Ensuring Inspection Success

CASSS Virtual Summit: Opportunities and Challenges of Expanding US-based Pharmaceutical Manufacturing

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Case for Change

FDA fires off another manufacturing-related CRL, this one to Hyloris

Incyte's Lung Cancer Expansion Bid Thwarted by Issues at Novo's Catalent-Acquired Site

US FDA declines to approve Scholar Rock's muscle weakness drug; shares fall

U.S. Food and Drug Administration Issues Complete Response Letter for Lebrikizumab Based on Inspection Findings at Third-Party Manufacturer

FDA Issues AbbVie Complete Response Letter for ABBV-951 in Parkinson Disease

FDA Issues CRL for Odronextamab in Relapsed/Refractory Follicular Lymphoma

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Types of Facility Issues Causing Delays to Approvals

Sterility Assurance Controls

- Airflow visualization studies
- Aseptic techniques
- Environmental monitoring
- Aseptic process simulation
- Microbial control risks

Process

- Hold time studies
- PPQ performance
- Procedural adherence
- Inadequate procedures

Quality Systems

- Quality of deviation & OOS investigations
- CMO oversight
- Supplier management
- Training

Equipment and Facilities

- Cleaning validation
- Equipment (re)qualification
- Leaks
- Disinfectant efficacy studies
- Equipment & computerized system DI controls

FDA Compliance Manual for Pre-Approval Inspections Updates
CPGM 7346.832

Objectives of the PAI

1. Readiness for Commercial Manufacturing
   - Manufacturing/lab capabilities, change controls, deviations, and trending programs are in place
   - Sampling, testing, and evaluation of components, in-process materials, and finished products + robust supplier qualification program is in place
   - Facility & equipment controls are sufficient to prevent contamination of and by the application product
   - Batch release, complaint, adverse event, and FAR/BPDR programs are in place
   - Proposed commercial process and MBR are reasonable
2. Conformance to Application
   - Verification that methods and batch records are consistent with CMC portion of application
3. Data Integrity Audit
   - Audit of raw data associated with the product
4. Commitment to Quality in Pharmaceutical Development
   - Resources provided to perform activities related to product/process development
   - Procedures, reports, and actions ensure comprehensive product and process understanding
   - Management awareness of residual risks
   - Adequacy of QMS to ensure robust manufacturing, prevent defects and errors, and enable continual improvement

Withhold Recommendation Rationales

1. Significant DI concerns, including misrepresented data
2. Serious CGMP concerns with pivotal clinical, exhibit, or validation batches
3. Significant differences between process used for clinical batches and application exhibit batches
4. Lack of complete manufacturing/control instructions in the MBR or lack of data to support these instructions
5. Lack of capacity to manufacture DP or API
6. Failure to meet application commitments/firm not performing functions described in the application
7. Full scale PQ studies attempted and failed before the PAI without resolution
8. Where full scale data is provided in the application, lack of data to support that product can be reliably manufactured or meet CQAs at scale
9. Incomplete or unsuccessful analytical method validation/verification
10. Equipment/parameters not clearly documented in records for biobatches, clinical batches, or exhibit batches
11. Significant failures related to the stability study
12. Failure to report adverse finding or failing test data
13. Delaying, denying, limited, or refusing a drug inspection

What do we need from each other?

FDA Request:
Industry to be able to meet the objectives of its PAI/PLI program

Industry Request:
Consistent approach to inspections and citing of issues; more health authority reliance

Patients' Request:
Access to newly developed safe, effective, and high quality medicines

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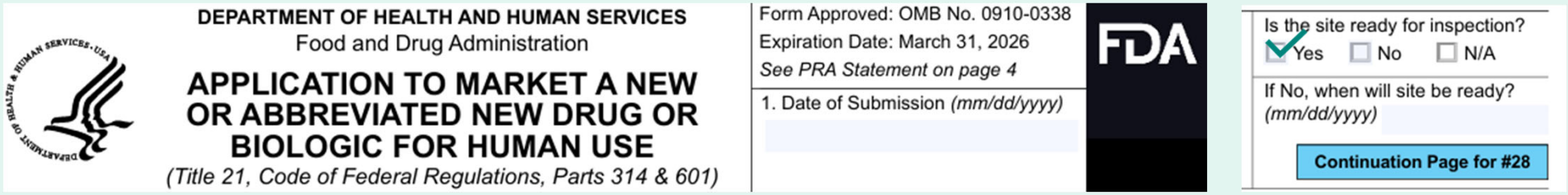
Our Company's Change in Approach for PAI Readiness

from



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2026
See PRA Statement on page 4

1. Date of Submission *(mm/dd/yyyy)*

FDA

Is the site ready for inspection?
☑ Yes ☐ No ☐ N/A

If No, when will site be ready?
(mm/dd/yyyy)

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Q9(R1) Quality Risk Management

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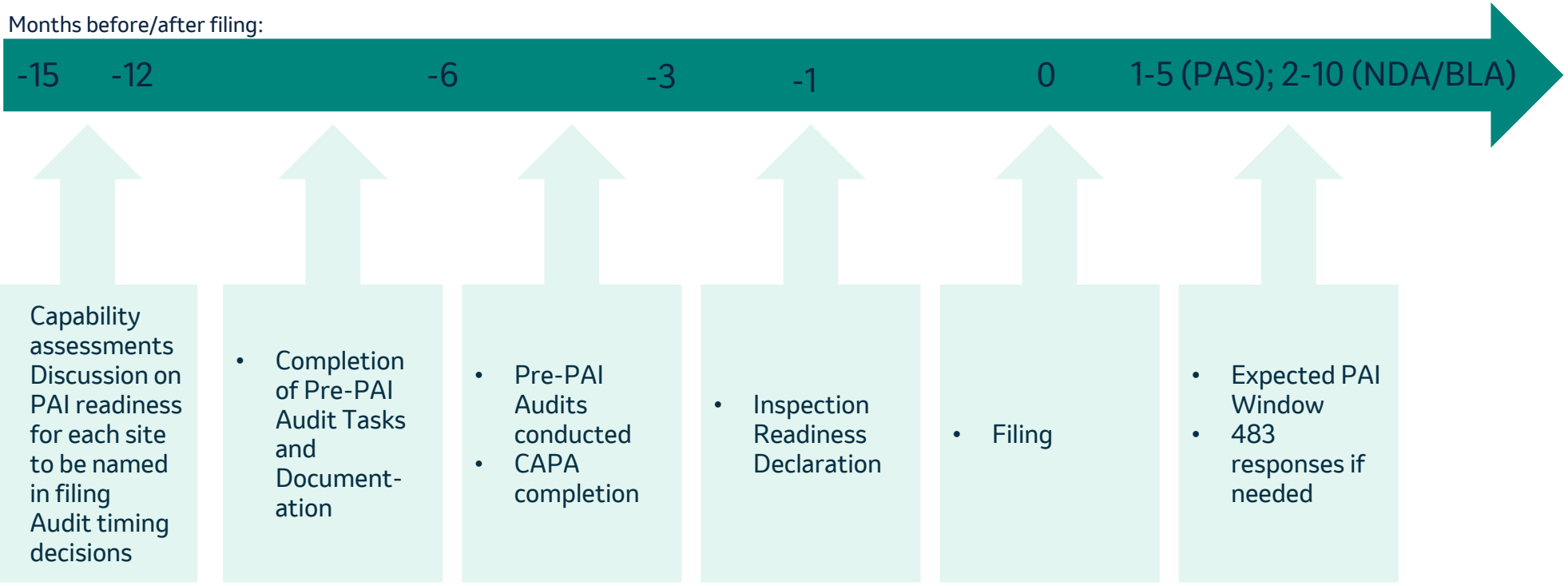
Our Company's Change in Approach for PAI Readiness

Three-pronged approach

	From	To
QMS Updates	SOPs focused on "check-box" activities	SOPs focused on risk identification, communication, and mitigation. Required activities (audits, etc.) moved to earlier in the pre-filing timeline to allow more time for issue resolution. Risk ID and mitigation continues following inspection readiness declaration.
Risk Communication	Risks communication tools focused on inline products to meet GMP requirements	Pipeline Quality Tier developed to focus on PAI/PLI and analytical readiness risks. Tier program includes discussion of characterization of risks along with mitigation measures. Tools developed for inspection risk tracking
Capability Build	Fragmented understanding of inspectional risks across functions	Understanding built through extensive training, discussion of peer company 483 and CRLs, and discussions at the tier programs.

An Altered Timeline

Everything must come earlier in the new paradigm



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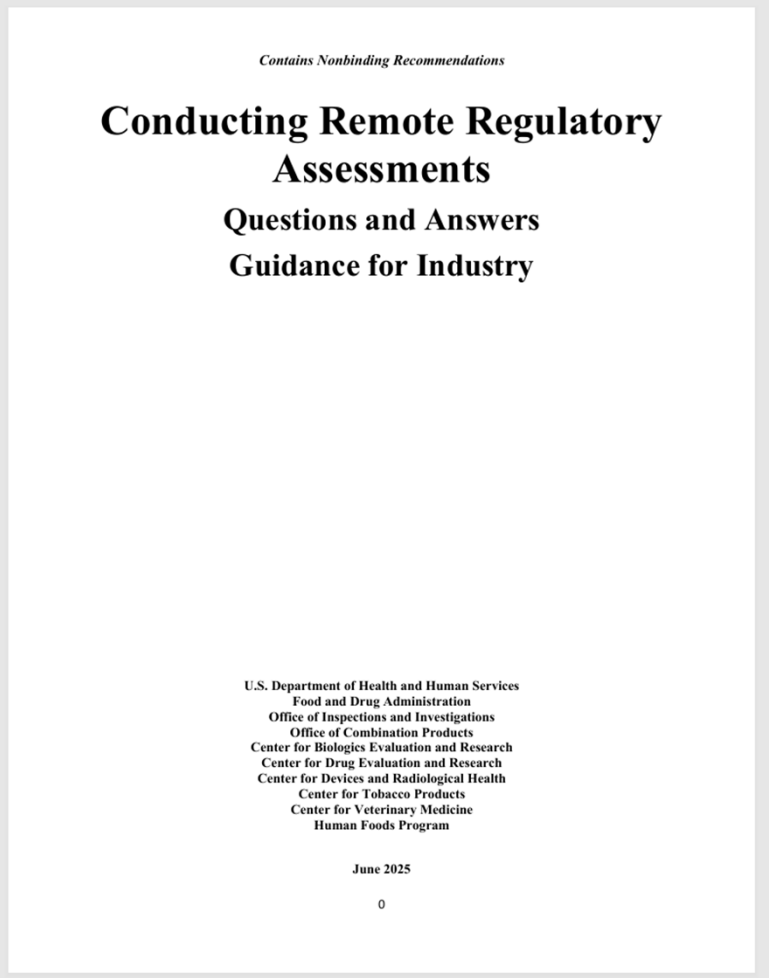
Remote Regulatory Assessments

Tips for Success

- ✓Clarify R&R
- ✓Prepare responses to common questions and expected questions; use independent/naïve reviewer
- ✓Prepare for rapid turnaround
- ✓If request is not clear, seek clarification from FDA to ensure that the request is addressed right-first-time



Contains Nonbinding Recommendations

Conducting Remote Regulatory Assessments

Questions and Answers

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Inspections and Investigations
Office of Combination Products
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Devices and Radiological Health
Center for Tobacco Products
Center for Veterinary Medicine
Human Foods Program

June 2025

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Onshoring presents new opportunities:

- Strengthen the resiliency of our supply chains
- Workshop to apply new technologies
- Chance to demonstrate the success of our compliance programs and leverage alternate ways of compliance assessments