The Harmonized PAT Solution:

Application of Risk-Based Tools & PAT Strategies in Pharmaceutical Product Manufacture

Jeffrey A. Priem

Cubist Pharmaceuticals

Presentation Objectives

- Provide Overview of FDA's PAT Initiative
- Provide Overview of Risk Management & Risk Assessment Tools
- Provide PAT Strategy for Pharma Industry
- Present Case Example on PAT Strategy

Take Home Message

➔ *PAT = Process Understanding + Risk Mitigation*

PAT Elements

- Process Understanding
- Principles & Tools
  - PAT Tools
    - Multivariate Data Acquisition & Analysis tools
    - Process Analyzers
    - Process Control Systems
  - Risk-Based Approach
  - Integrated Systems Approach
  - Real Time Release

PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, & Quality Assurance, Sept 2004

PAT Challenges

- Technology
- Regulatory Driver
- Product Pipelines
- Automation
- Product Characterization

➔ *Process Understanding, Variation, Specificity, Robustness, Technology, & Regulatory Uncertainty*

Risk, Risk Assessments & Risk Management

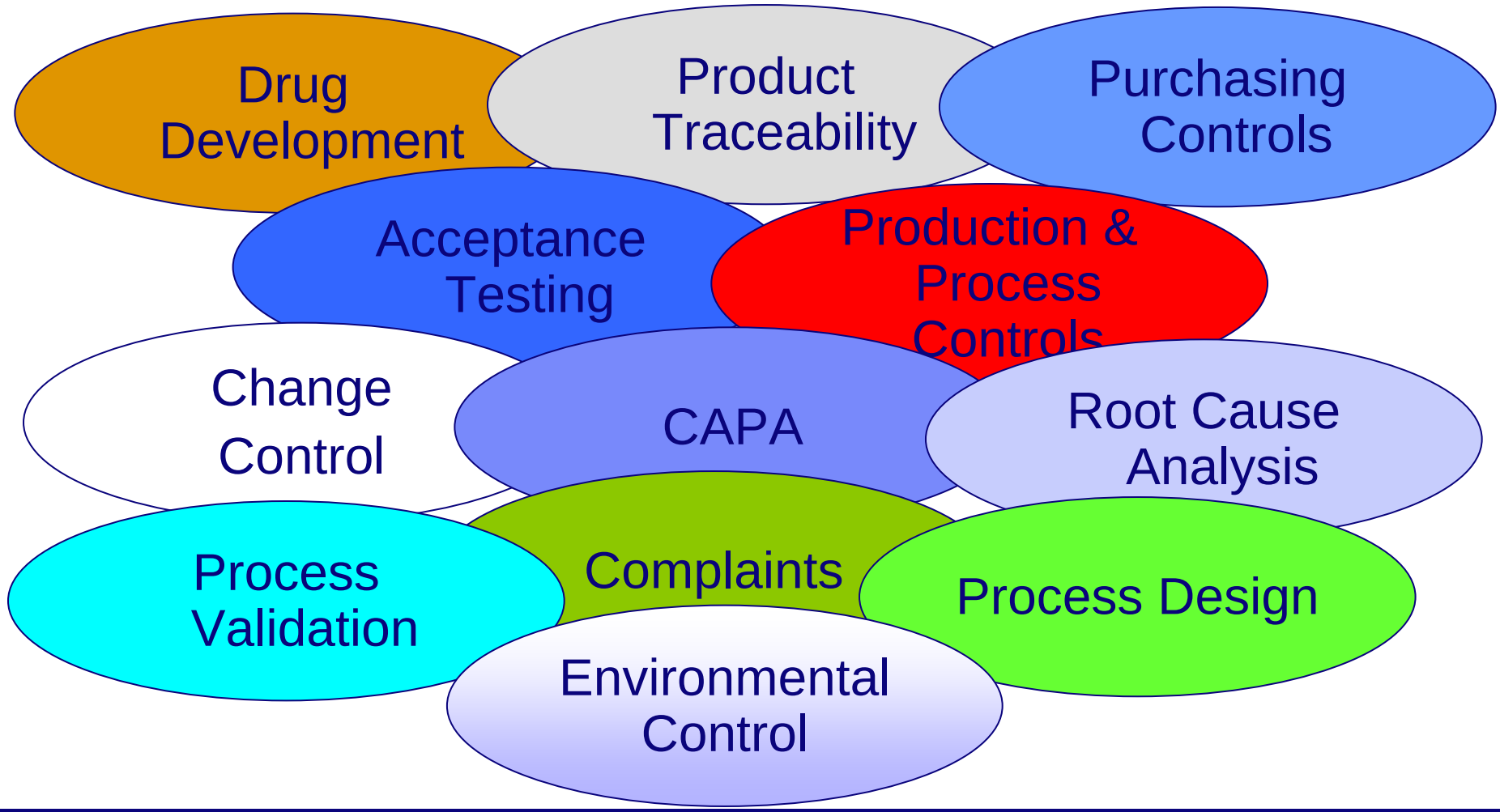
Risk Assessment:
Applications

Risk Assessment Project Type	Risk Assessment Application	
	Proactive Situation	**Reactive Situation**

Regulatory	• Due Diligence
	• GCP & GMP Assessment
	• New Product (Beginning of Lifecycle)
		• Crisis Management
		• Regulatory Issues
		  ◦ *Complaints & Adverse Events*
		  ◦ *Consent Decree & Warning Letter*

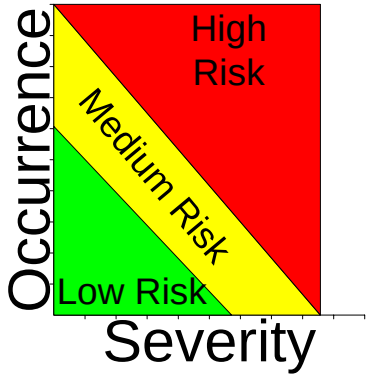
Product (Patient Focus)	• Drug Development	• Drug Development "Remediation"
Process	• Re-Engineering (Middle of Development Lifecycle)	• Mature Process – Risk Mitigation
Financial	• Merger & Acquisition • Feasibility	• Crisis Management

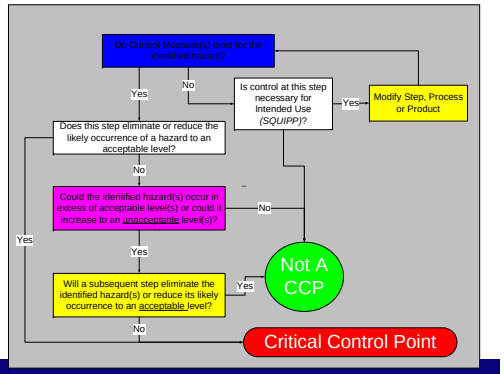
Quality System Applications & Risk Assessments



Risk Analysis Approaches

- Risk Matrixes
  - Probability vs. Severity = High, Medium, or Low
- "Risk" Definition & Categorization
  - Level I = …
  - Level II = …
  - Level III = …
- Pre-Defined Question & Decision Tree
  - *"If then, else…"*





Risk Assessment Tools

- **FMEA** - Failure Modes Effects Analysis
- **FMECA** - Failure Modes Effects & Criticality Analysis
- **FTA** - Fault Tree Analysis
- **HACCP** - Hazard Analysis Critical Control Points

And

- ***Combination Methods –*** *Tools & Approaches*

Combination Methods Overview

- Key Questions to Ask & Understand
  - *What is the Risk Focus?*
  - *What are the Risk Requirements?*
  - *What are the Risk Metrics to be quantified & Measured?*
  - *What is the Outcome of the Exposure?*

  As well as…
  - *What is it you need?*
  - *How do you plan to do it?*
  - *What is the ultimate outcome?*
  - *What are the challenges?*

Balance RA Tools vs. RA Approaches

- ← Format
- ← Content
- ← Context
- ← Intent
- ← Implementation
- ← Integration
- ← Effectiveness

Risk Management:
Applications

Risk Assessment Categories *(Project Type)*	Risk Assessment Application	
	Proactive Situation	**Reactive Situation**
Regulatory	• Due Diligence • GMP Assessment • New Product (Beginning of Lifecycle)	• Crisis Management • Regulatory Issues •Consent Decree •Warning Letter •FDA-483
Product	• Product Development •	• Design Control (Middle of Design Lifecycle or After Design)
Process	• Re-Engineering (Middle of Development Lifecycle)	• Mature Process – Risk Mitigation
Financial	• M&A • Feasibility	• Crisis Management

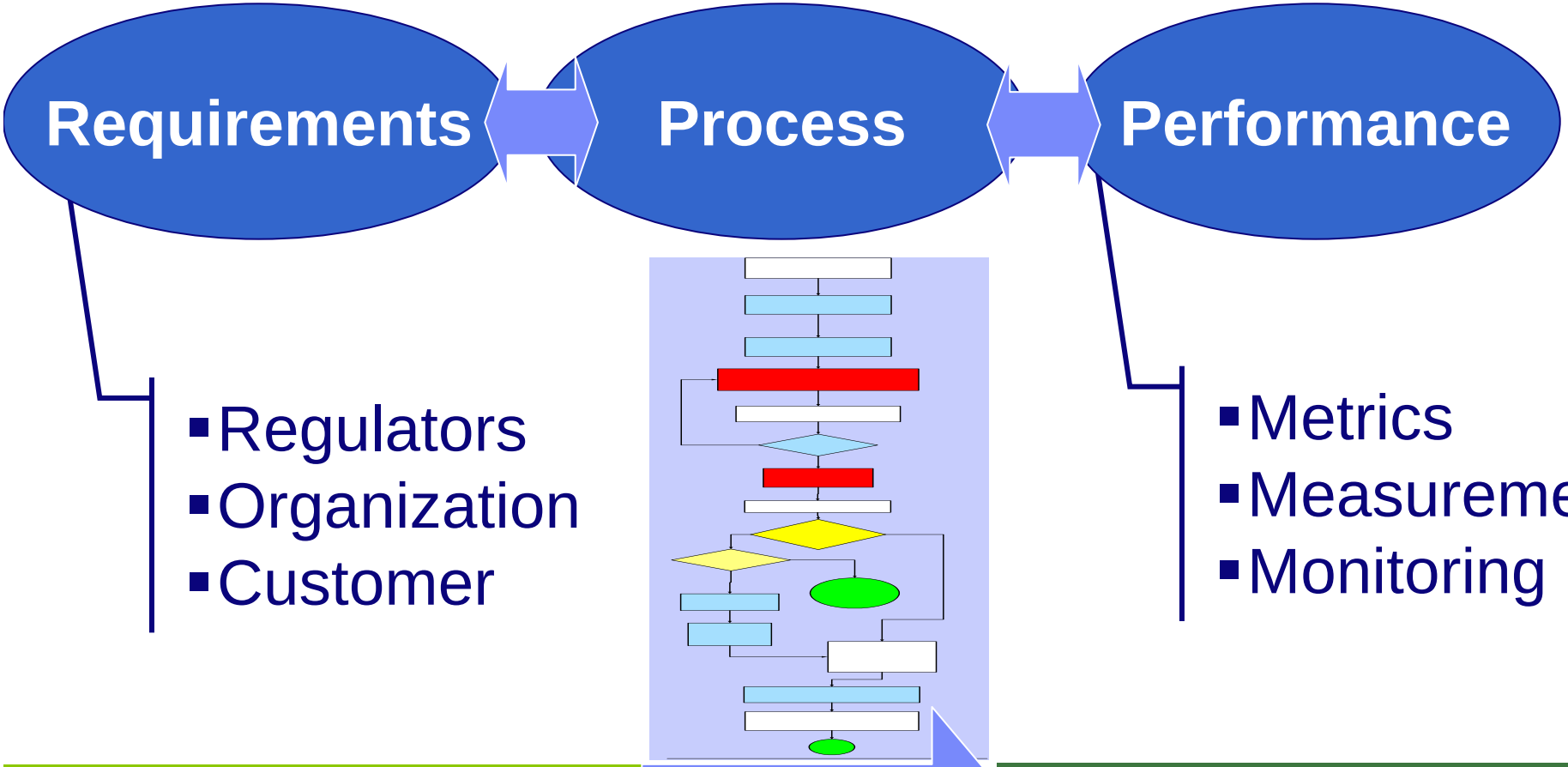
….How do I relate these to one another?

Risk Management Concept

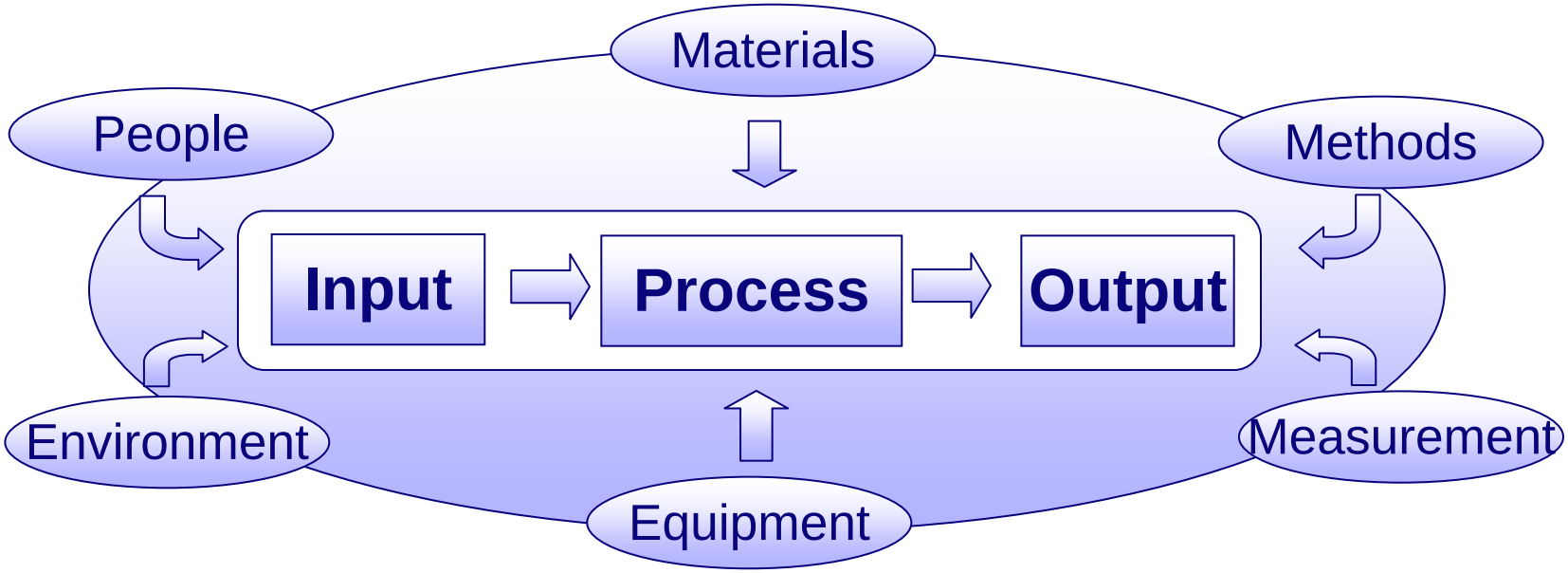
ICH Q9: Quality Risk Management

The Harmonized PAT Solution

The “Simplified” Process Model



Process Understanding Concept: *Process Variation*



Harmonized PAT

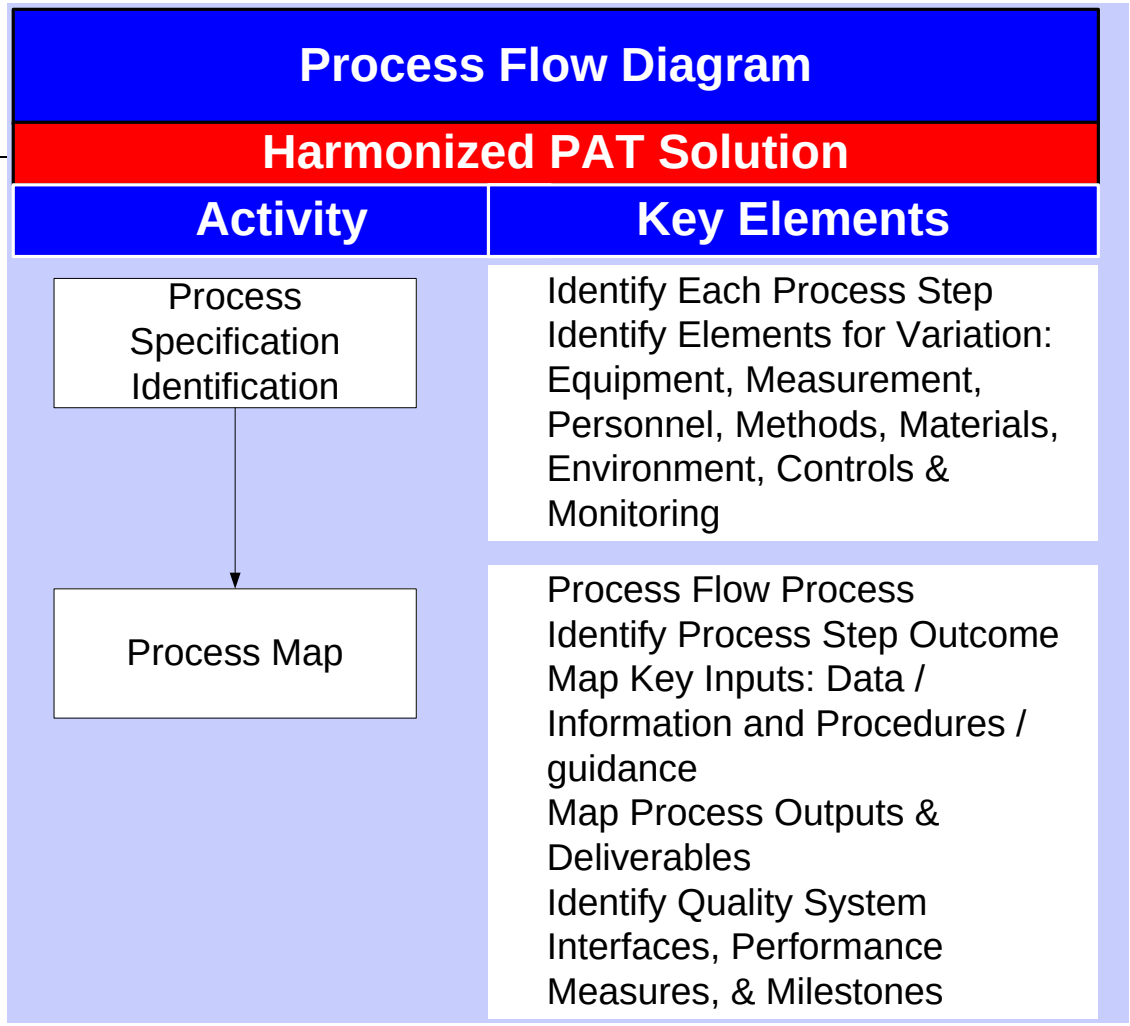
PAT Elements	PAT Strategy			
	Risk Management	Process Understanding	Process Analysis	Process Optimization
PAT Tools • Multivariate Data Acquisition & Analysis Tools • Modern Process Analyzers / process analytical chemistry tools • Process & Endpoint monitoring & control tools • Continuous Improvement & KM	• Provide Risk Based Decision Processes • Provide Rationale on where to apply Technology • Provide Framework to facilitate Process Understanding & Decision Making Process • Provide Framework to execute Risk-based strategies	• Identify critical attributes • Identify automation attributes • Identify monitoring & control elements • Obtain Knowledge of product & process specifications & requirements • Provide understanding of QS interfaces • Analyze risk at product, process, & quality systems perspective • Define Mitigation Strategy		• Implement test strategies • Optimize Process • Implement Optimization points • Apply Technology
Process Understanding				
Risk-Based Approach				
Integrated Systems Approach				
Real Time Release				

PAT Application Example

Technology Transfer & Process Validation

Process Understanding

- Identify product requirements
- Define how they were derived
- Quantify robustness & adequacy
- Correlate Attributes to Interfaces
  - Process
  - System
  - Component



Process Understanding
Process Identification Deliverable

- Matrix of those Elements of Variation

Process Step: <Description>

Each Process Step is described by:

Equipment Table
- Equipment
- Computer
- Computer Interface
- Instruments
- Utilities

Personnel Table
- Department
- Function
- Skills

Methods Table
- Procedure No.
- Process Instruction No.
- Process Parameter
- Process Attribute
- Process Variable

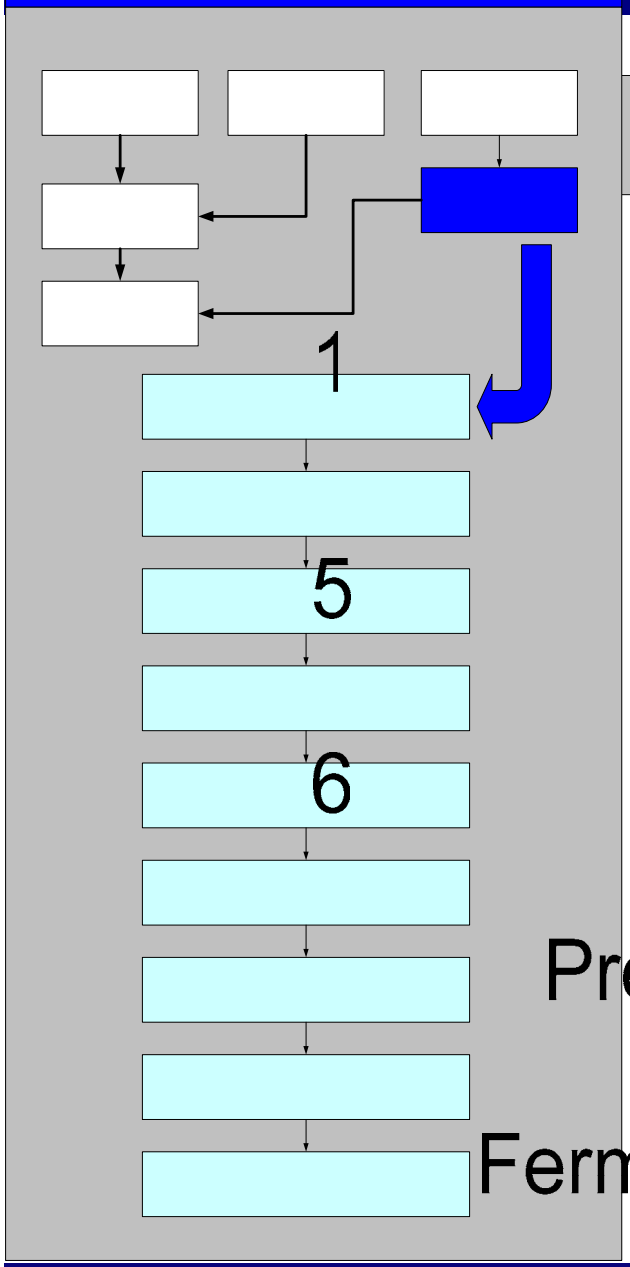
Measurement Elements Table
- Procedure No.
- Method Type
- Personnel
- Equipment
- Verification Element
- Specifications / Metrics

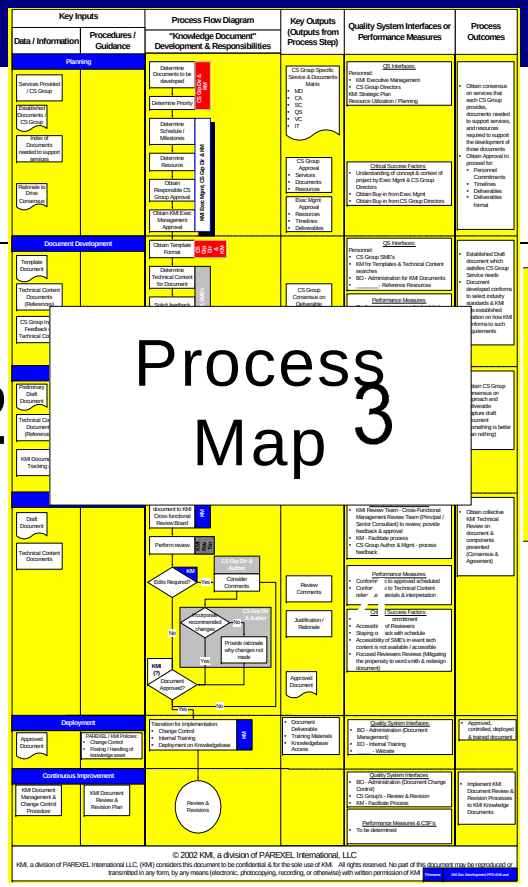
Materials Table
- Component
- In-Process Product
- Consumables
- Specifications
- Attributes

Environment Table
- Element
- Requirements Description

Controls & Monitoring Table
- Quality System Interface
- Procedure No.
- Personnel
- Method
- Requirements

Process Workflow





Specifications

Product and Process		
	Procedures	Environment
	Materials	Measurement
	Equipment / Systems	Personnel

Process Map

Process Workflow
- Flow diagram of processes & activities

Process Outcome
- Per each level

Key Inputs
- Date & Information into the Process
- Procedures & Guidance that Drive Process

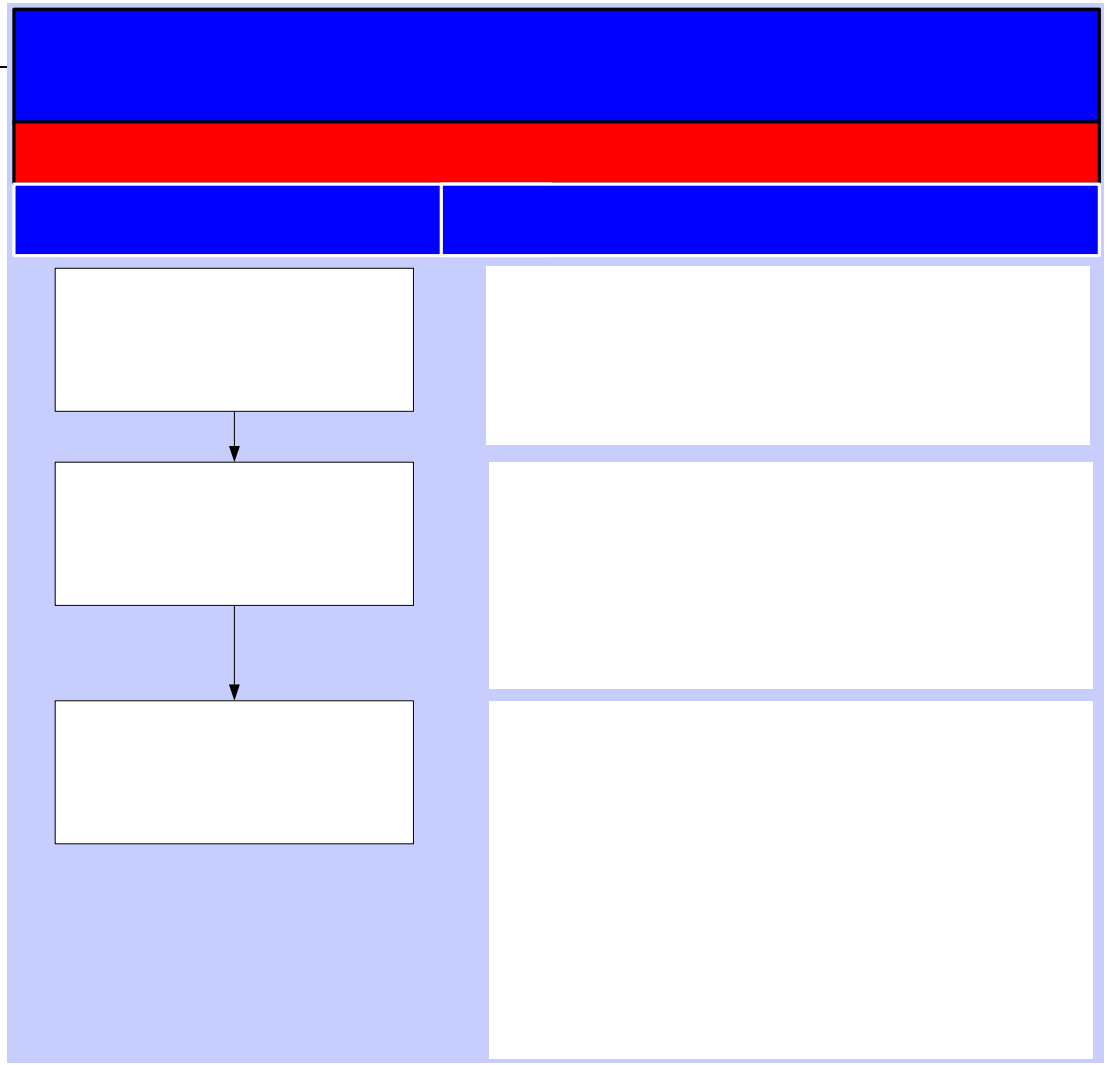
Key Outputs
- Deliverables Result for Process
- Activities Result from Process

Quality System Interfaces
- Quality Program Linkage Points

Performance Measurement
- Metrics to measure performance

Process Analysis

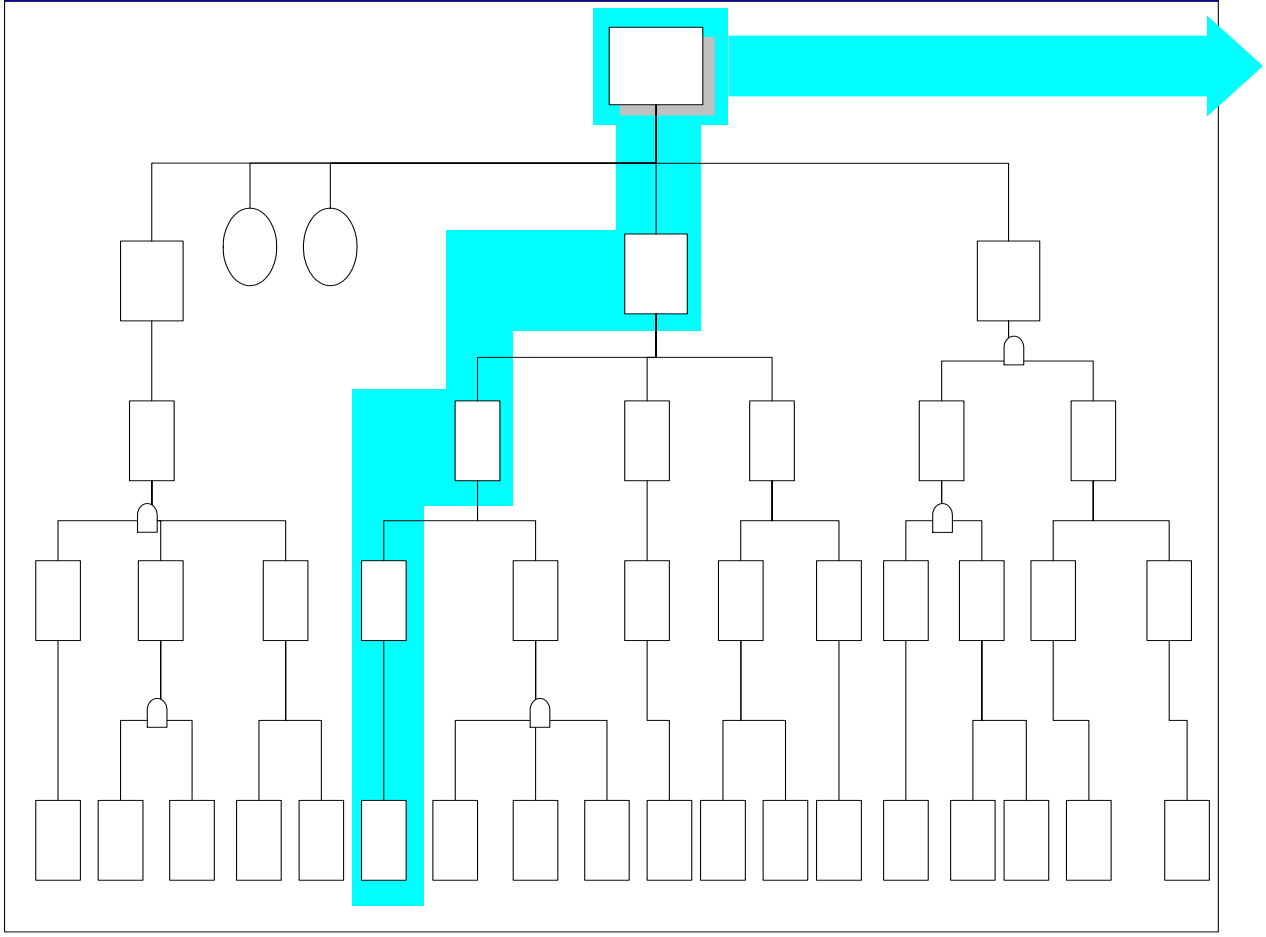
- Define Product Risks
- Identify Process Risks
- Identify Quality System Risk Areas
- Correlate Risks to Mitigation Strategies



Pr

Process Analysis
Process Risk Assessment

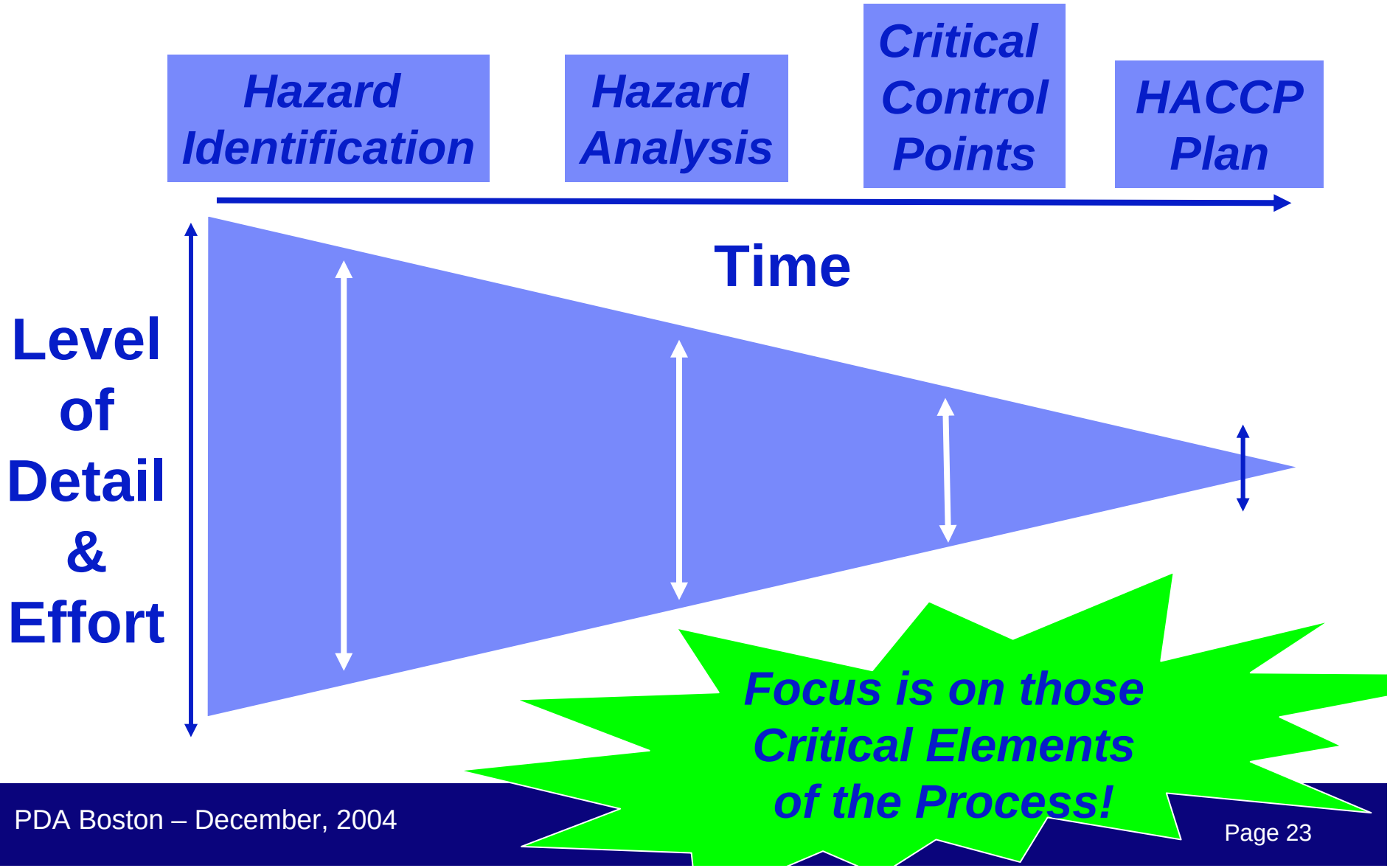
Process Fault Tree Analysis



Tree Example

- Failure of Sterility
- Fermentation Process
- Sampling Process
- QC Test Equip 1149 Failure
- QC Test Eq 1149 out of Calibration

Process Analysis
Process HACCP Deliverables



Process Analysis
Quality System Risk Quantification

File Edit View Insert Format Tools Data Window Help Acrobat

	A	B	C	D
1	Quality System	System Design	System Performance	Business Performance
2	Adverse Events	9.0	8.1	7.6
3	Annual Product Review	2.0	2.0	2.8
4	Audit	2.9	4.3	6.8
5	Change Control	8.5	8.5	8.8
6	Deviation / CAPA	8.2	9.8	8.8
7	Document and Records Management *	9.0	6.9	4.8
8	Environmental Control	2.5	8.4	4.8
9	Equipment System	2.9	2.7	2.8
10	Facilities System	2.9	2.8	2.4
11	Lot Release	8.5	8.9	6.8
12	Management Controls	4.7	10.0	3.2
13	Materials Management	2.9	4.7	9.2
14	Out of Specification	6.0	6.8	7.2
15	Packaging & Labeling	3.0	2.0	6.0
16	Production	3.9	2.8	4.4
17	Regulatory Agency Submissions	5.5	2.0	7.6
18	Stability Testing	3.0	2.9	7.6
19	Technical Complaints	2.9	6.1	2.0
20	Testing	6.5	4.1	9.6
21	Training	9.0	6.8	8.0
22	Validation	9.0	6.9	9.2

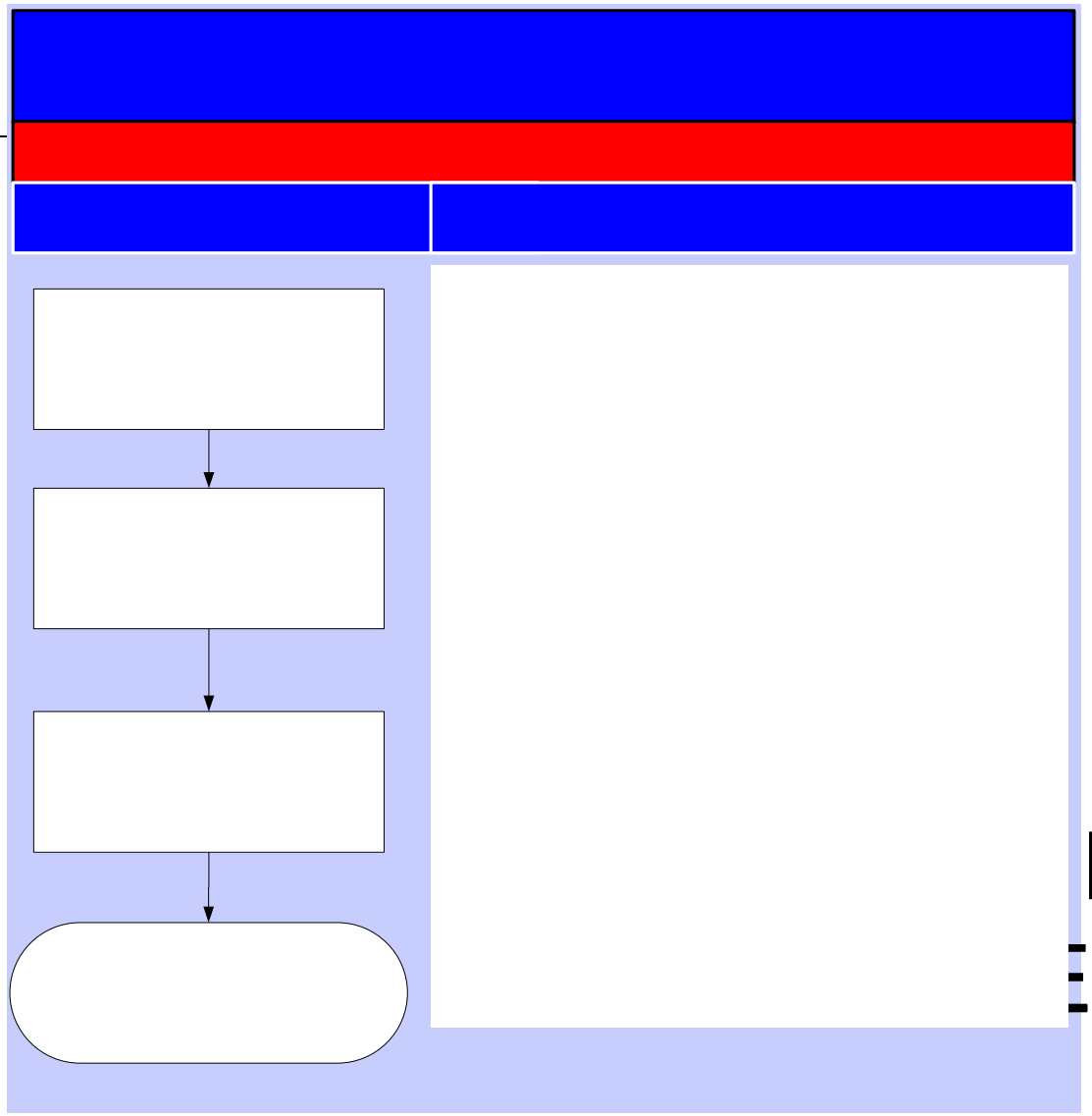
Sheet1 Sheet2 Sheet3

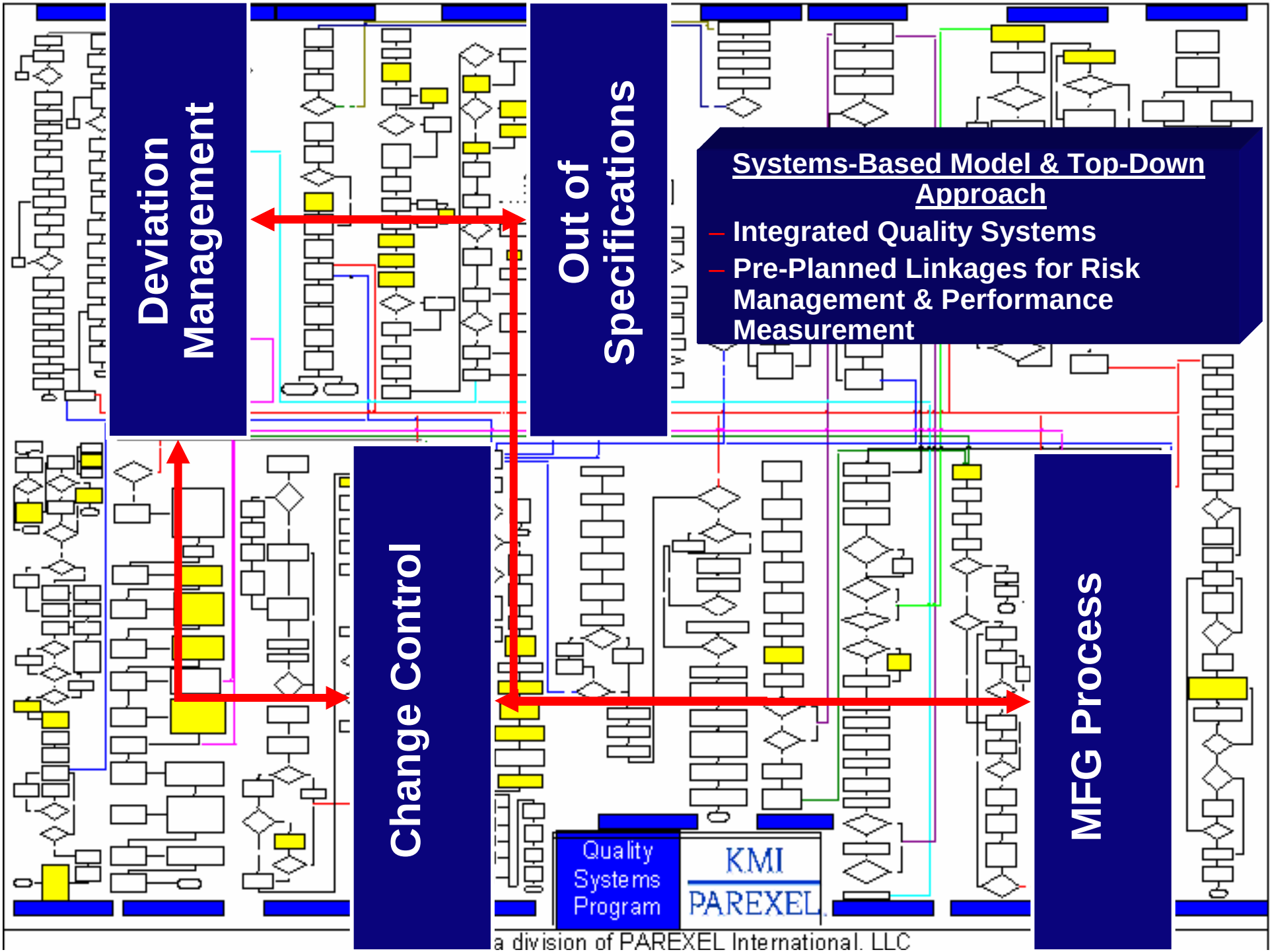
Close Full Screen

Low: 0 to 3.9 | *Medium: 4.0 to 7.9* | *High: 8.0 to 10*

Process Optimization

- Define Analysis Areas
- Implement Corrective Action Plan
- Execute Optimization Strategies
- Implement Technology & Solutions




Deviation Management
Out of Specifications
Change Control
MFG Process
Systems-Based Model & Top-Down Approach
– Integrated Quality Systems
– Pre-Planned Linkages for Risk Management & Performance Measurement
Quality Systems Program
KMI
PAREXEL
a division of PAREXEL International, LLC

Implementation

- Measure
- Control & Monitor
- Analyze

➔ ***Review***

➔ ***Refine***

➔ ***Revise***

Again…

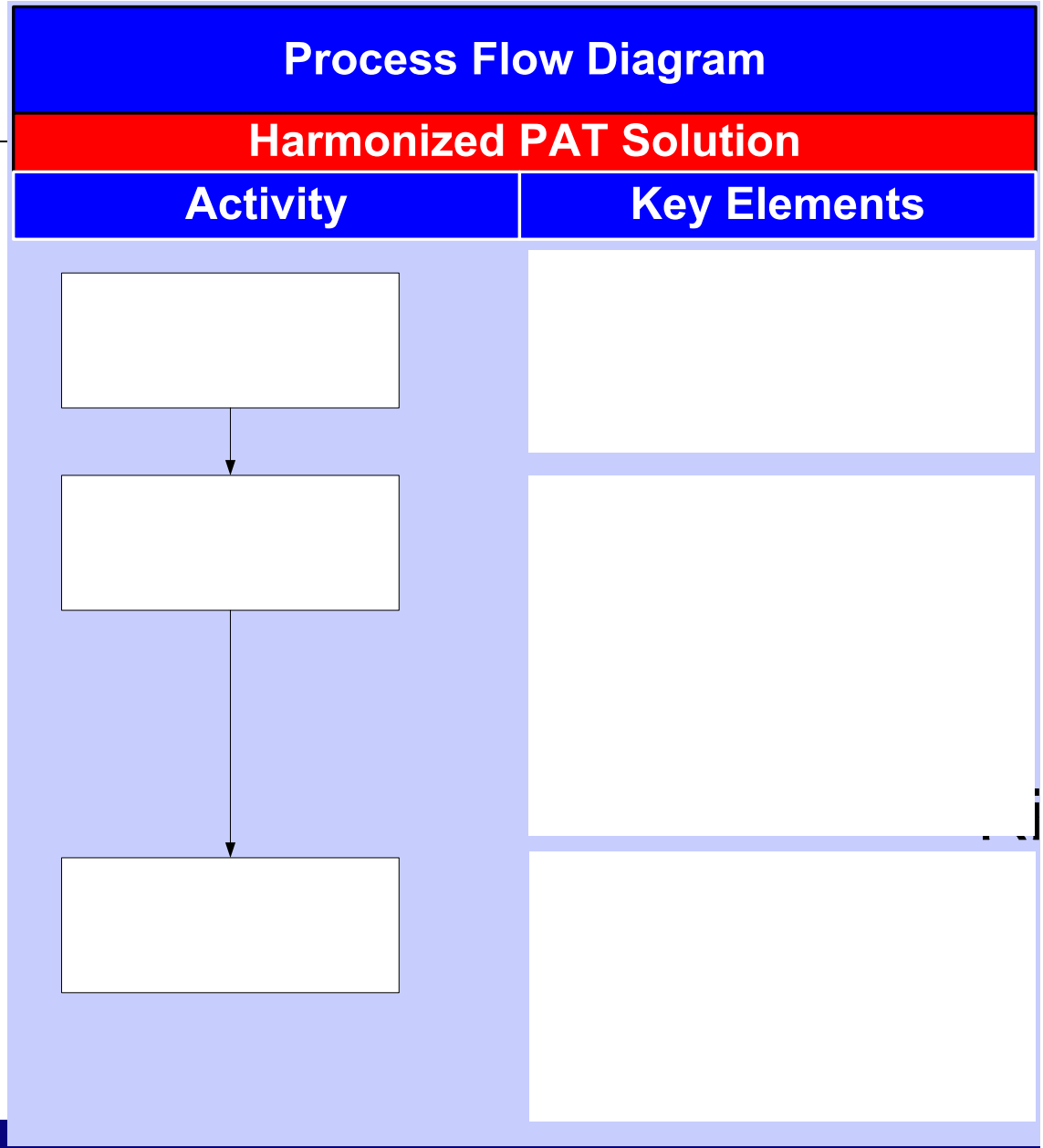
Requirements

DRIVE

Performance

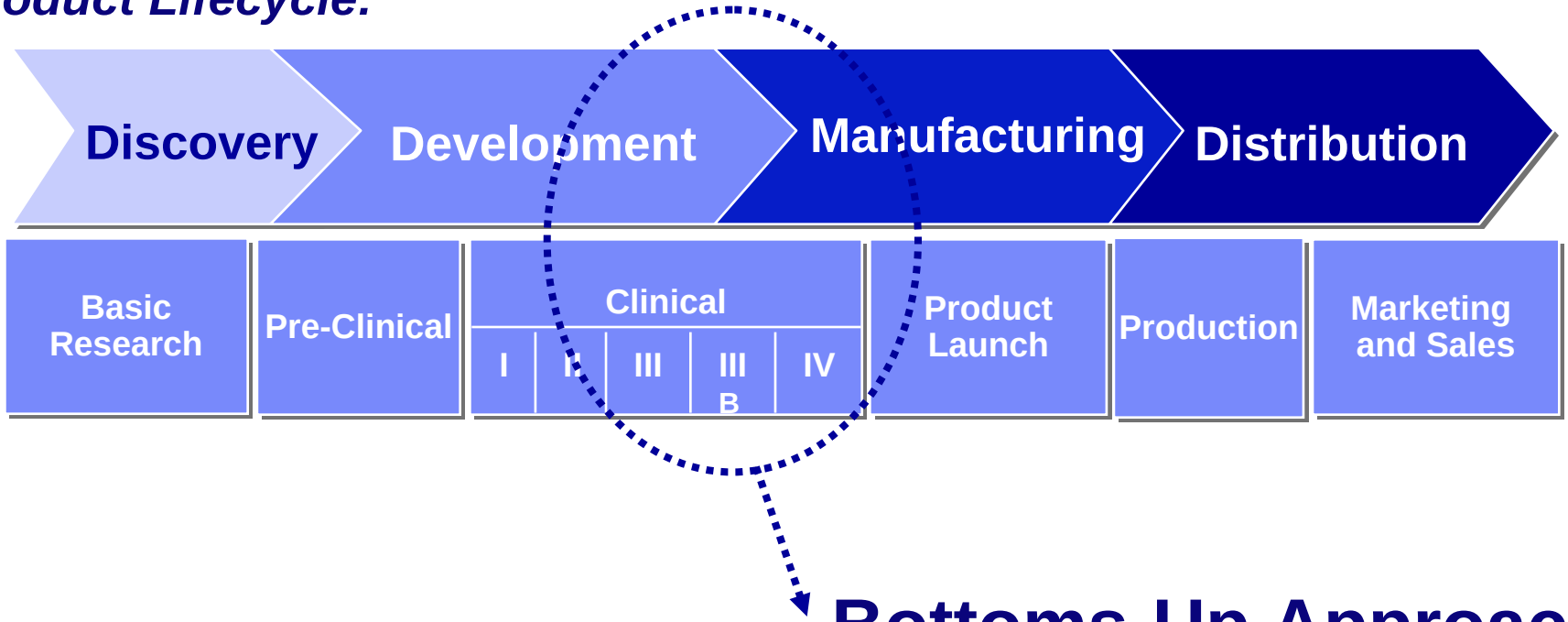
Risk Management

- Define
  - Scope
  - Approach
  - Interfaces
  - Outcome



Risk Management & Drug Development Lifecycle

Product Lifecycle:

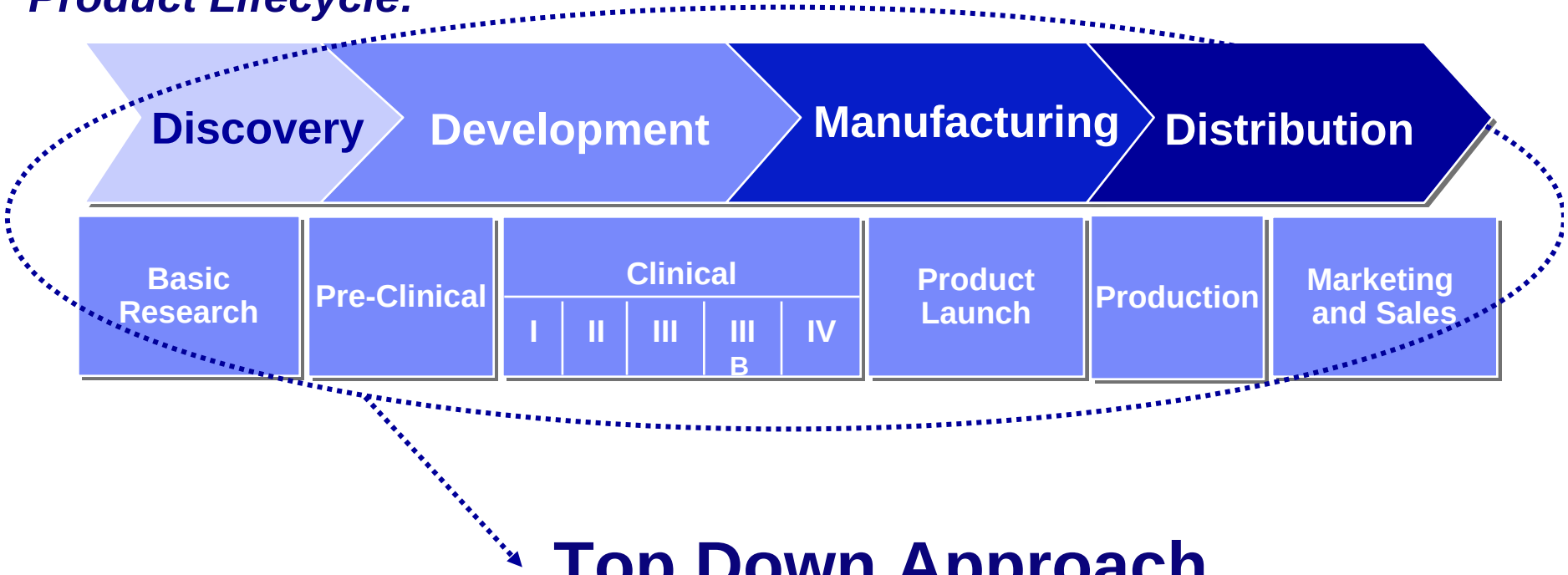


Bottoms-Up Approach

- **Risk Management & Drug Development**

Risk Management & Drug Development Lifecycle

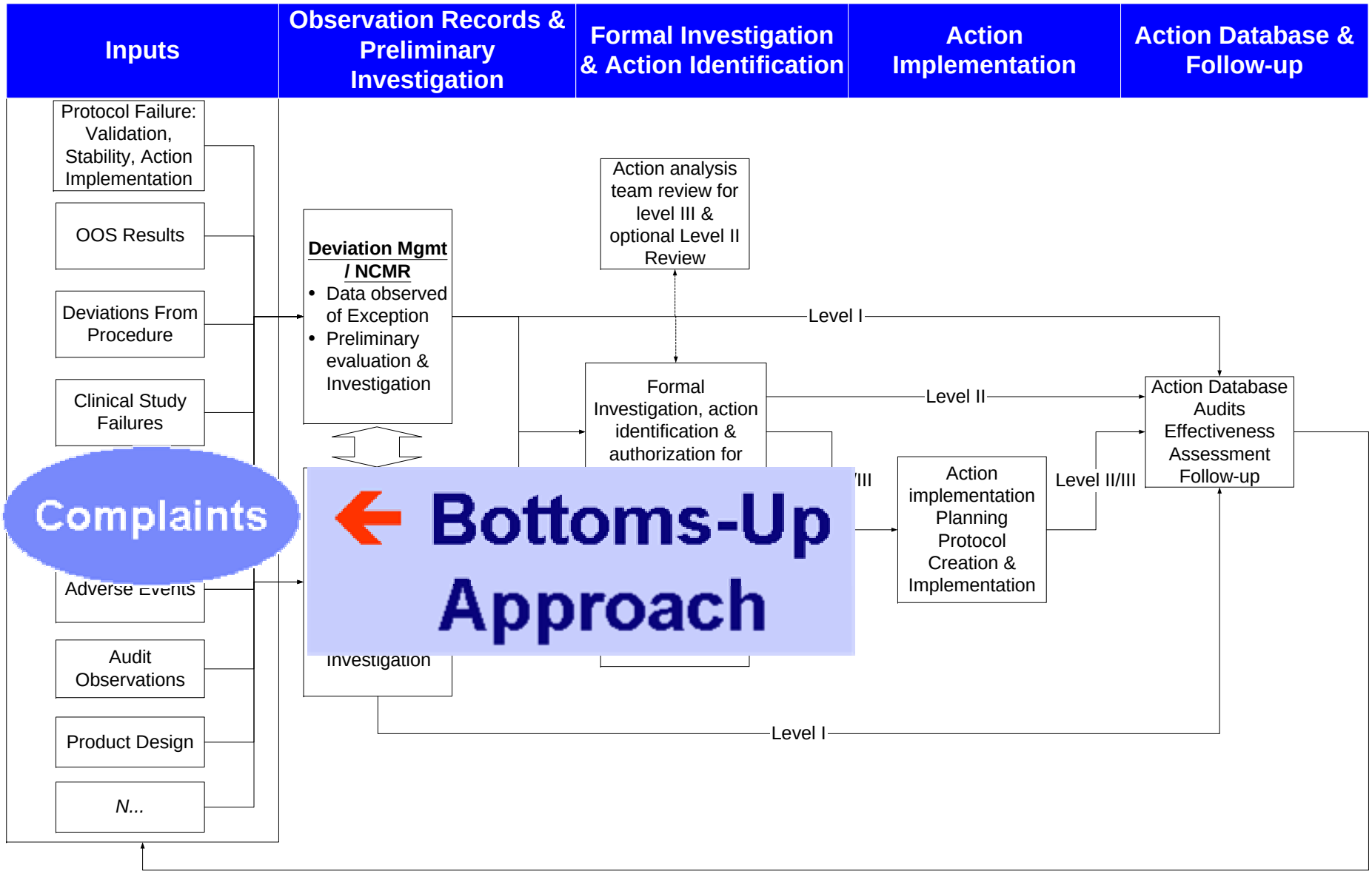
Product Lifecycle:



Top Down Approach

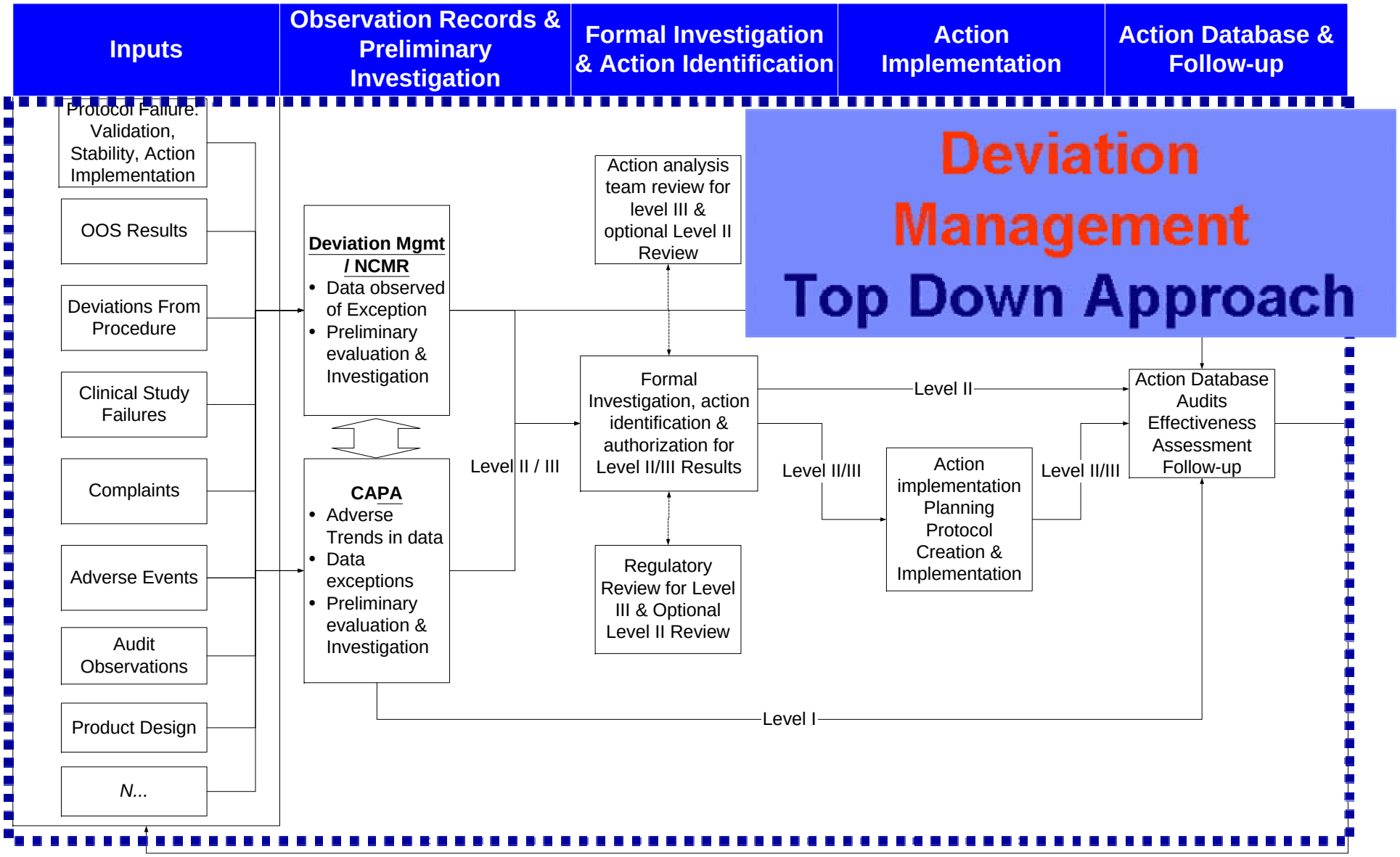
- Risk Management & Product Lifecycle

Risk Management "System"



Reference: "Risk Management Basics", DeSain, Vercimak, Sutton

Risk Management "System"



Reference: "Risk Management Basics", DeSain, Vercimak, Sutton

Outcomes

PAT Elements	PAT Strategy			
	Risk Management	Process Understanding	Process Analysis	Process Optimization
PAT Tools • Multivariate Data Acquisition & Analysis Tools • Modern Process Analyzers / process analytical chemistry tools • Process & Endpoint monitoring & control tools • Continuous Improvement & KM	• Risk Management Program – Program Plan & Document • Risk Management System – Methodology – Guideline – Procedures – Templates • Projects – Top Down – Bottom's Up	• Process Specification Identification • Process Maps • Process FTA • Process HACCP • Quality System Assessment • Project Plan		• Development Testing • DOE • QS Optimization • Technology Integration
Process Understanding				
Risk-Based Approach				
Integrated Systems Approach				
Real Time Release				

PAT Application

Project Outcomes

- Improved Product Quality
- Optimization of Processes & Interfaces
- Reduction in Production Cycle Time
- Variation Mitigation
- Process Epiphany: The “Ah Ha!” Factor
- Cost Savings & Optimized Resources
  - Technology
  - Personnel
  - ROI

➔ Defendable Compliance vs. Minimal Compliance

The Harmonized PAT Solution:

Application of Risk-Based Tools & PAT Strategies in Pharmaceutical Product Manufacture

By:

Jeff Priem

Tel: 781.860.8661

Email: jeffrey.priem@cubist.com