



Preparing for a Pre-Approval Inspection & Managing Risk

A Case Study



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Audio Conference

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Introduction

BioTechLogic, Inc. is a team of manufacturing management professionals that serves the Biopharmaceutical industry by collaborating with companies to meet aggressive project timelines. We specialize in process validation and inspection readiness. Through our extensive experience in process development, production, and third party management, we are able to define the path, focus the resources, and drive the process to meet every milestone.

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Overview

- 1. Case Study: A Global Pre-Approval Inspection (PAI) Readiness Program for a complex supply chain that commences with process validation.**
- 2. Evaluate the use of a Site Approval Master Plan; a tool for facilitating readiness.**
- 3. Evaluate a prioritization/selection process for risk ranking PAI remediation.**



Global PAI Readiness Program: An Overview

STEP	ACTIVITY/ACTION	DESCRIPTION
1.0	Readiness Scope	Include all US and EU registered sites , and identify responsibilities
2.0	Readiness Timeline	Starts with Process Validation Readiness and includes key milestones. Readiness is first built and then assessed .
3.0	Site Approval Master Plan (SAMP) (PAI tool)	Develop a SAMP for all critical sites that identifies the key responsibilities (SAMP components) performed by the site as they relate to the product.
4.0	Site Risk Evaluation	Evaluate all supply chain sites . Assess the risk a site poses to product approval and a successful PAI.
4.1	Site Ranking	Rank Sites as High or Low Risk based on Evaluation criteria
5.0	Readiness Plan: High Risk Site	a) Build : Commences with Process Validation (PV) Readiness b) Assess : Activities (Plan) that follows PV and Submission
6.0	Readiness Plan: Low Risk Site	Analyze site PAI capabilities based on prior success. May necessitate mock PAI for product assurance.
7.0	Risk Management	Deficiencies are a) categorized, b) ranked according to risk severity, c) ranked according to risk severity, time to completion, and analyzed in sub-categories and d) mitigated.



Step 1.0: Readiness Scope Sites, Responsibility and Registration

- List all locations and site responsibilities
- Identify both US and EU supply chains

Supply Chain	Responsibility	Registration
Sponsor	NDA/BLA Holder, Product Release and Control	NDA and MAA
API Manufacturer	API Manufacturing, Cell Bank Storage, Stability, Development, Analytical Testing	NDA and MAA
Drug Product Manufacturer	Drug Product Manufacturing and Limited Release Testing (microbiological)	NDA and MAA
US Analytical Lab	Bioassay	NDA
EU Manufacturing	QP, All Release Testing and Bioassay DP Labeling, Packaging and Distribution	MAA
Support Lab	Cell Bank Storage and Stability	NDA and MAA
Raw Material Supplier	Polyethylene Glycol (PEG) Supplier	NDA and MAA
Analytical Lab	Limited Release Methods (excipients)	NDA
US Packaging	DP Labeling, Packaging and Distribution	NDA



Step 1.0: Readiness Scope

EMEA PAI Inspection Perspective

- The EMEA has two important tasks to accomplish for product approval: Review the MAA and grant the Manufacturing Authorization (GMP certificate).
- Request for inspection will occur between day 120 and day 150.
 - Inspection Report from the Inspectorate should be submitted to EMEA – CPMP by day 180.
 - All inspection activities/reports must be completed by day 210.
- Inspections may be carried out to verify compliance with European Community Good Manufacturing Practice (Annex) and Guidelines and/or specific manufacturing and control activities related to the assessment of an application.



Step 1.0: Readiness Scope

EMEA PAI Inspection Perspective, cont.

- Eudralex: The Rules Governing Medicinal Products in the European Union
<http://pharmacos.eudra.org/F2/eudralex/index.htm>
- Eudralex: Volume 3 (Medicinal Products for Human Use Guidelines)
 - Volume 3A - Quality and Biotechnology
- Eudralex: Volume 4 (GMP's)
 - Annex 1 (Sterile Products)
 - Annex 2 (Manufacture of Biological Medicinal Products)
 - Annex 15 (Qualification and Validation)
 - Annex 18 (API)
- Inspectorate spend a lot of time “at the site” to verify how closely manufacturing operates according to what is written in SOP's and quality system documents.

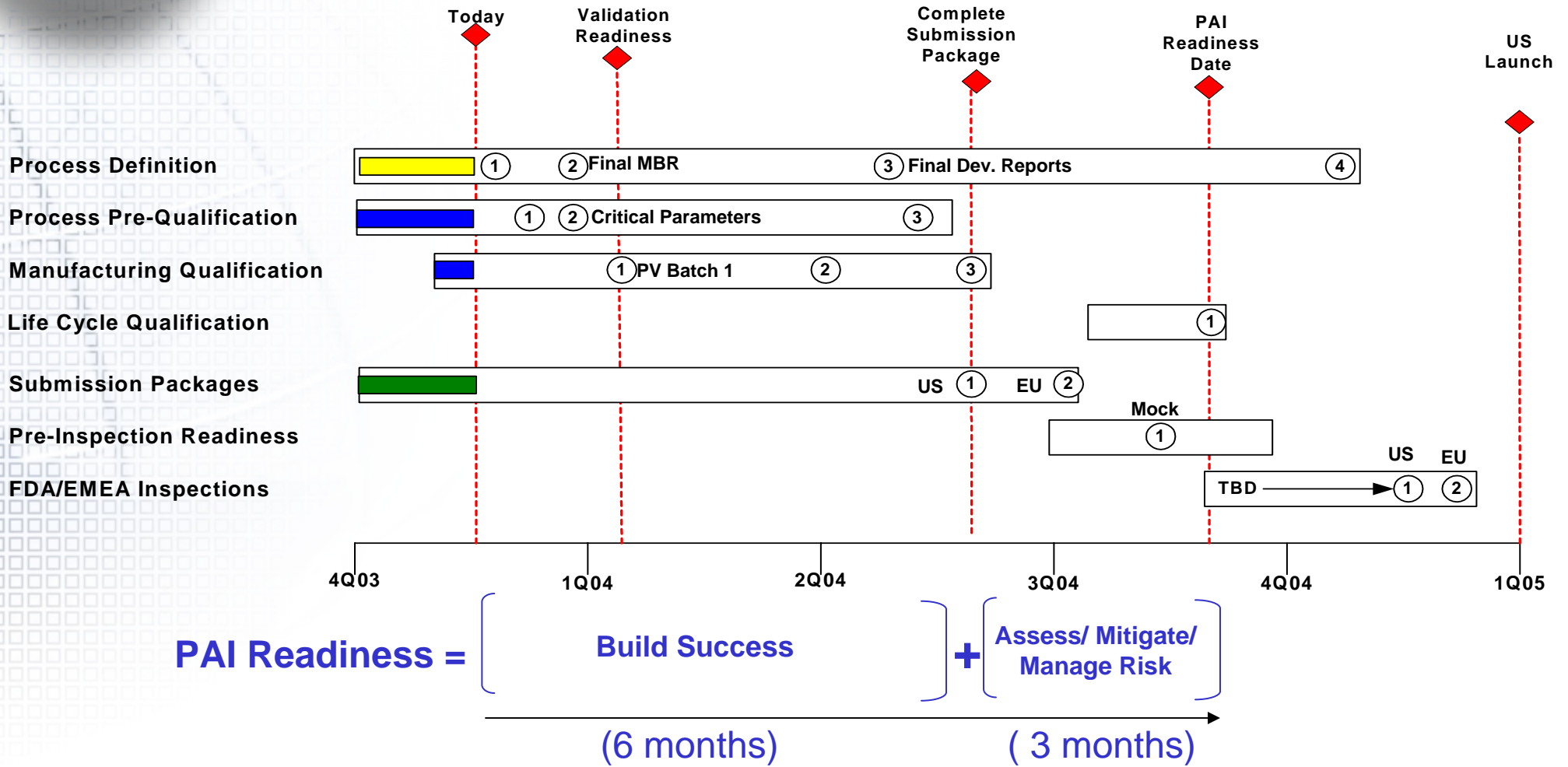


Step 2.0: Readiness Timeline

- Develop Milestones:
 - Validation Readiness **Date**
 - Complete Submission Package Date
 - PAI Readiness Date for US and EMEA
 - Launch Date
- Stages of Readiness:
 - **Build:** Process Definition and Pre-Qualification
 - Build: Manufacturing Qualification and Life Cycle Qualification
 - Build: Submission Package
 - Assess: Pre-Inspection Readiness
 - Assess: FDA/EMEA Inspection
- Majority of **Process and Analytical** documentation is generated during this period.



Step 2.0: Readiness Timeline Example





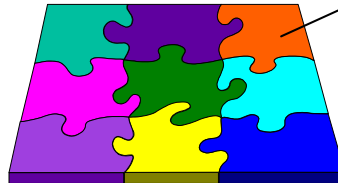
Step 3.0: PAI Readiness Tool Site Approval Master Plan (SAMP)

- A tool to track remediation efforts and documentation
- At minimum, develop a SAMP for each site likely to be inspected

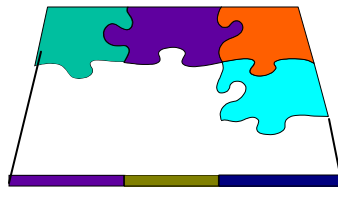
Supply Chain
Sponsor
API Manufacturer
Drug Product Manufacturer
US Analytical Lab
EU Analytical Lab
Support Lab
Raw Material Supplier
Analytical Lab
US Packaging
EU Packaging

Components:

Based on site responsibilities



Many Responsibilities
i.e. API, DP and Analytical



Limited Responsibility
i.e. Support Lab



Column Headings

- Component and Sub-categories
- Deficiency
- Action Plan
- Prioritization
- Risk Level
- Time to completion
- Status
- Comments



Step 3.0: PAI Readiness Tool

Example SAMP Components and Subcategories

1. Product Description

- Technology Transfer
- Development

2. Process

- Manufacturing Instructions
- Historical Batch Performance
- Process Development
- Support Validations
- Process Equipment

3. Analytical

- Lab Practices
- Analytical Equipment
- Lab Investigations and Method Issues
- Method Validation and Qualification:

4. Facility

- Systems and Utilities
- PM / Calibration
- Change Over / Cleaning
- Support Equipment (i.e., freezers, stopper and glass washers etc)
- Environmental Monitoring

5. Quality and Compliance

- Quality Systems & SOP's
- Quality Agreements
- Investigations / Deviations
- CAPA Closeouts
- Batch History & Quality Trends
- Change Control
- Training
- Raw Material and Components
- Storage and Warehousing

6. Storage and Distribution

- Shipping Procedures
- Shipping Validation

7. Stability



Step 4.0: Site Risk Evaluation

Aspects of Risk

Perform an Inspection Risk Evaluation

Consider the following as increasing risk:

- No regulatory history: FDA and/or EMEA inspections
- Perform multiple product support functions: Manufacturing, Stability, Analytical Method Development, Bioassay, Release and Stability Analytical Testing, etc.
- Poor performance and compliance history: failed batches, nature of investigations, number of OOS and deviations
- “State” of commercial readiness: outstanding audit items, outstanding support validations (i.e. resins re-use, cleaning, filter validation, etc.)



Step 4.1: Site Risk Evaluation

Site Ranking

Risk Assessment:

- Determine risk level based on evaluation criteria.

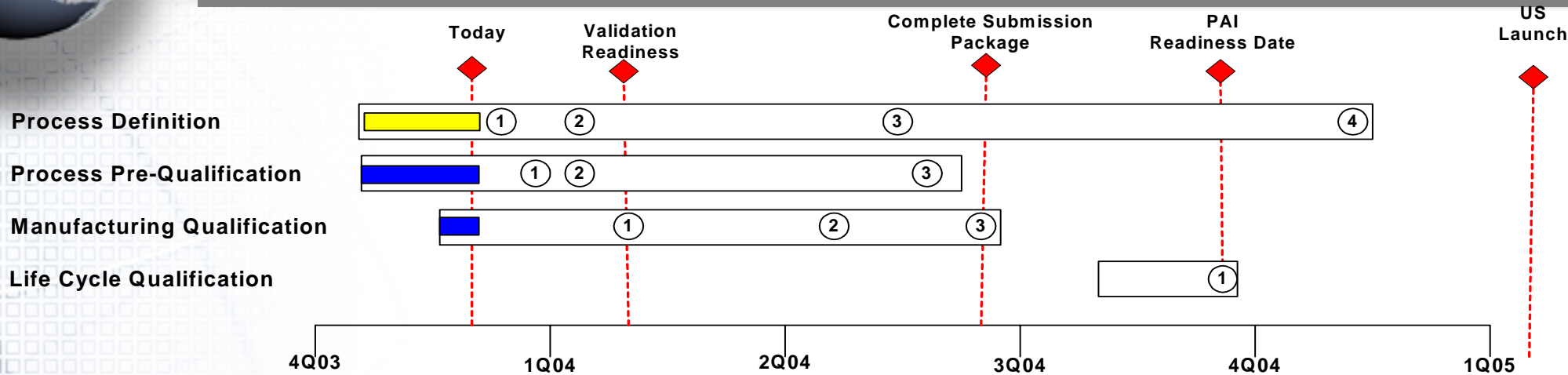
SUPPLY CHAIN	RESPONSIBILITY	EVALUATION	RISK
Sponsor	NDA/BLA Holder, Product Release and control Examples	- Virtual Company - First compound with FDA	Low
API Manufacturer	API Mfg., Cell Bank Storage, Stability, Development, Analytical	- No FDA or EU Inspection History - Multiple Functions	High **
Drug 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/EMEA Inspection

* FDA Inspection



Step 5.0a: High Risk Site Plan Build Success



Organization for the PAI starts with the preparations for Process Validation

- Perform parameter and critical process parameter evaluation. Also define In-Process Controls and Specifications (Process and Analytical Development).
- Process defined with Final Batch Record.
- Perform analytical method validation and establish commercial specifications.
- Facility GMP Status Review
- Equipment Qualifications Execution / Review (IOQ, PQ)
- Support Validations (i.e. resin re-use, filter validation, membrane re-use, depyrogenation, etc.) commenced.



Step 5.0b: High Risk Site Plan Assess, Mitigate, Manage Risk

Readiness activities that follow completion of Process Validation and Regulatory Submission of drug application:

- Prepare document tracker (i.e. SAMP categories) that includes sponsor, site and analytical documents.
- Perform site GMP and process assessment (i.e. corporate auditors). Note: You may choose to do this right before PV starts.
- Institute risk management process.
- Establish a steering team and core teams for managing remediation process and actions.



Step 5.0b: High Risk Site Plan Assess, Mitigate, Manage Risk

Readiness activities that follow completion of Process Validation and Regulatory Submission of drug application: (continued)

- Establish sponsor (i.e. NDA or BLA license holder) and site inspection team roles and responsibilities.
- Select development, process and analytical experts to present during inspections.
- Schedule “Mock” PAI Audit (i.e. post submission).
- Evaluate mock inspection risks at both the individual deficiency level and systemic level.
- Consider live inspection management tools that link inspection room, war room and client room.



Step 6.0: Low Risk Site Plan

- PAI Readiness Checklist
 - Site Readiness Program
 - Product Specific Questions
 - Government Agency Communication Record
 - Sponsor's role during PAI Inspection
 - FDA/EMEA Response Process
- Site visit to review PAI readiness plans and strategy
- Schedule QA audit (i.e. vendor audit)
- Low risk sites with a significant chance of a PAI inspection should have a Mock PAI performed to challenge site on product/process specific knowledge.



Step 7.0: Risk Management Process

7.0a: Categorize Deficiencies

7.0b: Risk Determination

7.0c: Risk Ranking

7.0d: Risk Mitigation



Step 7.0a: Risk Management Process

Categorize Deficiencies

1. Categorize deficiencies in appropriate SAMP Component: Product Description, Process, Analytical, Facility, Quality and Compliance, Supply Chain or Stability
2. Create Sub-Categories to group deficiencies

Example:

Mock Audit Deficiency: No quality agreement between the MAA sponsor, the site performing batch release and analytical testing (NDA sponsor), and the site doing manufacturing and limited analytical release testing (microbiological).

Component: Quality and Compliance

Sub- Categories: Quality Agreements



Step 7.0b: Risk Management Process

Risk Determination by deficiency

Factors: (Most Risk = 5)

- A. Severity (Compliance and Safety)
- B. Probability of Occurrence
- C. Time to mitigate deficiency

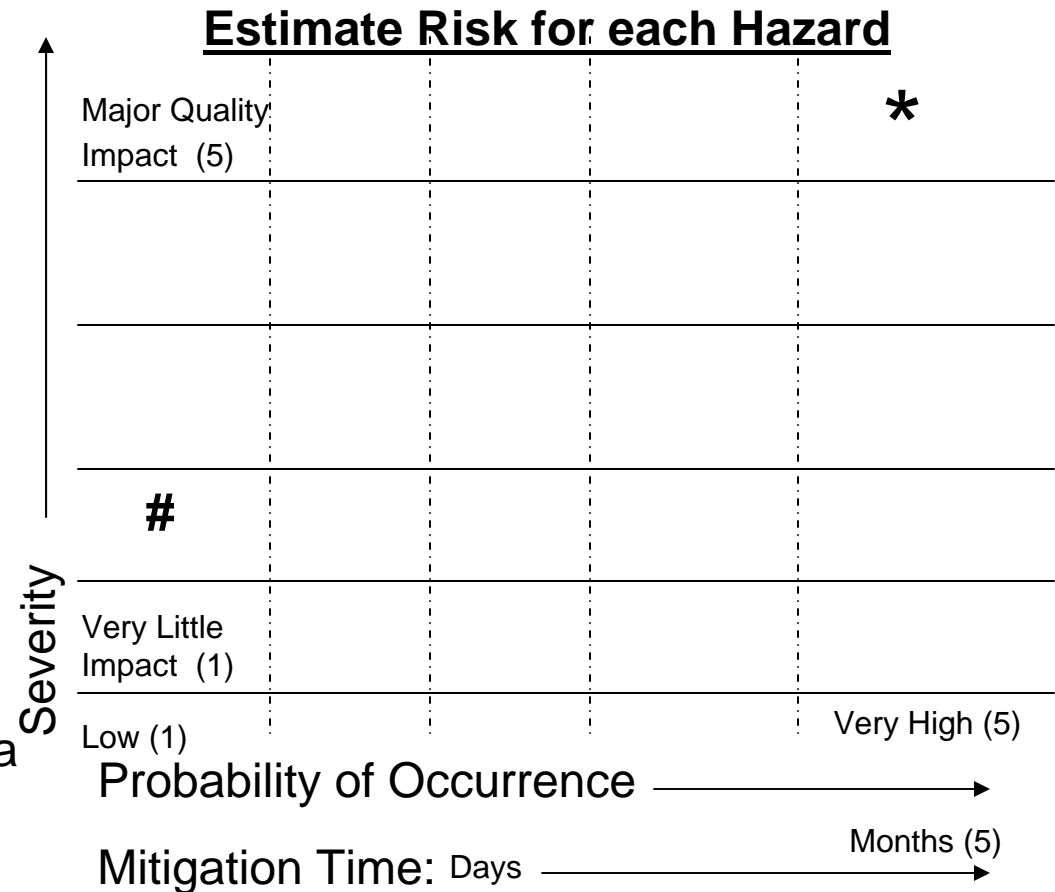
Mock Audit Deficiency (Examples)

* Resin Re-Use: Impurities were not resolved at end of column life

Issue – change in impurity profile in product pool. (Risk = 5)

Environmental monitoring out of spec in a closed system processing area

Issue – has closed system been validated? If yes, not likely to impact microbiological profile of product. (Risk = 1)



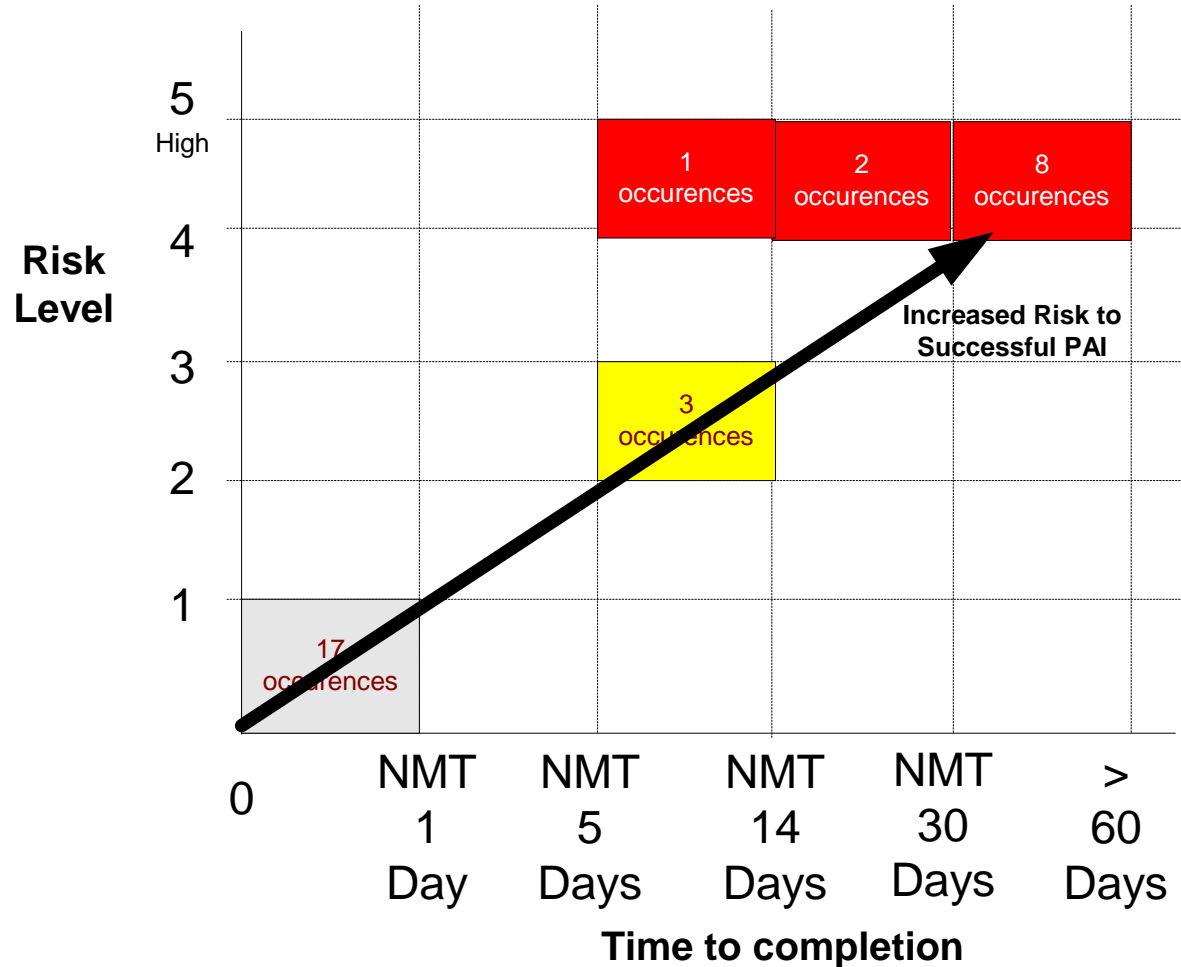


Step 7.0c: Risk Management Process

Risk Ranking

Determine **systemic issues** for each site category based on tallying number of risk level occurrences and time to completion for all deficiencies in a sub-category

Category: Facility
(Systemic Evaluation)
Sub-category: Systems and Utilities





Step 7.0d: Risk Management Process

Risk Mitigation

1. Mitigate specific individual high risk deficiencies starting with Level 5.
2. Mitigate systemic issues as follows:
 - a. Identify major site component and sub-category containing the most significant number of high risk deficiencies.
 - b. Create remediation plans.
 - c. Evaluate the overall system, including SOP's, policies, practices and performance history.

Example: Five critical areas for risk mitigation based on risk assessment and ranking;

- *Analytical*: QC Lab Practices (OOS procedures and practices)
- *Process*: Operational Observations (manufacturing consistency)
- *Facility*: General Utilities and Systems
- *Quality and Compliance*: Environmental Monitoring
- *Quality and Compliance*: Compliance Program (CAPA)



Summary

- Site Risk Evaluations are critical to prioritizing sites within a supply chain.
- Identification of specific site components (i.e. process, analytical, facility), a thorough risk assessment of each component (audit's + knowledge), and risk ranking of the observations provide the frame work for commencing risk mitigation.
- An organized effort utilizing risk ranking tools provides a much higher probability of success.