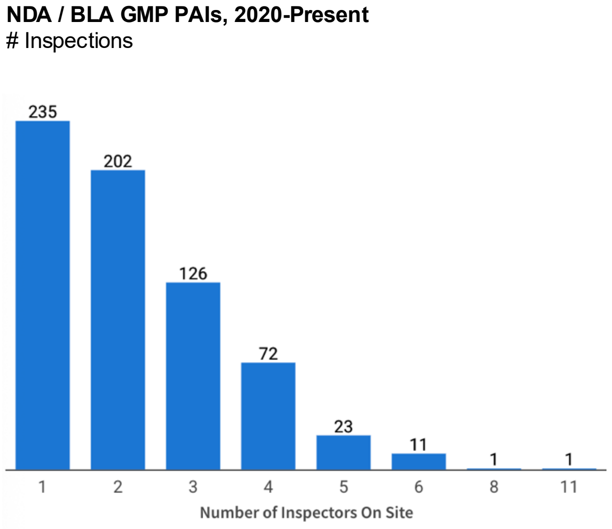
PAIs Linked to CRLs

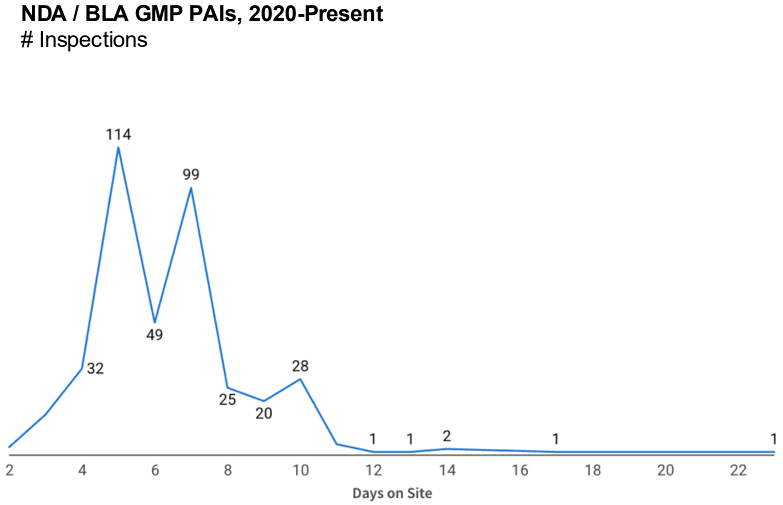


System Controls is the #1 data integrity issue in 483s linked to CRLs

Analysis based on 1690 Form-483 observations from PAIs/PLIs, 182 of which were linked to CRLs

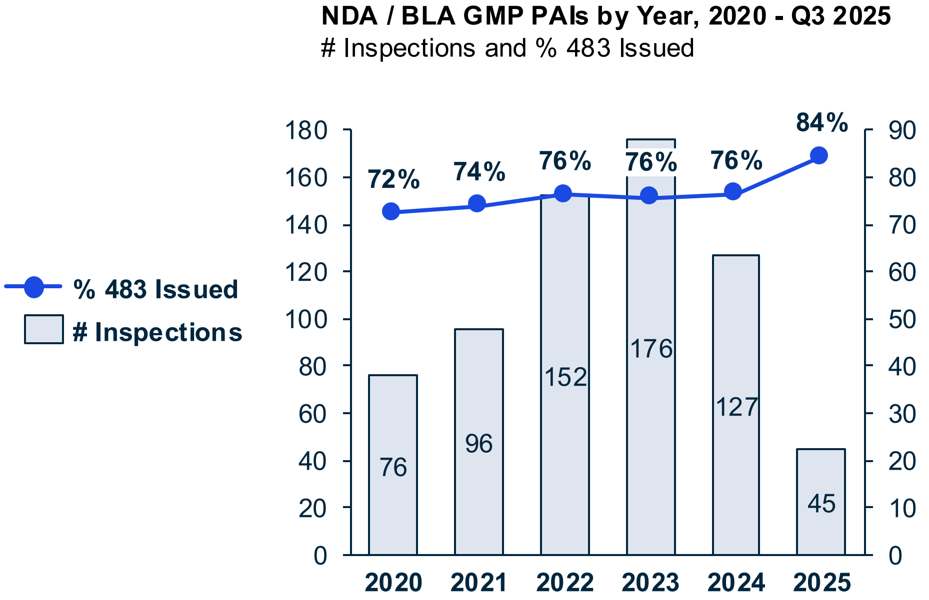
Number of Inspectors and Days on Site for PAI/PLI (2020-Present)

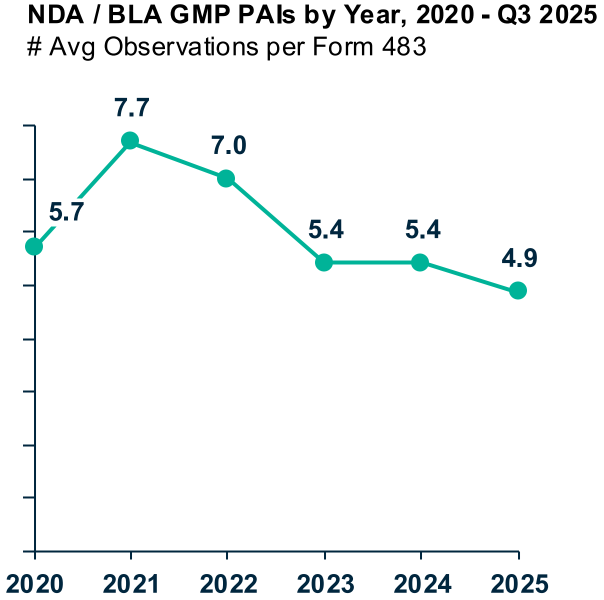




- Average number of investigators that show up is between 2 to 3 people
- Average number of days spent on-site is ~6 days

Human Drugs and Biologics GMP PAI/PLI + Form-483 (2020-Present)





- **483 issuance is on the rise** with 483s consistently containing **5 or more observations** on average

Key Takeaways

- **Inspection Readiness Starts in Development, Not After Filing.** PAI success is built from early design of experiments, data traceability, and quality risk management.
- **Every Site Touching the Product Impacts Approval.** Regulators evaluate the compliance of entire product supply chain. One underprepared API lab, test site, or packaging partner can compromise approvability.
- **Risk-Based Planning Enables Strategic Inspection Readiness.** Use staged readiness and quantitative site risk scoring to decide where to start early, when to escalate, and how to communicate confidence to regulators.
- **Quality System and Data Integrity Are Still the Weak Links.** Across PAIs, system control, record integrity, and Quality Unit oversight remain the top cited gaps.
- **Benchmarking enables Data Driven Decisions.** Data trends show that more inspectors and longer inspections correlate with higher 483 rates. Knowing your industry's averages helps you calibrate your internal preparedness

Q & A

Thank you