Engineering Global Pharmaceutical Manufacturing Systems in the New Environment

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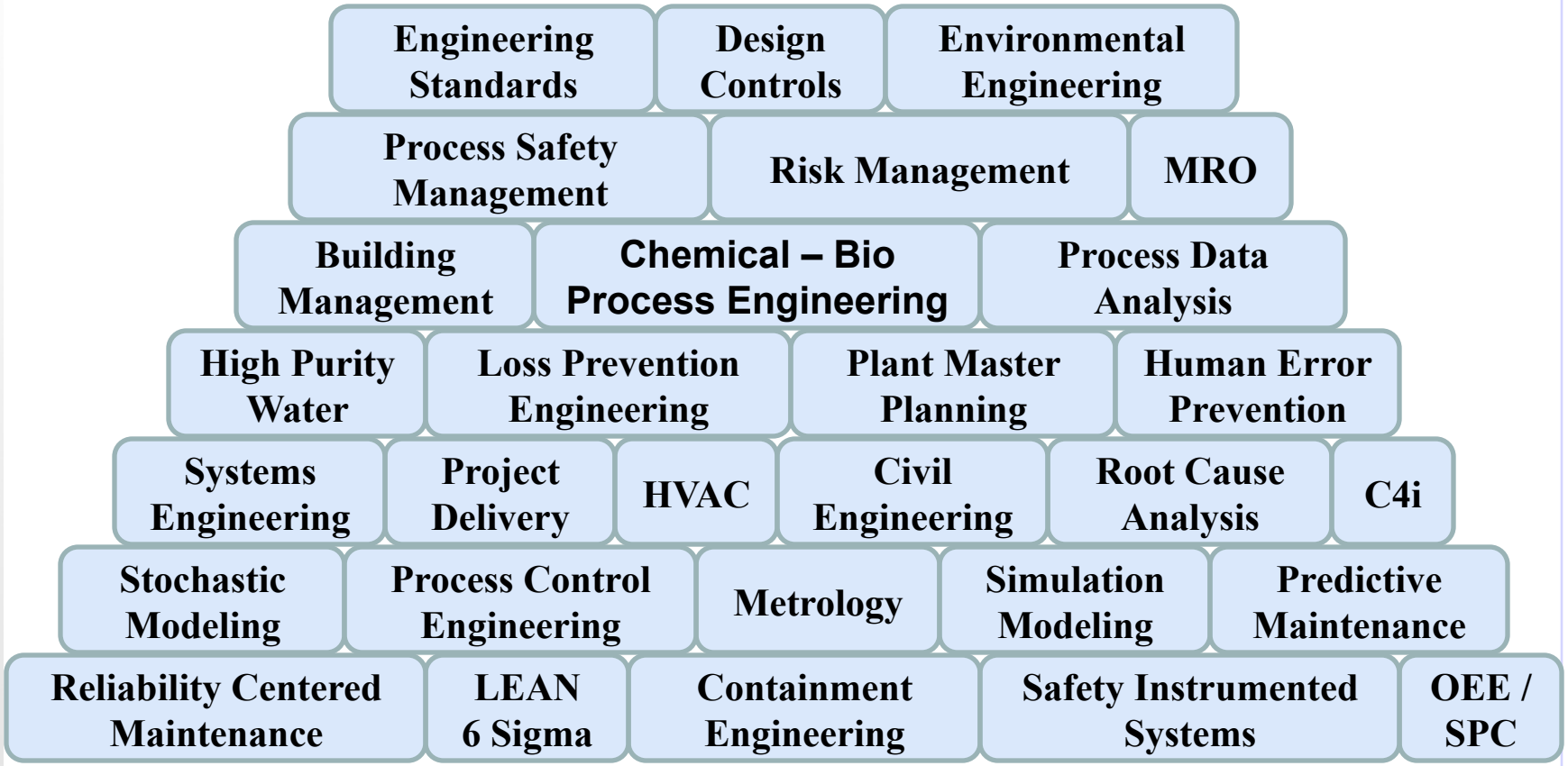
Typical Engineering Disciplines in Pharmaceutical Manufacturing



What was the "Old Environment" ???

For decades pharmaceutical manufacturing relied on 'quality by inspection'

Regulatory compliance took precedence over fundamental improvements

- Use of "***Good Manufacturing Practices***" (GMPs)
- "Predicate Rules" (laws) and Guidance, e.g.
  - U.S. FDA
  - E.U. EMEA
  - Irish Medicines Board
  - and others….

For example, applicable U.S. FDA regulations include:

- 21CFR 210, 211
- 21CFR Part 11
- 21CFR 820

What was the "Old Environment" ???

Traditional Drivers:

- Few revisions to regulatory GMPs interpreted to suggest "status quo"
- Decades of regulatory inspections and enforcement actions provided 'learning'
- Continued focus on patient safety relied on quality by inspection
- Essential need to remain "compliant with GMPs"
- Regulatory Expectation: "If it wasn't documented, it didn't happen."

Outcomes:

- Conservative designs
- Status quo approaches
- **Excessive Verification, Validation and Documentation practices, e.g.**

1. **DOCUMENTING EVERYTHING**
2. **Reviewing, verifying and documenting that you documented everything**
3. **Documenting and explaining any documentation errors and/or omissions…**
4. **Then Reviewing and Approving these reviews and approvals…**

What was the "Old Environment" ???

"Documentation-centric
Quality by Inspection?"

….perhaps there is a

better way….

What's Driving Change?

Pharmaceutical cGMPs

for the

21st Century

- A Risk-Based Approach

Final Report - Fall 2004

Department of Health and Human Services
U.S. Food and Drug Administration

September 2004

What's Driving Change?

"The Desired State"
A Mutual Goal of Industry, Society, and Regulators:

"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."

Janet Woodcock, M.D.
Deputy Commissioner for Operations
Office of the Commissioner, FDA
October 5, 2005

"Pharmaceutical Quality Systems"
"Sound process and product understanding"

What's Driving Change?

Typical Pharma Manufacturing vs. World Class Operational Excellence (OPEX)

Key Performance Indicator	Typical Pharma Plant (2005)	A Winning Pharma Plant	World Class OPEX
Stock Turns (x / Year)	3 - 5	14	50
OTIF	60 – 80 %	94 %	96 %
RFT	85 – 95 %	96 %	99 %
Cpk	1 -2	2.5	3.2
OEE	30 %	74 %	92 %
Cycle Time (WIP Hrs.)	720	48	8

(Source: The Metamorphosis of Manufacturing © IBM Corporation, 2005)

OITF = (Order Filled) On Time In Full
RFT = Right First Time

Cpk = Process Capability Index
OEE = Overall Equipment Effectiveness

Emerging Trends:

Product and Process Quality Knowledge
Science-based and Risk-based Business Execution
Use of First Principles

Quality by Design

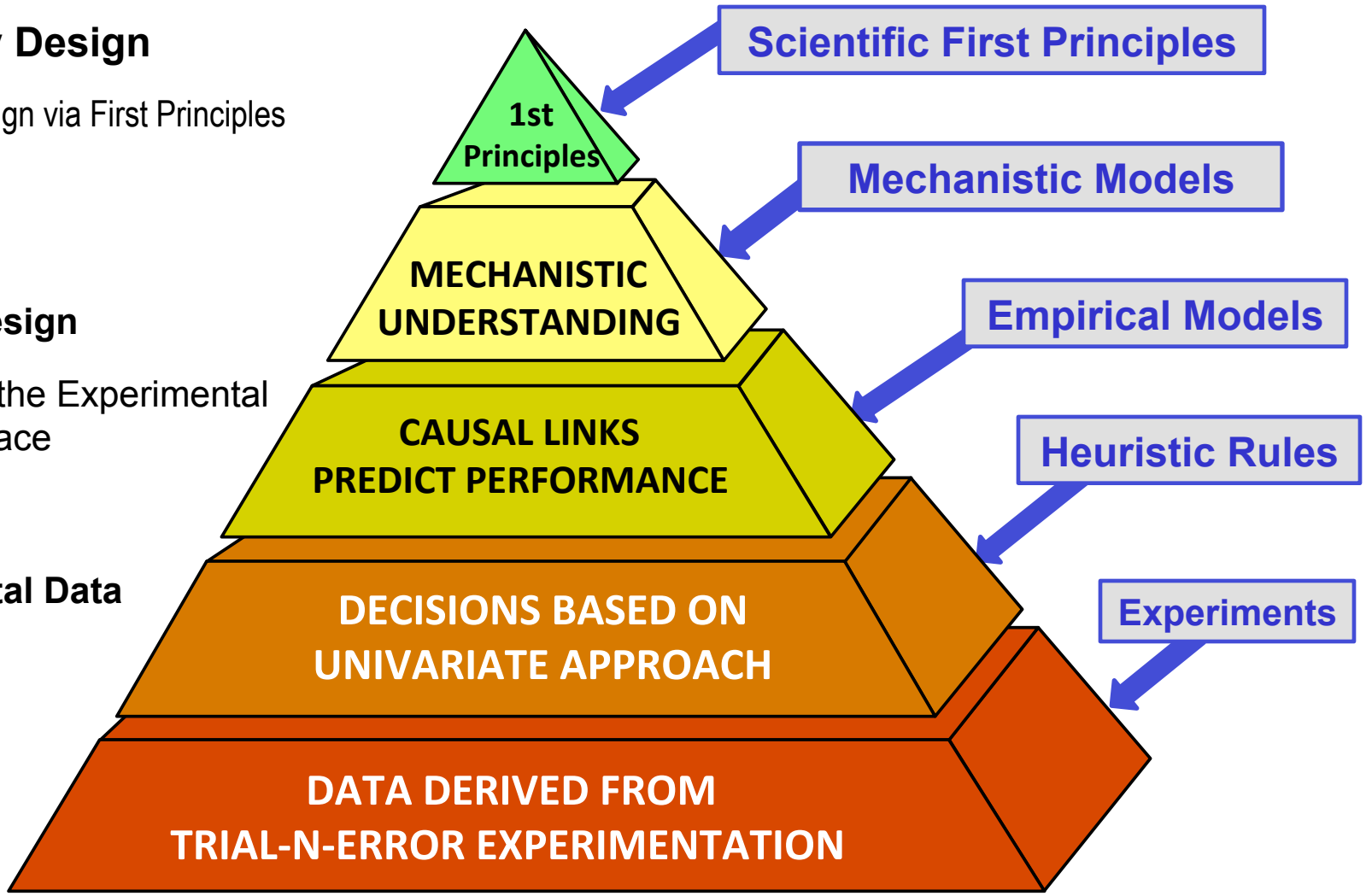
- Process Design via First Principles

Process Design

- Limited to the Experimental Design Space

Experimental Data

- Difficult to Assesses



Emerging Trend:
Quality by Design (QbD)

OUTCOMES from QbD:

Robust process & product understanding
Manufacturing Systems:

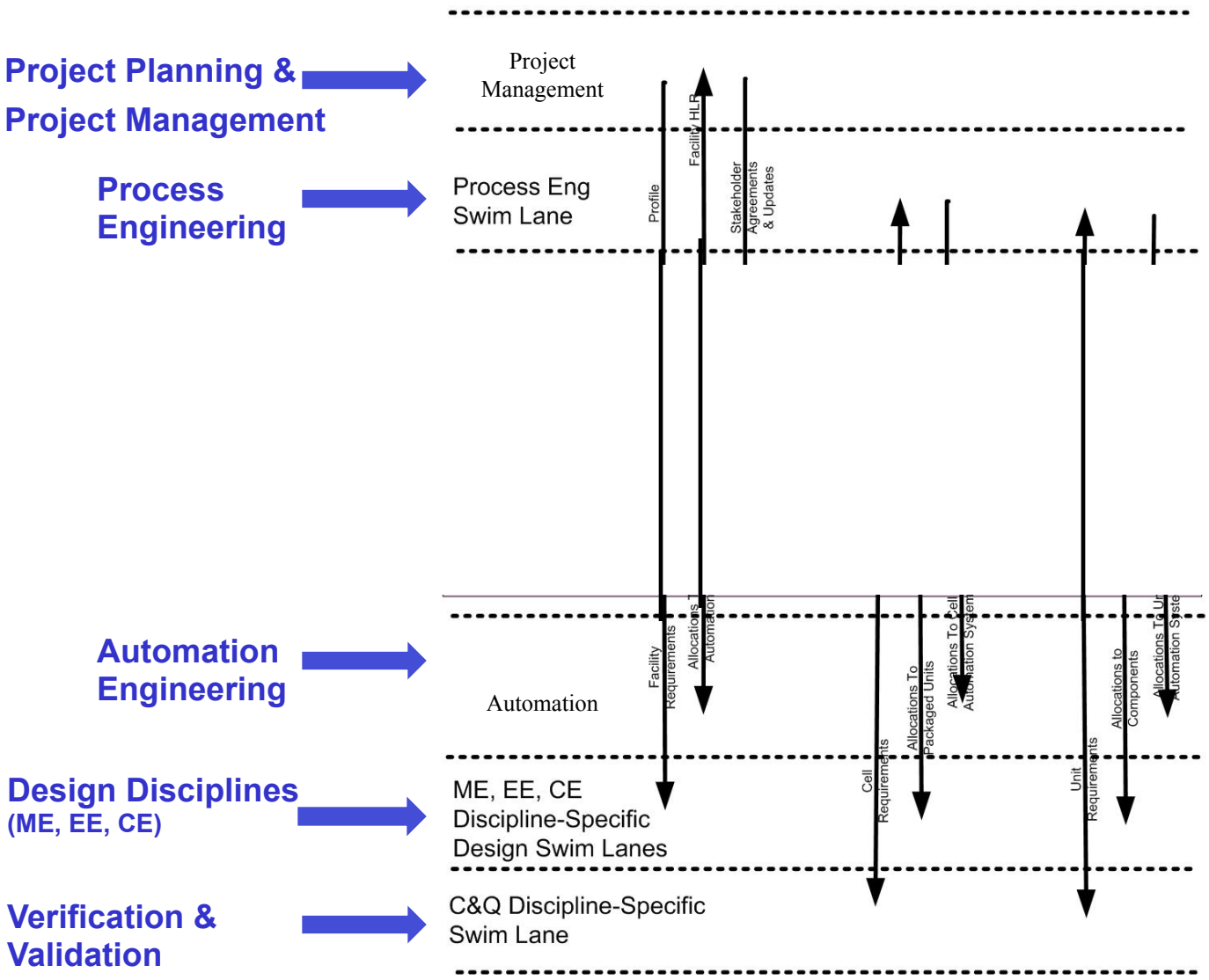
"In-Control"
"Capable"
"Compliant"
"Continuously Improving"

IMPLICATIONS:

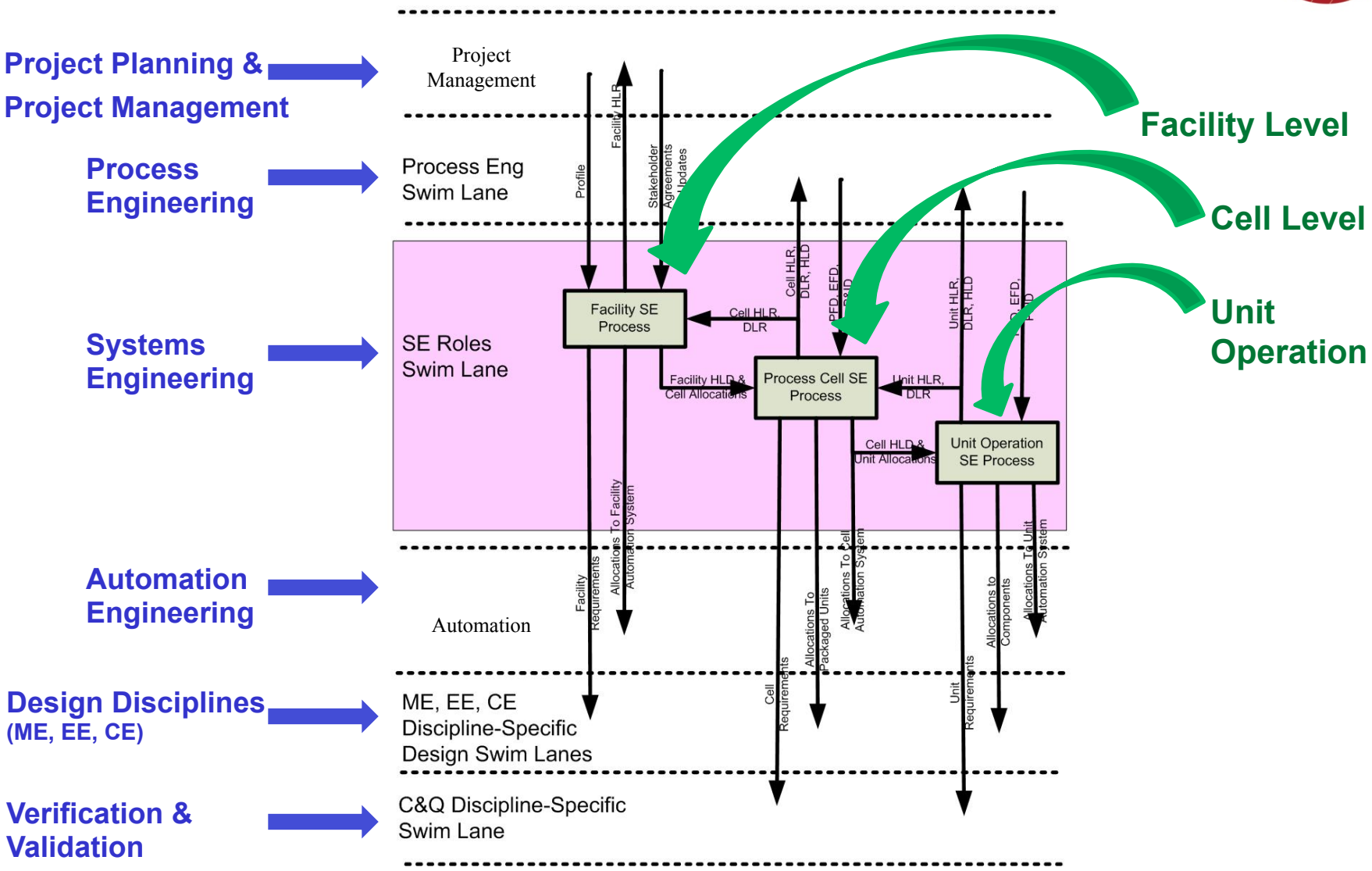
Systems - of - systems performance
Robust data & knowledge management
Across the full lifecycle

Systems Engineering Based on First Principles

Business Process Workflows



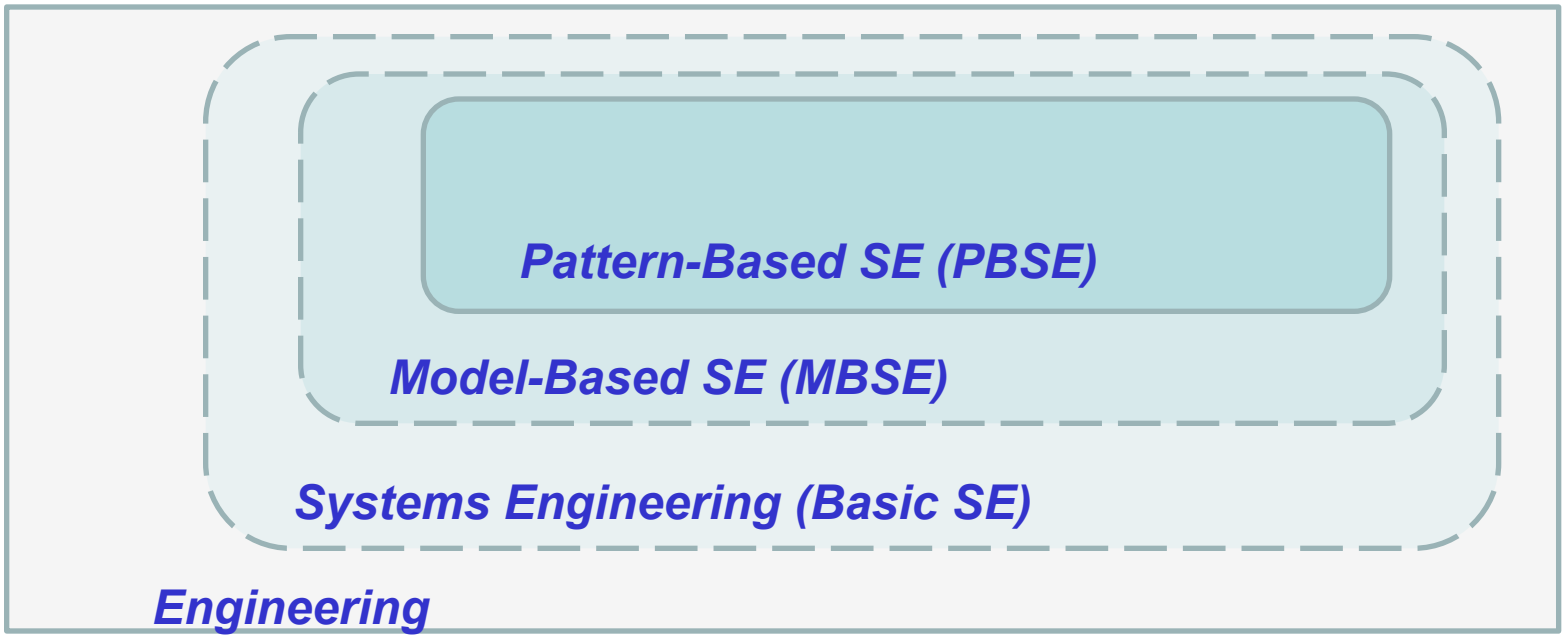
SE Integration of Business Process Workflows



Systems Engineering as a Progressive Discipline

Summary of Approach

Systems Engineering includes scalable and progressive levels: SE, MBSE, PBSE, IBSE



Pharmaceutical Manufacturing …
complex and interdependent Systems of systems

Hierarchy	Types	Characteristics
Site		One Site = 1 – 5 Manufacturing Facilities
Facility		Typical Facility = 80 – 140 Subsystems
Area		Some are ‘Area Systems’
Cell		Many are ‘Cells’
Unit Operation		Cells contain ‘Unit Operations’

Without SE, engineering of systems typically focused on the Facility, and the 80 – 140 subsystems within the Facility, regardless of their hierarchy.

SE recognizes the Facility is a type of System, and… the Facility and the 80 - 140 subsystems exist at various levels of hierarchical relationships.

SE introduces many important concepts, including Emergent Systemic Behavior, Information Modeling, Abstraction Hierarchy vs. Containment Hierarchy, Interoperability, Specialization, Configuration….

Pharmaceutical Manufacturing …
complex and interdependent Systems of systems

Hierarchy	Types	Characteristics
Site	**1 – 5 Manufacturing Plants**	
	United States of America # 1	
	United States of America # 2	
	Ireland	
	France	
	Italy	
Facility		
Area		
Cell		
Unit Operation		

API = Active Pharmaceutical Ingredient

Parenteral = administered other than via digestive canal, e.g. Injectable, Transdermal

Pharmaceutical Manufacturing …
complex and interdependent Systems of systems

Hierarchy	Types	Typical Facility Characteristics
Site		
Facility	Administration	Primarily Office Space
	Manufacturing	Product Networks by Type of Product / Process
	R&D / Pilot Plant	Pipeline R&D / Commercialization / Scale Up
	Distribution	Warehousing, Geographic Repackaging
	Utilities	Central Utility Generation & Distribution
	Multi-purpose	(Permutations and Combinations of Above)
Area		
Cell		
Unit Operation		
Component		

Pharmaceutical Manufacturing …
complex and interdependent Systems of systems

Hierarchy	Types	Typical Area Characteristics
Site		
Facility		
Area	General GMP Area	General manufacturing space – GMPs apply
	Aseptic Products	Free from contamination / cross contamination
	Dry Products	
	cGMP Laboratory	Analytical Lab Operations
	Administration	General office space
	Utility	Central Utility Generation & Distribution
Cell		

Pharmaceutical Manufacturing …
complex and interdependent Systems of systems

Hierarchy	Types	Typical Cell Characteristics
Site		
Facility		
Area		
Cell	**Dispensing**	**Design & Control - Flow of People, Process, Material**
	Coating	**Process Safety Critical Operations**
	Fill / Finish	**Coating, Filling**
	Bio Reactor	**Large Molecule Replication – Living Cells**
	Packaging	**Primary and Secondary Packaging, Blister – Packing**
	Labeling	**Identification as required for Country of Distribution**
Unit Operation		

Pharmaceutical Manufacturing …
complex and interdependent Systems of systems

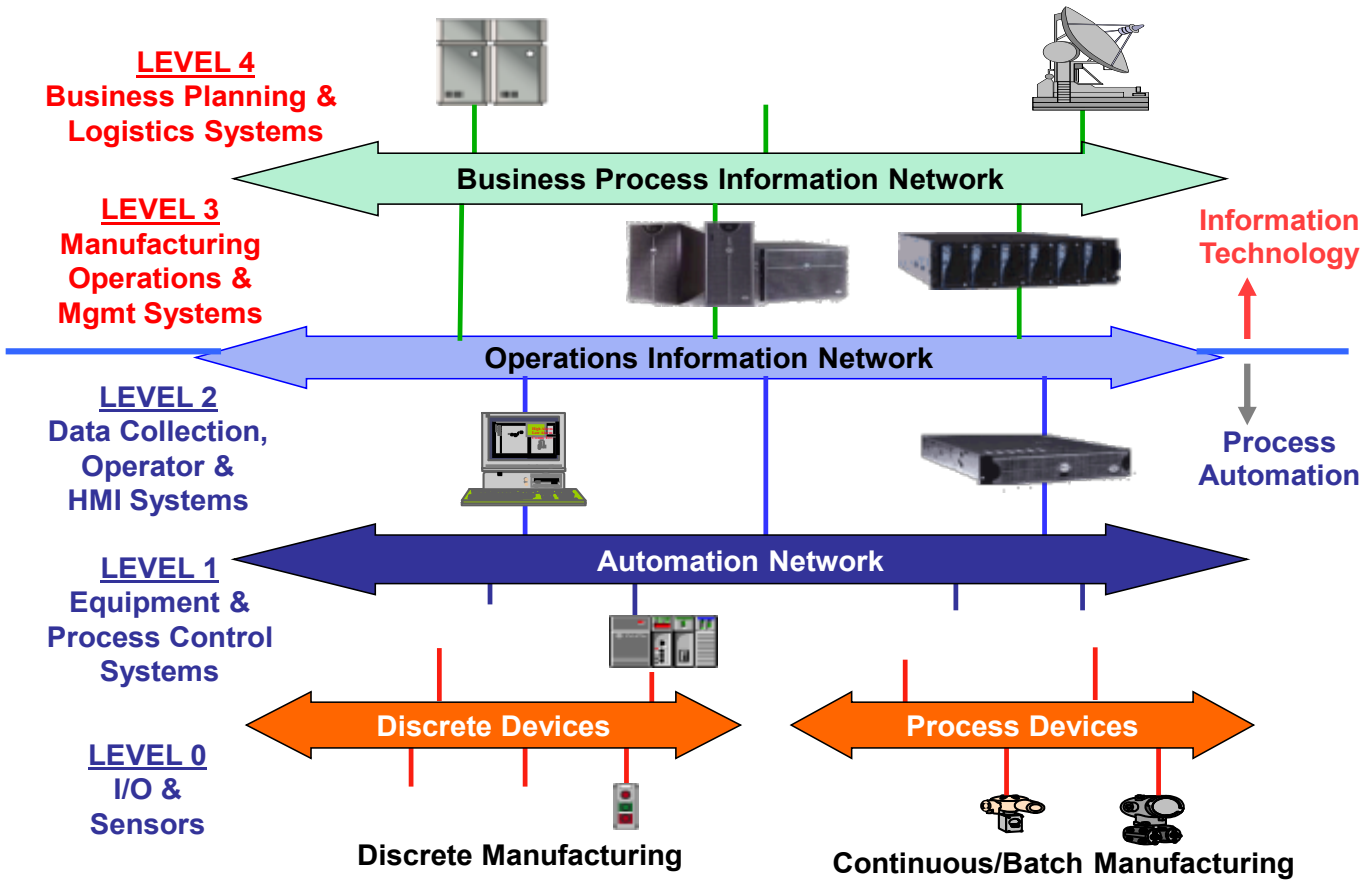
Hierarchy	Types	Typical Unit Operation Processes
Site		
Facility		
Area		
Cell		
Unit Operation	**Transverse Flow Filtration**	**Precise Filtration**
	Lyophilization	**Freeze Drying**
	Decontamination (Autoclave)	**Sterilization**
	Roller Coating (Roll Coater)	**Tablet Coating**
	Inoculation Lab	**Media Seeding**

Pharmaceutical Manufacturing …
complex and interdependent Systems of systems

Hierarchy	Types	Typical Characteristics
Utilities	HVAC / Aseptic / Dry / non-GMP	HEPA / Diff. P / Laminar / Humidity
	Water Utilities	WFI, HWFI, HPW, PWEC, Potable
	Gas Utilities	Oxygen, Nitrogen, Breathing Air, Steam
	Data Infrastructure	Enterprise LAN, Automation, SCADA
	Electric	Dual – Feed, Emergency Generation
	Piped Liquid Distribution	Site / Local Distribution & Collection
	Aqueous Waste	Sanitary Sewer Load
	Solid Waste	Landfill Impact
	Other	Noise

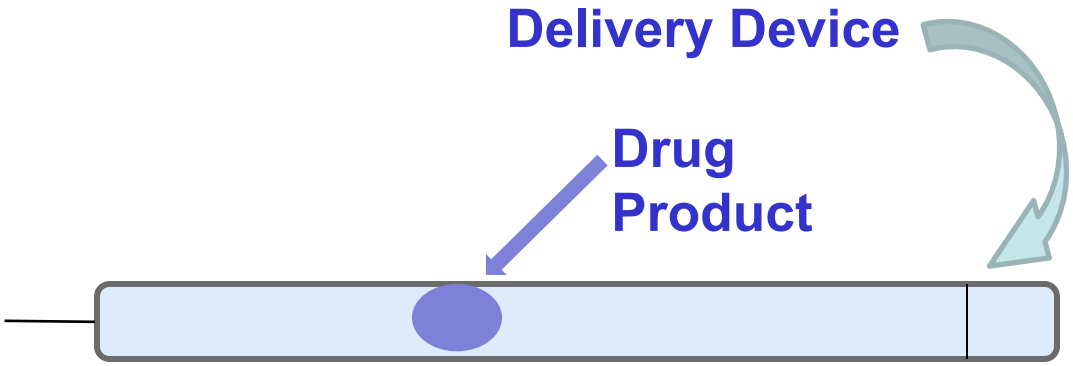
Hierarchical View: Logical & Physical Systems

ANSI / ISA S-95



Physical Hierarchy
Site
Facility
Area
Cell
Unit Operation
Component

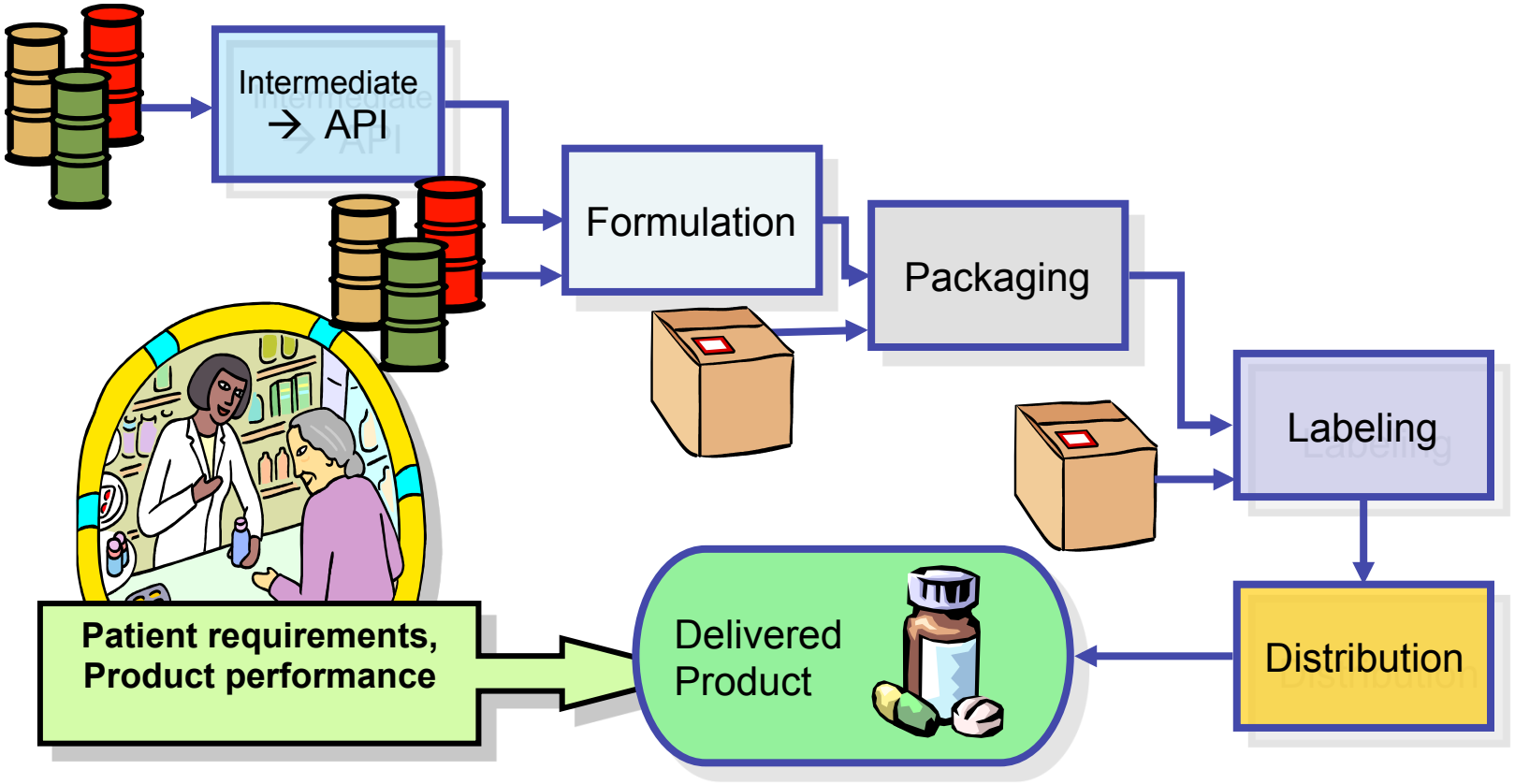
Parenteral Drug Products in Devices / Combination Devices



Typical Engineering Considerations Include:

Lifecycle States / Interactions	Key Considerations
User Needs, Requirements	Ease of use, injection force
Design Development, Design Controls	Critical assembly characteristics
Manufacture, Distribution and Storage	Stability, storage conditions
Customer Storage and Use Conditions	Ease of use, stability, storage
Device and Drug Product Interactions	Drug delivery volume
Disposal	Environmental impact

Pharmaceutical Product Manufacturing Process Overview

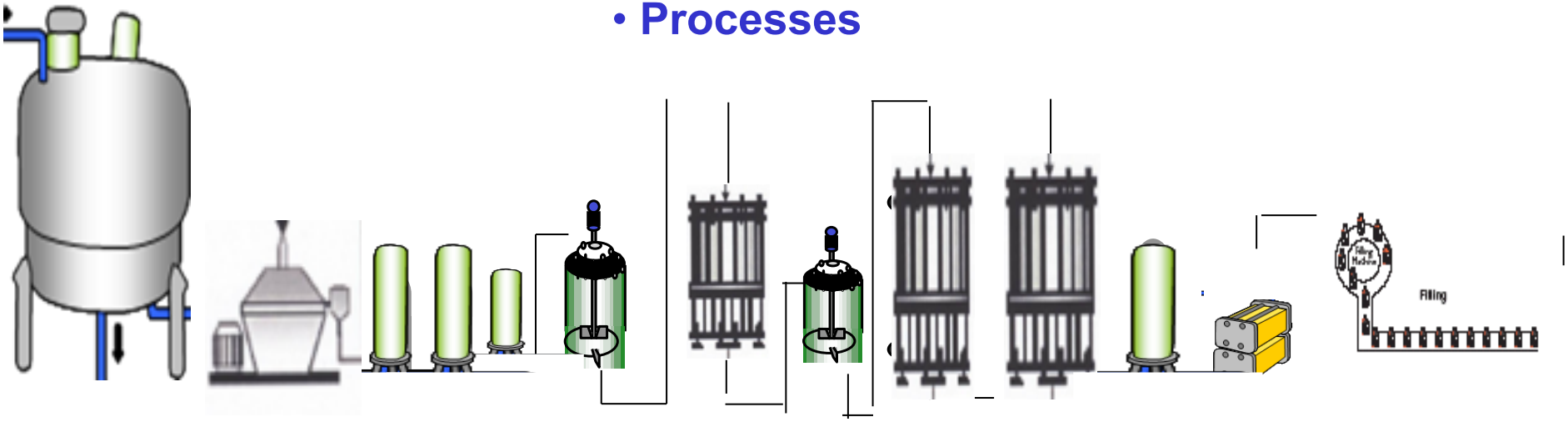


Typical API Manufacturing

Systems of Systems

Interactions of

- Systems
- Processes



API = Active Pharmaceutical Ingredient

Typical API Manufacturing

Warehouse

Dispensing

Starting Materials

Material In-Process

QC Laboratory

Limited Environmental Impact

Maint. Data

Process Data

API

Automation

Master Schedule
Recipes
Procedures
Process Steps

Basic SE Workflow
Implementing New Manufacturing Asset

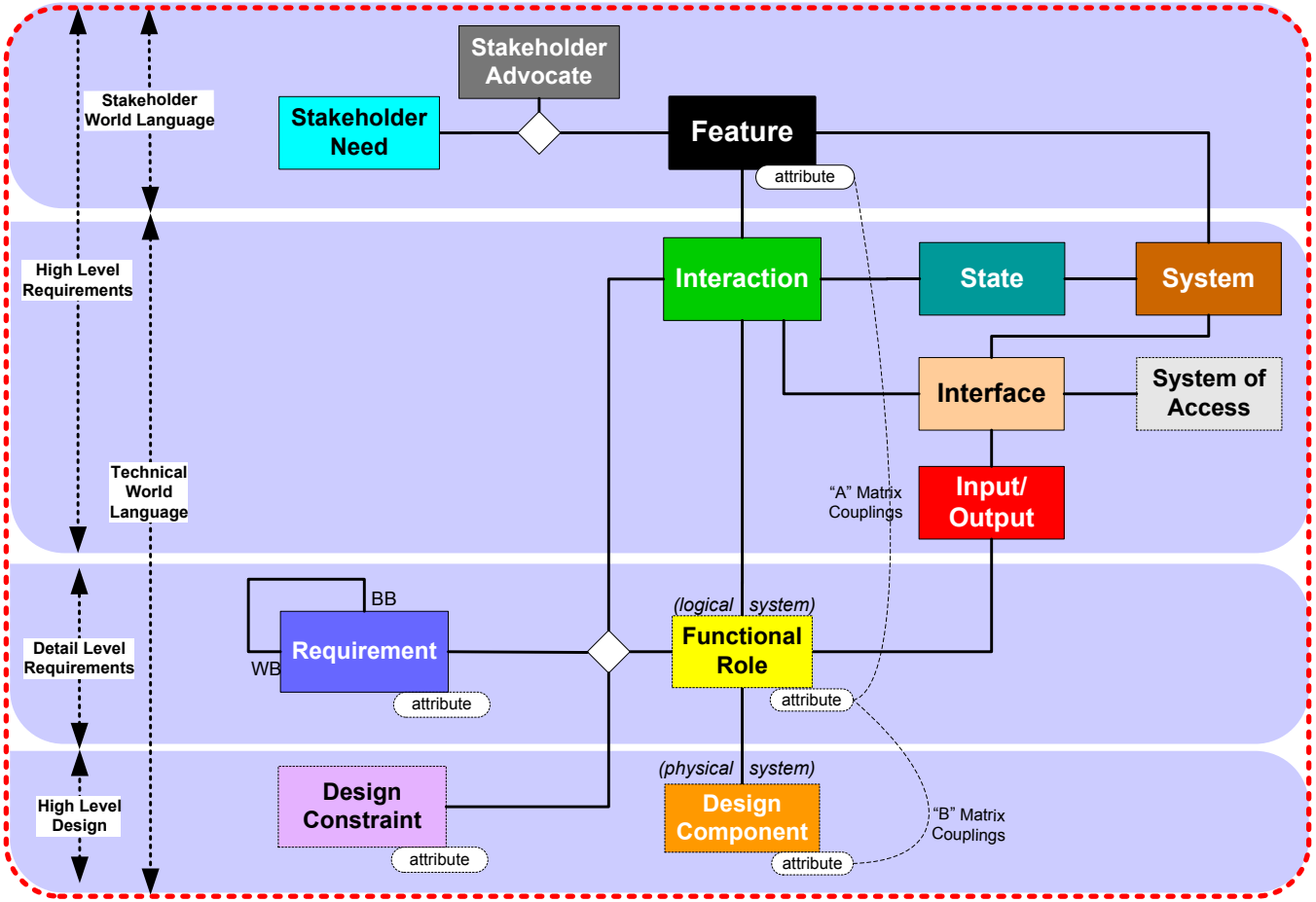
1. Characterize Project
2. Identify Functional Areas & Stakeholder Representatives
3. Identify Stakeholder Needs & Resolve Inconsistencies
4. Translate Needs into Requirements, Technical Specifications and Attributes
5. Publish Accepted Technical Specifications as Basis of Acquisition
6. Publish Accepted Requirements as Basis of Design
7. Purchase / Build Asset
8. Verification (Commissioning, etc.)
9. Validation
10. Release for use

- Basic SE does not rely on modeling of Features, Interactions, States, Roles…
- Similar to Quality Function Deployment (QFD)

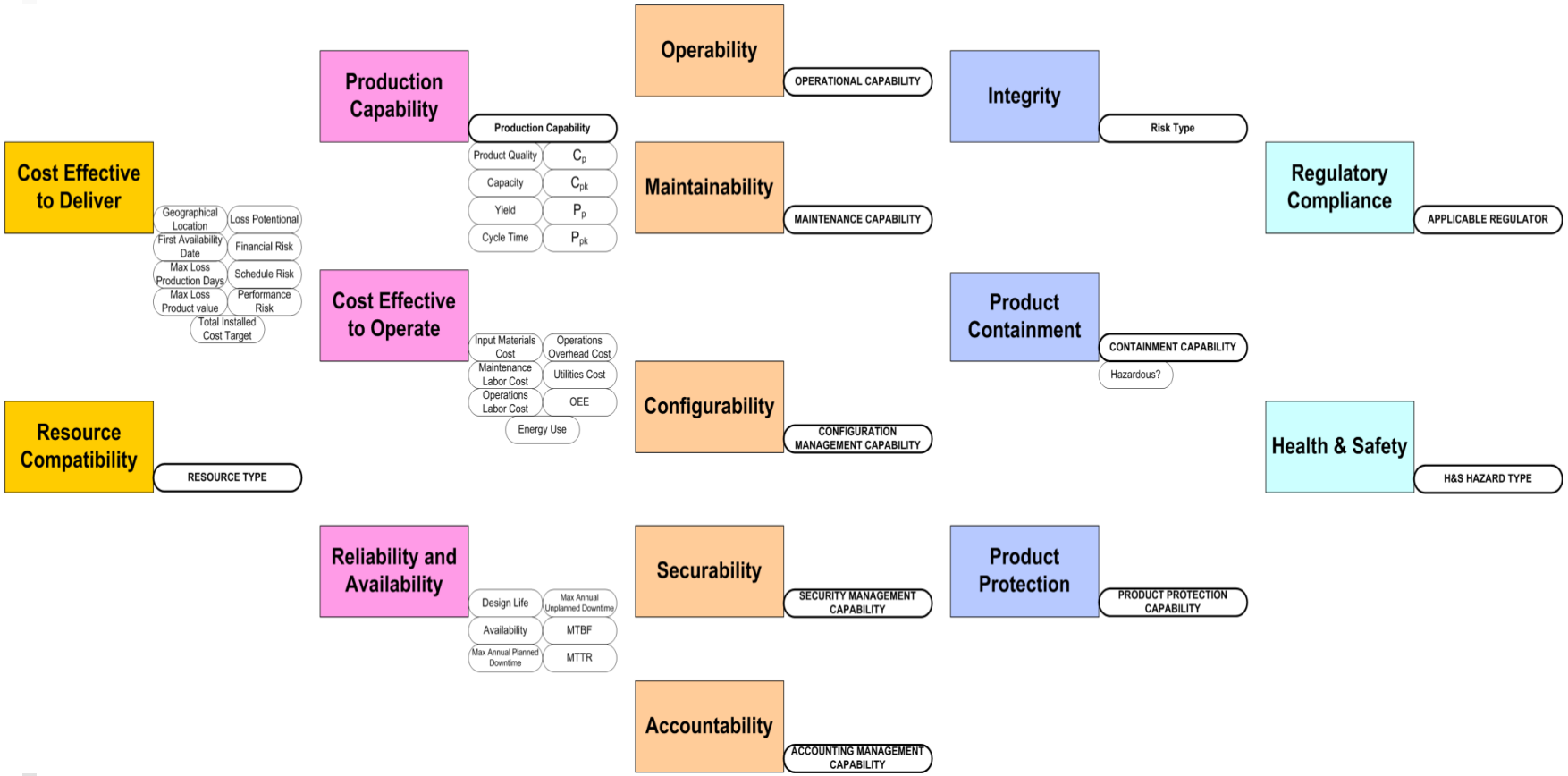
SE Information Model

Systematica™

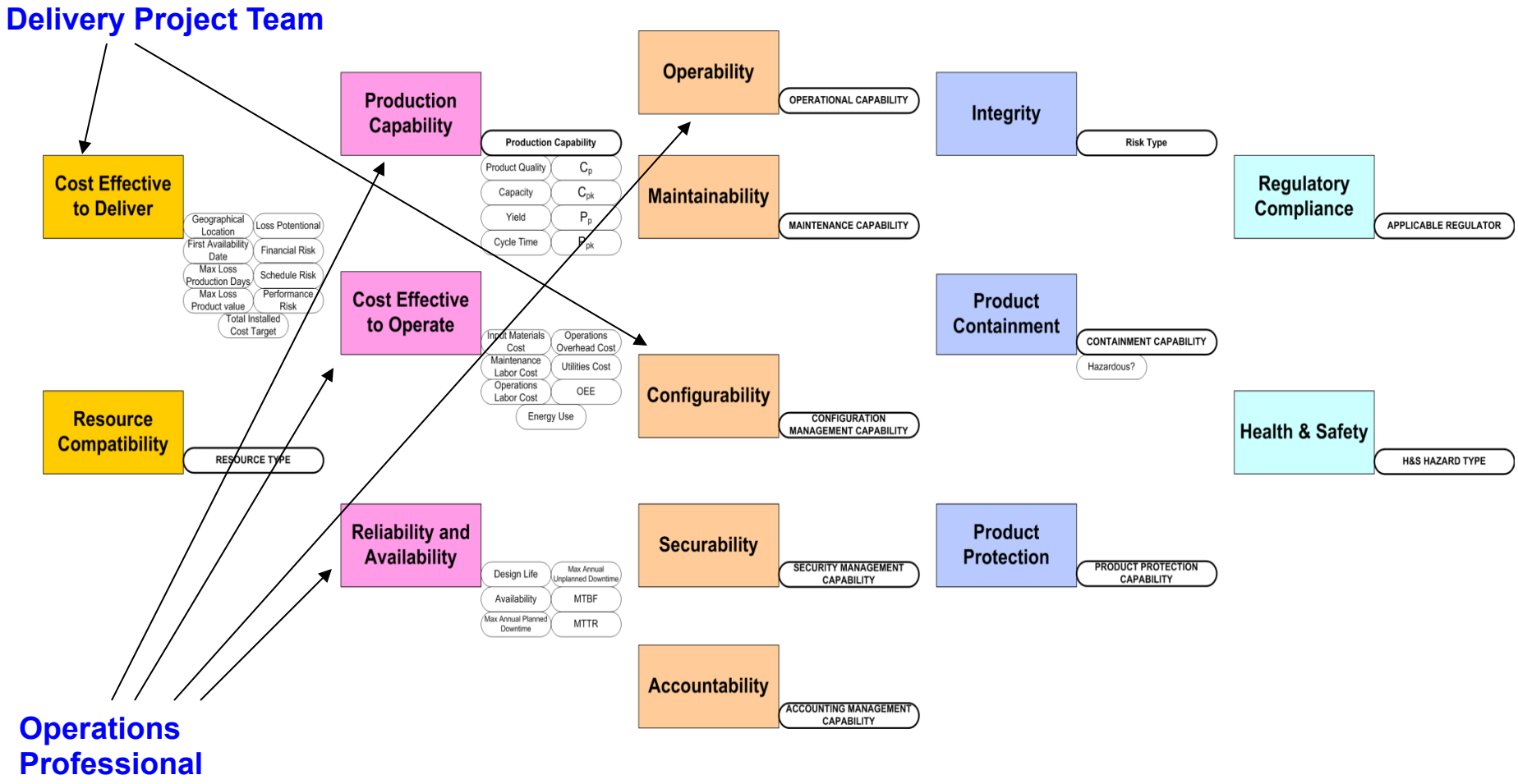
Do more with less



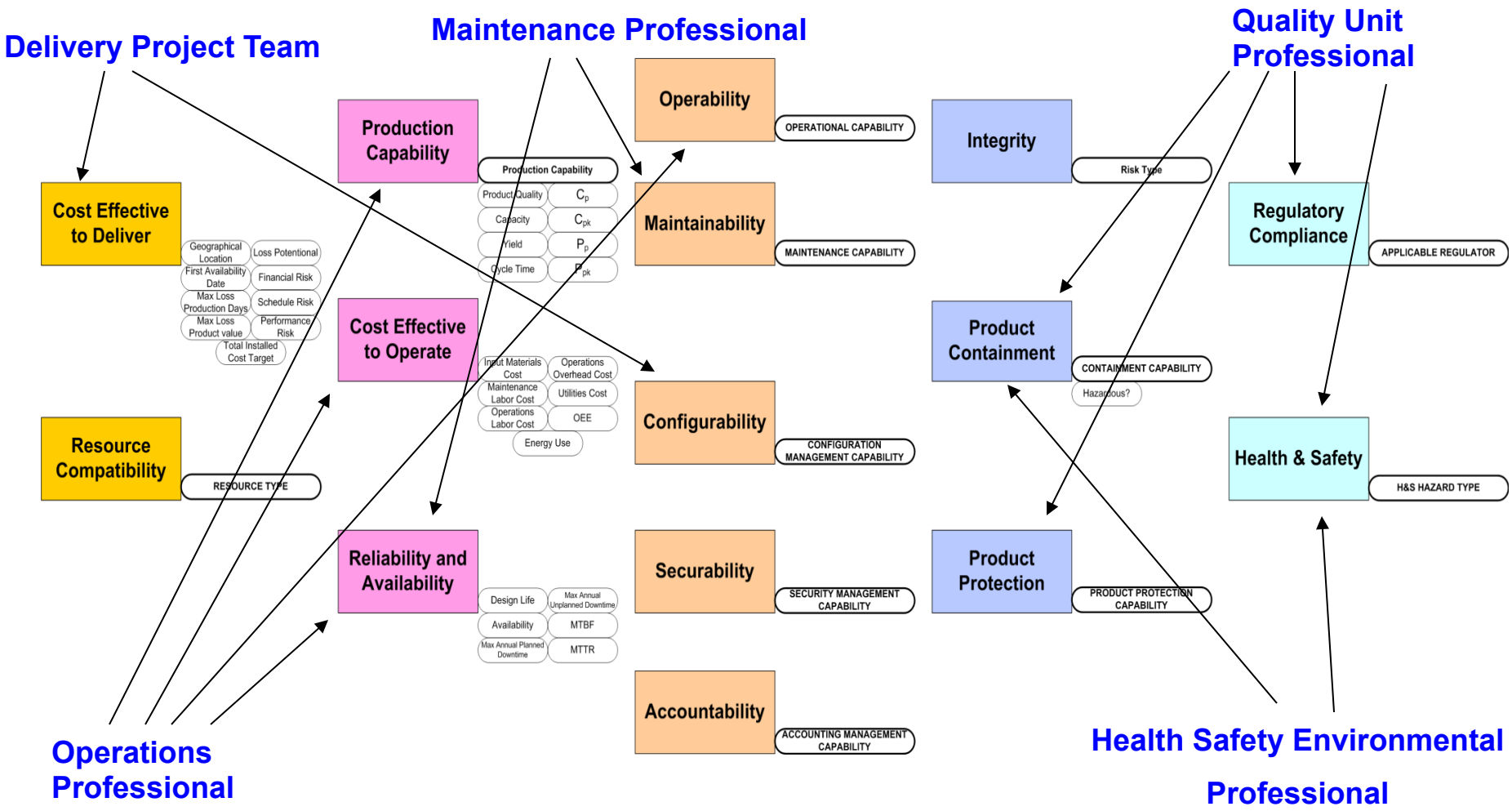
MBSE
SE Feature Class Model, Pharma Manufacturing



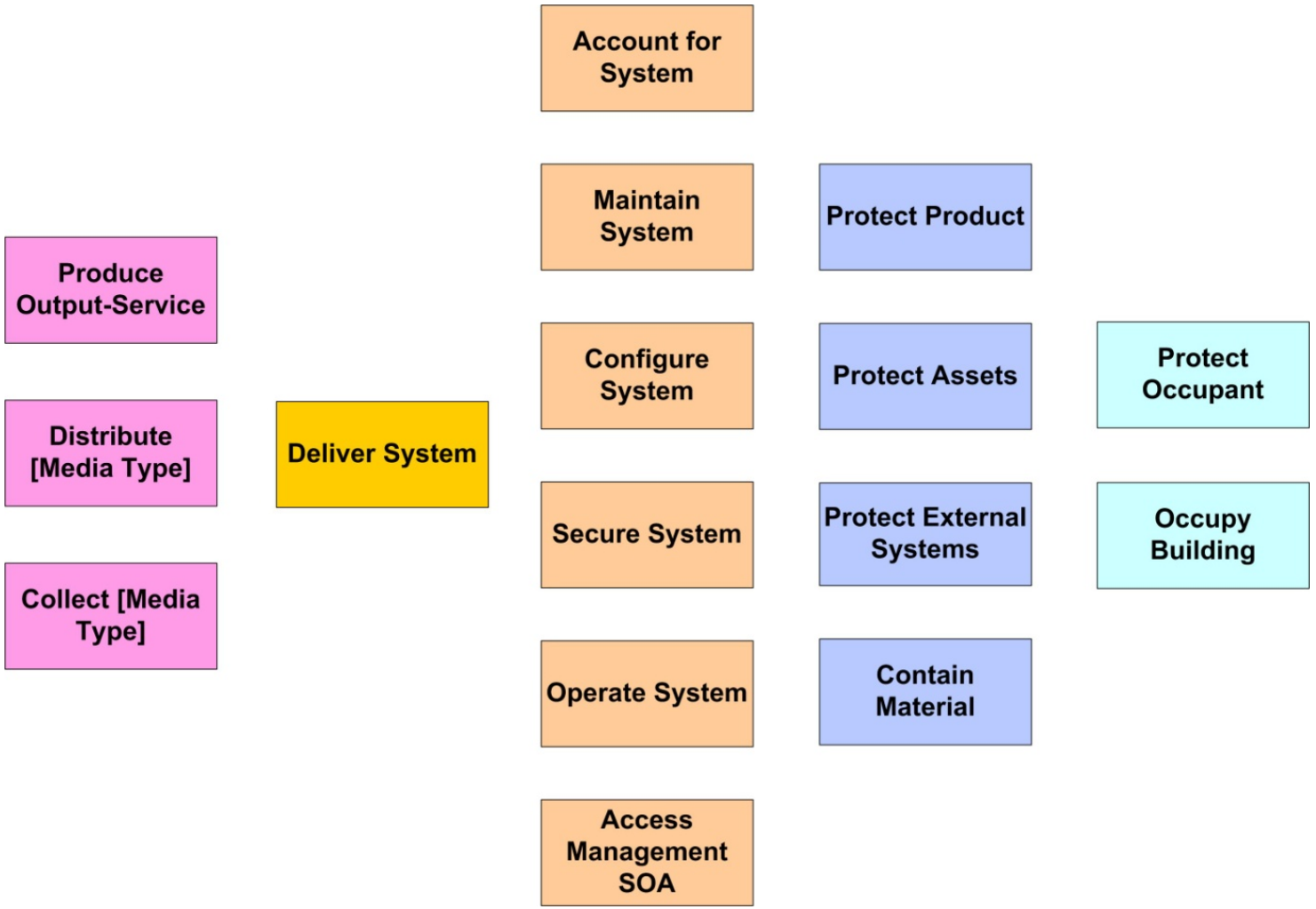
MBSE
SE Feature Class Model, Pharma Manufacturing



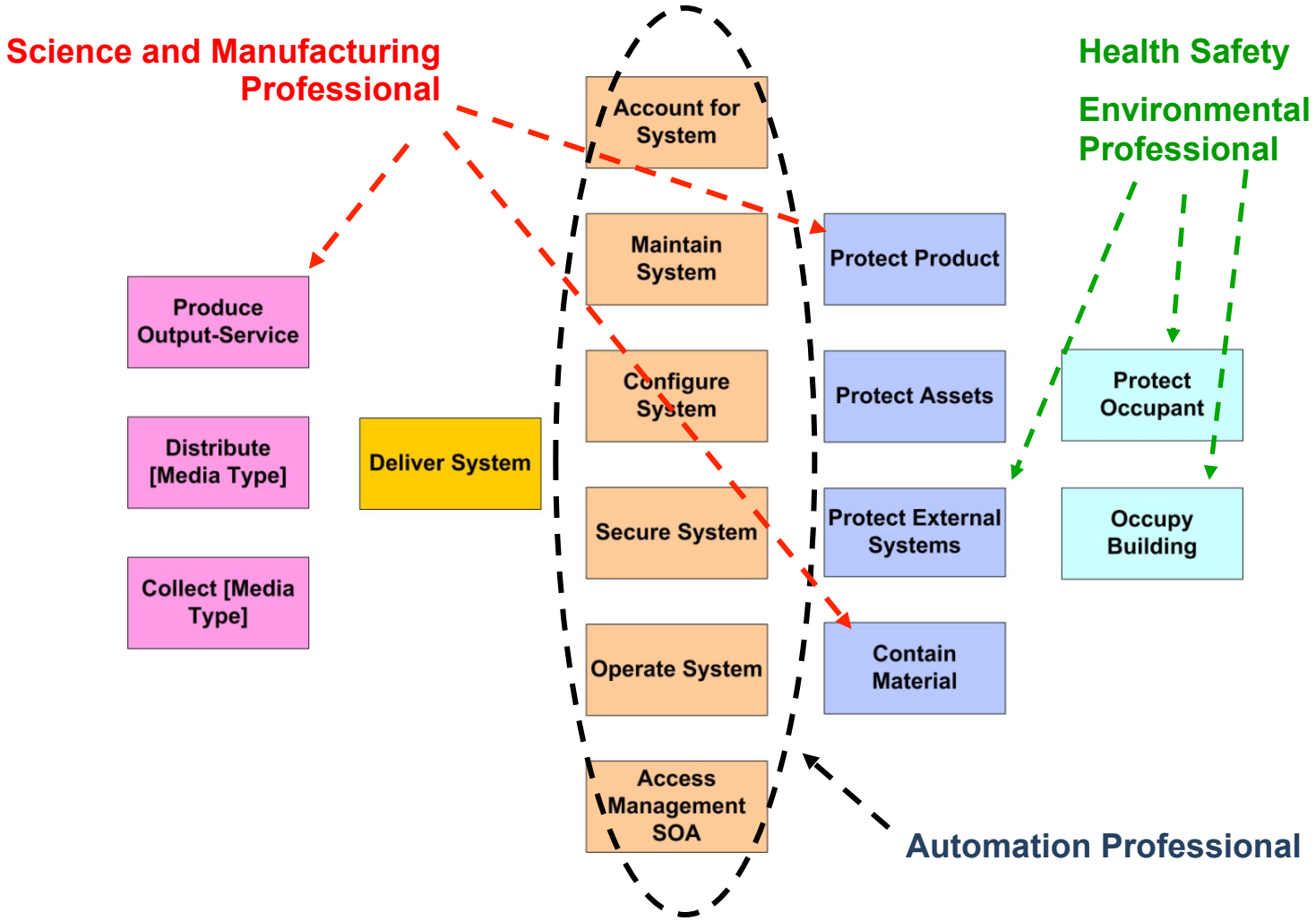
SE Feature Class Model, Pharma Manufacturing



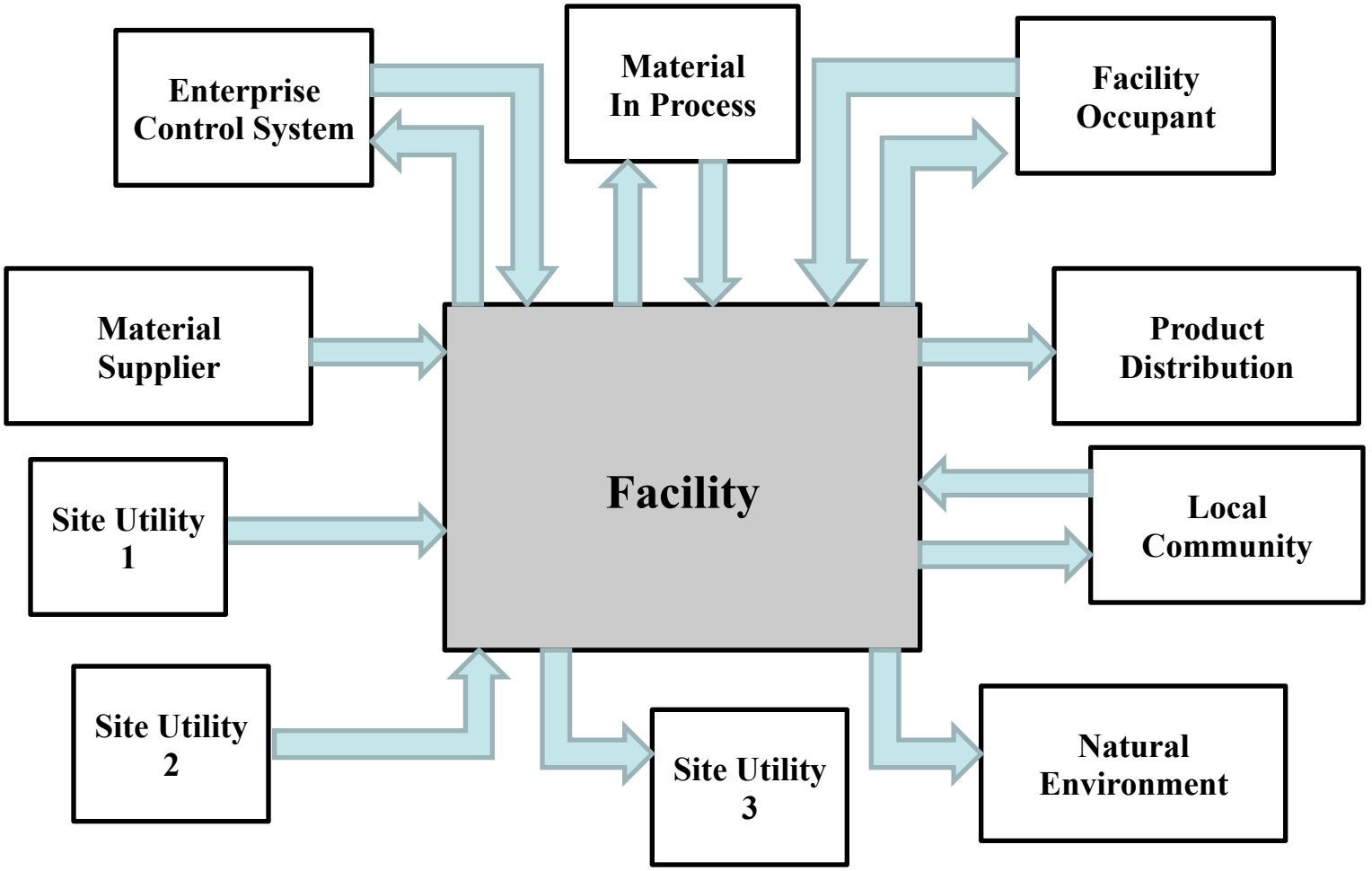
MBSE
SE Interaction Class Model



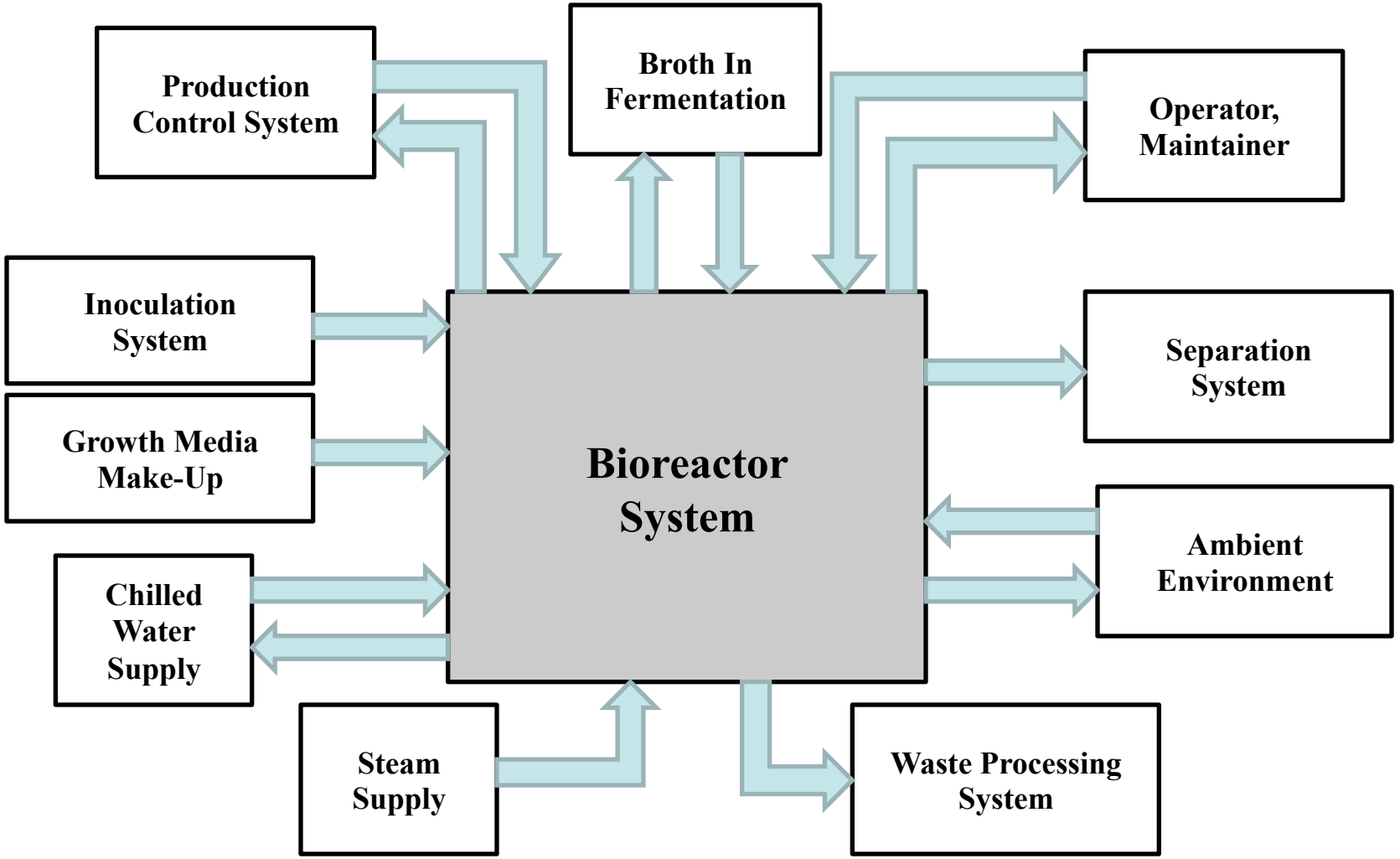
MBSE
SE Interaction Class Model



Pharma Facility Domain Model *(Simplified)*



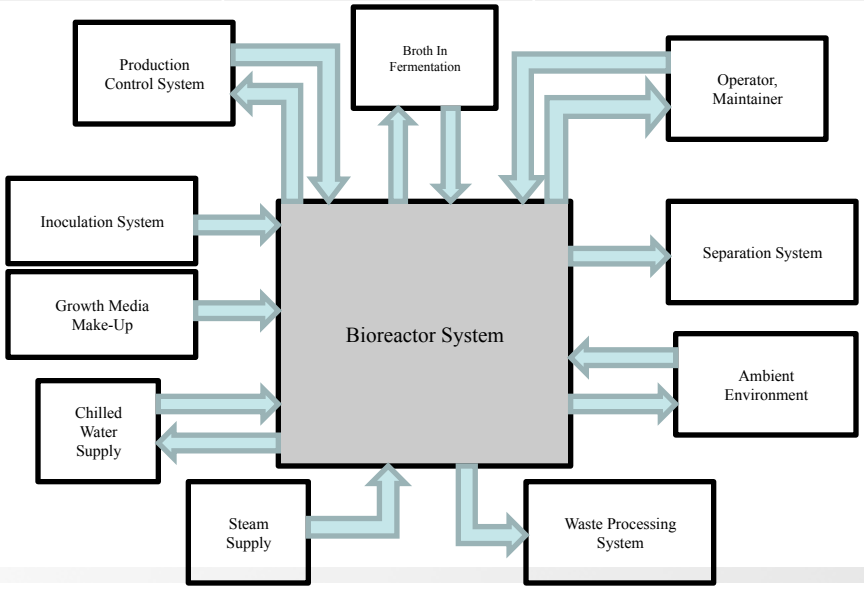
Bioreactor Domain Model *(Simplified)*



Requirements Statements and Attributes

"During the specified phase, the Bioreactor System shall maintain temperature of the bioreactor vessel contents between [Min Temperature] and [Max Temperature]."

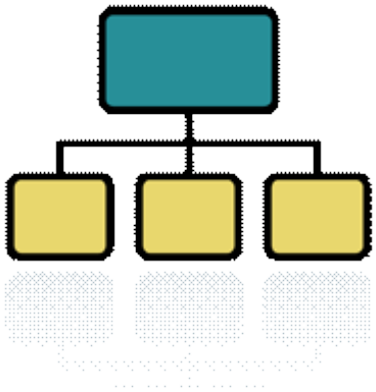
Recipe	Min Temperature	Max Temperature	Control Strategy	Acceptance Criteria
Product A	68 Degrees F	73 Degrees F	PID Strategy 3	Test Case 9
Product B	84 Degrees F	89 Degrees F	PID Strategy 3A	Test Case 23
Product C	69 Degrees F	73 Degrees F	PID Strategy 4	Test Case 25



Implementing and Sustaining SE
via a Collaborative Environment

Web-based Collaborative Platform

Security & Privacy
Global Real Time Connectivity
Collaboration Portals
Documents
Applications
Forms
Blogs
Wiki



Opportunities
(Challenges)

1. **New Engineering Workflow**

   Transitioning a mature and highly-skilled engineering staff to the use of SE:

   - **Basic SE**
   - **MBSE**
   - **PBSE**

2. **Value Creation Outcomes**

   SE is well-positioned via SE First Principles, but we need to demonstrate:

   - **Hard Metrics - Quantified ROI**
   - **Anecdotal Success Stories**
   - **SE Workflow Utilization**

Thank you so much !!

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