Pre-Approval Inspection Readiness for NDA/BLA Holder and Sponsor

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BIO TECH LOGIC
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PAI Readiness Overview

1. NDA/BLA Holder Readiness Strategy

- US: Food and Drug Administration
- Europe: European Agency for the Evaluation of Medicinal Products
- ROW

2. Probability of Success

– Calculate Inspection Success Rate

– Increase likelihood of “Approvable PAI”

PAI Readiness Strategy

Components of Readiness Strategy:

- Establish PAI readiness date
- List registered sites and responsibilities
- Perform site risk evaluation
- Develop individual site readiness plans
- Allocate resources based on risk
- Manage time

Components of Readiness

Establish PAI Readiness Date:

Estimated time point for completion of all high risk action items:
Around NDA/BLA (or MAA) Filing, but well before anticipated inspection.

Factors to consider:

- Initial readiness focus occurs during development.
- Understand NDA/BLA registration review timelines:
  - Orphan Drug (priority review) or standard PDUFA approval timelines (ie. 9 - 12 months).
  - Inspections follow shortly after filing (~ 2-3 months)
- EU's CPMP (now CHMP) will request an inspection to occur between day 120 and day 150 of the procedure.
  - Inspection Report from the Inspectorate should be submitted to EMEA – CPMP by day 180.
  - All inspection activities/reports must be completed by day 210.

Components of Readiness

Site Registration and Responsibility:

- List location, responsibility and CMC reference
- Establishes the scope of the PAI readiness

SUPPLY CHAIN	RESPONSIBILITY	CMC Reference
Sponsor	NDA/BLA Holder, Product Release and control	Product Release and Control
API Manufacturer	API Mfg., Cell Bank Storage, Stability, Development, Analytical testing	API Mfg
Drug Product Manufacturer	Drug Product Mfg and Limited Release Tests	Drug Product Mfg
Analytical Lab	Bioassay	API & DP Mfg
Support Lab	Cell Bank storage and stability	Cell Bank Stability
Raw Material Supplier	Polyethylene Glycol (PEG) supplier	Critical Raw Material
Analytical Lab	Limited Release Methods (excipients)	DP
Analytical Lab	Release and Stability Methods	API and DP
Packaging	Label, Packaging and Distribution	DP

Components of Readiness

Perform a Site Inspection Risk Evaluation:

Consider the following as increasing risk

- No Regulatory History: FDA and/or EMEA Inspections
- Performed multiple product support functions: API Manufacturing, DP Manufacturing, Stability, Analytical Method Development, Bioassay, Release and Stability Analytical Testing…
- Performance History: Manufacturing, Nature of Investigations and deviations
- "State" of commercial readiness: Outstanding audit items, outstanding support validations (ie. resins re-use, cleaning, filter validation, etc.)

Components of Readiness

Risk Assessment:

- **Determine risk level based on evaluation criteria.**

SUPPLY CHAIN	RESPONSIBILITY	EVALUATION	RISK
Sponsor	NDA/BLA Holder, Product Release and control	- Virtual Company - First compound with FDA	Low
Examples			
API Manufacturer	API Mfg., Cell Bank Storage, Stability, Development, Analytical	- No FDA or EU Inspection History - Multiple Functions	**High ****
Drug Product Manufacturer	Drug Product Mfg and Limited Release Tests	- Successful PAI and EMEA Inspections	**Low ***
Analytical Lab	Bioassay	- No PAI History. Good GLP Inspections	High *
Support Lab	Cell Bank storage and stability	- Good CVM Inspection History	Low
Raw Material Supplier	Polyethylene Glycol (PEG) supplier	- No FDA or EU History - Supplier quality only	Low
Analytical Lab	Limited Release Methods (excipients)	- Recent GMP Inspection, 483 issued	High/Low
Analytical Lab	Release and Stability	- No FDA or EU History	High *
Packaging	Label, Pkg and Distribution	- Successful PAI Inspections	Low

*** * FDA and EMEA Inspection** *** FDA Inspection**

Site Readiness Plans

High Risk Sites:

- Create Site Approval Master Plans
- Perform full internal assessment: Process, Facility, Labs, Equipment, Validations, Analytical Methods, etc.
- Compile PAI Readiness Corrective Action List
- Categorize, Rank and Prioritize Action List
- Allocate Resources and Track List!
- Schedule “Mock” PAI Audit

Site Readiness Plans

Low Risk Sites:

- PAI Readiness Checklist
- Initial site visit to define organization's PAI readiness plans and strategy
- Schedule QA Audit, i.e. Vendor Audit
- Low risk sites (due to Regulatory history) with a significant chance of a PAI inspection should have Mock PAI performed. (ie. Established Drug Product Manufacturing site).

Probability of Success

Calculating Probability of Success:

- Determine "weighted percentage" of each location on the overall readiness program.
- Determine "percent readiness" of each site as of current date and PAI Readiness date
- Calculate "overall readiness percentage" by adding the up the weighted readiness percentages from each High Risk site.

Probability of Success

Basis for Total Weights of each site: (examples)

API / Development: 60 %

- New Facility
- No prior FDA Experience
- Numerous Process Operational Steps: Fermentation, Isolation, Recovery, Purification, Formulation of Final API
- Scope of Inspection: API and Drug Product Analytical, Manufacturing, Development, Stability, Facility and General GMP's, and Clinical Supplies

Drug Product Location: 20 %

- Scope of Inspection : Filling, Sterile Filtration, Lyophilization and Inspection of Final Drug Product
- Established Manufacturing Site: Proteins and Parenterals

Probability of Success

Calculate the current **percent readiness** of each site based on Site Plans, and then estimate the theoretical percent readiness at the time of PAI.

CLASS	Components of Readiness	Elements of Component	As of 1/19	As of 3/1
PROCESS	Validation (PV) [1]	Runs	90%	100%
		Report	0%	66%
	Analytical Validation [2]	All Analytical DP & DS by Covance or Coordinated by Covance	90%	100%
	Manufacturing History [3]	Batch Release and Control	50%[3A]	80%[3B]
	Validation [4]	General	75%	85%
FACILITY / GMP [5]	Environmental	Monitoring and Results – OOS	70%	70%
	Water	Document System		
	Audit Items	Closure of items to be confirmed		
Development	Development Reports[6]	Process Changes P1 – P2. FDA will request	60%	100%
	Site Master Plan[7]	Document Organization & completion	50%	≈ 75%
	Clinical Batch Records[8]	Clinical & Comm. Process	75%	100%

Probability of Success

Overall Readiness for PAI:

FUNCTIONAL OPERATION	Total Weight	Readiness as of 1/19	Total Readiness
API Mfg Site	60%	62%	37.2
Analytical Release lab	20%	98%	19.6
Drug Product Mfg Site	5 %	90%	4.5
Bioassay lab	15%	55%	8.25
Overall Readiness Percentage as of 1/19			69 %

FUNCTIONAL OPERATION	Total Weight	Readiness as of 3/1	Total Readiness
API Mfg Site	60%	80%	48
Analytical Release lab	20%	100%	20
Drug Product Mfg Site	5 %	100 %	5
Bioassay lab	15%	100%	15
Overall Readiness at PAI Readiness Date (3/1)			88%

Summary

- Establish a realistic PAI readiness date to which both you and the third parties agree.
- Perform a risk assessment to determine how to leverage your resources and improve likelihood for success.
- Plan and resource all major/high risk deficiencies by the PAI readiness date first, and then plan work on the others.

Thank You.

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