Focused Trends from the FDA

GXP INSPECTION READINESS

Jolly Bhatia
Sr. Director, QA
Alnylam
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Credits: Tim Maines, Arya Tavana, John French, Roan Martin

13% of FDA Complete Response Letters [refusal to approve drug] are related to failures in PAIs (data source 2008-2016)

On May 27th, 2016, AstraZeneca received a **Complete Response Letter (CRL) from the FDA** for their sodium zirconium cyclosilicate (ZS-9) NDA

Instead of being rejected due to safety or efficacy concerns, the CRL refers to **findings from a PAI.**

Once AstraZeneca addresses these **PAI concerns,** the CRL requires that their **resubmission** undergo **a new 6-month review cycle,** indicating **likely delays** of at least a year before this drug could come to market.

What is a Pre Approval Inspection?

GLP/GCP

FDA targets studies with data contributing to the label (i.e., pivotal studies); typically driven by volume of data and endpoints contributing to outcome of the study and interpretation of study results.

GMP

Onsite review to evaluate the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are adequate to ensure and preserve its identity, strength, quality, and purity.

Drug Safety and Efficacy data + ***Findings from Inspection result in site / sponsor compliance status*** = ***NDA APPROVAL***

Pre-Approval Inspection Goal as stated by FDA

Assure that establishments involved in the manufacturing, testing, or other manipulation of a new drug dosage forms and drug substances are evaluated for:

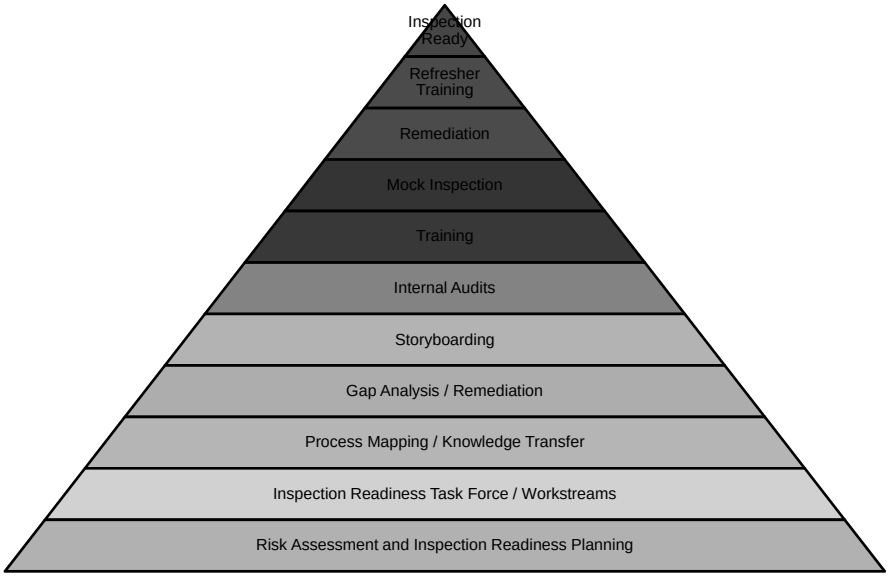
- Conformance with commitment in the application
- Site cGMP compliance
- Data authenticity, reliability and accuracy (Data Integrity)
- Adequacy of analytical methodologies
- Sponsor oversight for GCP vendors, Sponsor to CRO relationship

Focus of PAIs

- *Conformance with Commitment in Applications*
- *Data Integrity*

Mfg. Sites	*CROs*	*Investigator Sites*	*Non-Clinical Sites*
• *Site Compliance* • *Adequacy of Methods*	• *Investigator Site oversight* • *GCP Compliance*	• *GCP Compliance*	• *GLP Compliance*

Example Inspection Preparation approach

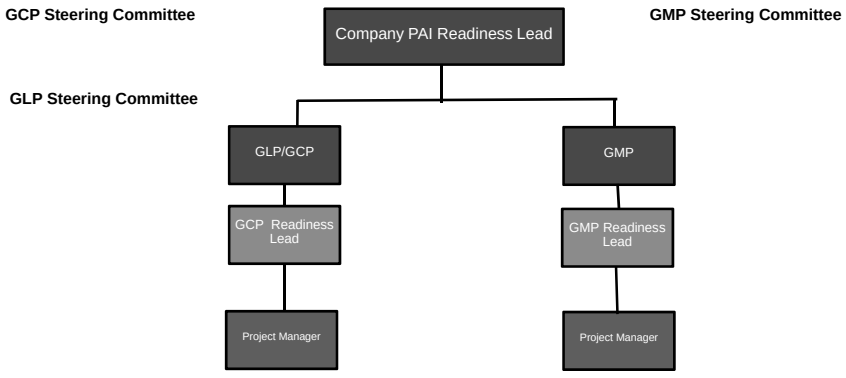


Readiness Strategy to Focus Resources

Complete Risk Analysis Profile of each site to determine concentration of Company Resources

- Higher Risk Sites receive heightened oversight in preparation activities and Mock PAI
- Medium Risk Sites will undergo Mock PAI
- Low Risk Sites will be managed by routine monitoring processes

Model PAI Readiness Team and Governance Structure



- Monthly Readiness Status Reporting to Steering Committees

Example Readiness Activities Matrix

Activity	Internal	High Risk CMO	Medium Risk CMO	Low Risk CMO
Risk Assessment	**Y**	**Y**	**Y**	**Y**
Kick-Off	**Y**	Y	Y	N
Gap Assessment	Y	Y	N	N
Remediation	Y	Y	N	N
Inspection Training	Y	Y	Y	N
Inspection Logistics	Y	Y	N	N
Mock PAI	Y	N	N	N
CAPA	Y	Y	N	N
Periodic Audit	Y	Y	Y	Y
Inspection Training	Y	Y	Y	N

Maturity Model Review Approach for Quality Systems

- **Level 1 –** GMP System or Process Exists
- **Level 2 –** GMP System or Process Meets Regulatory Requirements for a Commercial Manufacturer and system In-Use
- **Level 3 –** Objective Evidence Demonstrating that Company adheres to GMP System or Process

Preparing partner sites for Mock PAI

- Select right Inspector expertise
- Identify potential risk areas with inspectors upfront
- Timely provide List of Requested Documents to site
- Review opening presentation
- Provide on-site support during inspection
- Meet with inspectors to get inside story
- Develop remediation plan in consultation with inspectors

Top 3 Items of Concern in GMP!

Area of Concern	Action Required
CMO Quality Maturity and identifying unknowns	Senior Management influence key partners for assistance in Inspection Readiness
PPQ Package	Ensure Expertise Areas are prepared to present strategy which will ensure regulators agree with approach
Continued focus for a long term project of this scope	Senior Management ensuring that inspection readiness is critical to the future of and appropriate resources are assigned where needed

How to measure Successful PAI Readiness

- Plan adherence (communicated monthly to PAI Readiness Steering Committee)
- All Identified Gaps have remediation completed or playbook/storyboard to present position to Inspectors
- Mock PAI show robust Inspection Management Process
- Mock PAIs do not uncover areas or topics of risk not previously identified
- Mock PAI CAPAs are complete or inspection playbook/storyboard created
- No delay in approval of NDA/MAA due to PAI findings

Contact me with further questions:

Jolly Bhatia
Senior Director, Quality Assurance
Alnylam Pharmaceuticals
300 Third St., Cambridge MA 02142
jbhatia@alnylam.com
617-551-8386