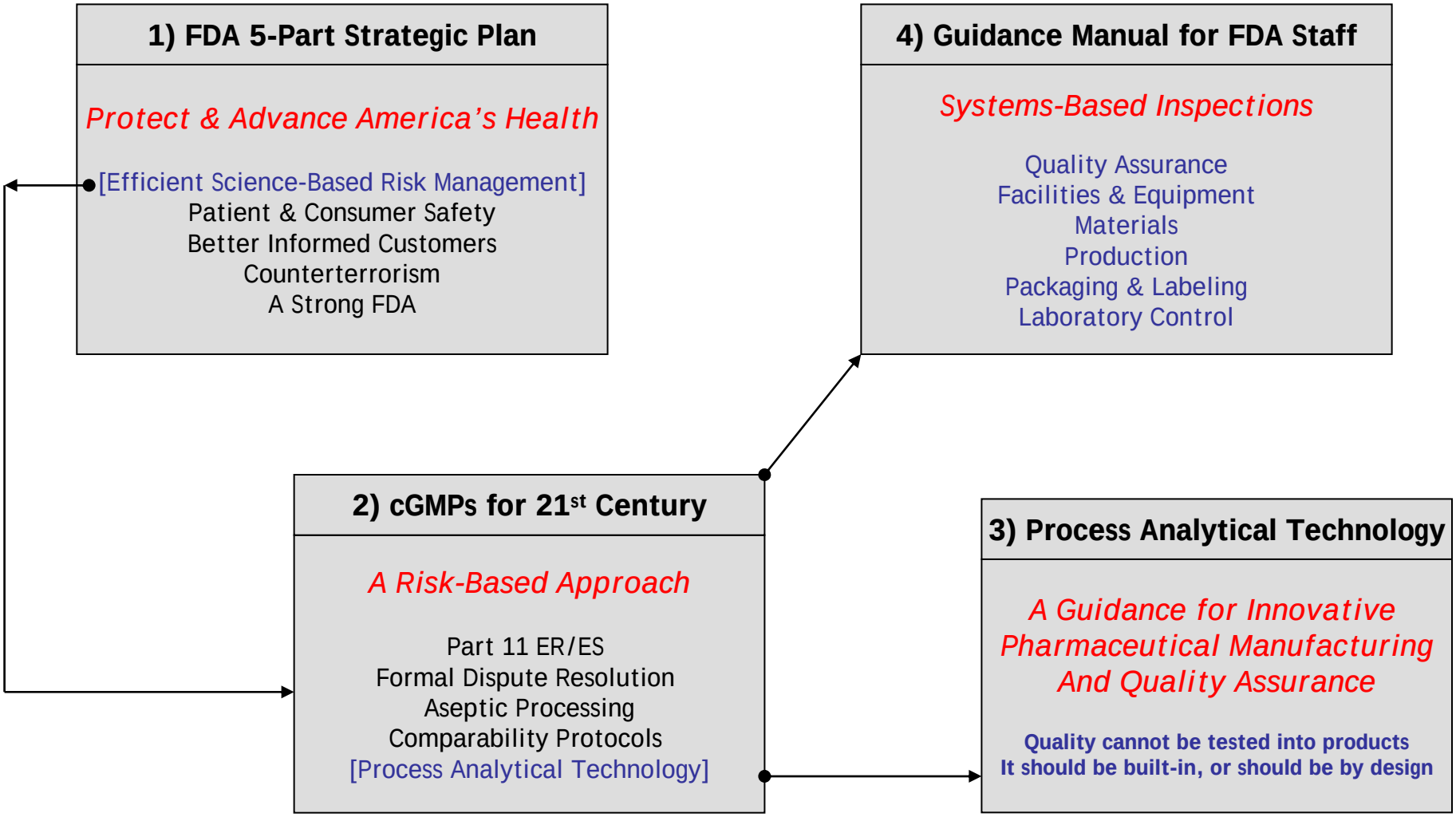
PAT & Risk-Based Initiatives: Implementation Issues

PDA New England - 8th Dec 2004

Cliff Campbell B.E., C.Eng.
CC&A Ltd., Cork, Ireland
cca@iol.ie

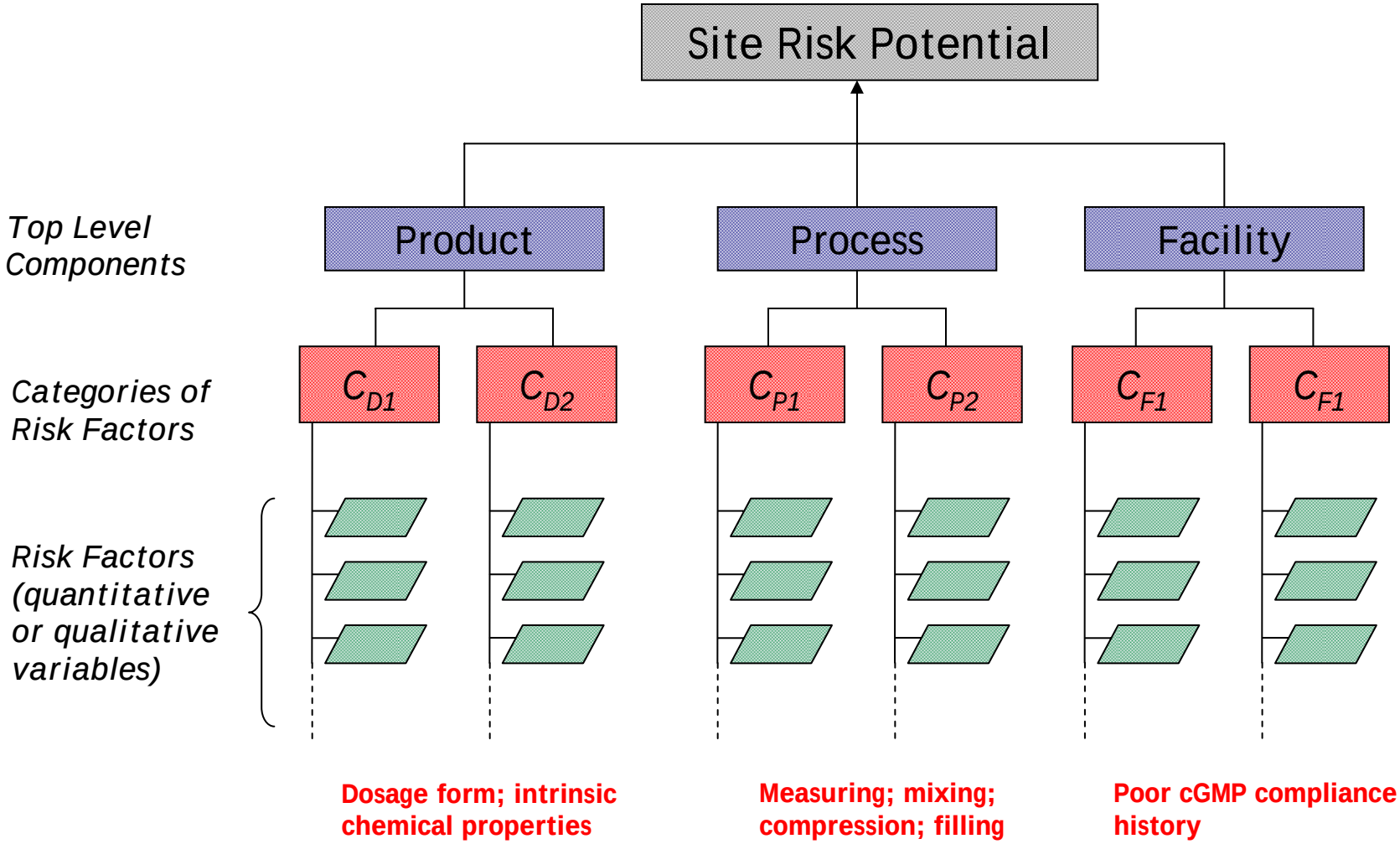
FDA Context


1) FDA 5-Part Strategic Plan
Protect & Advance America's Health
[Efficient Science-Based Risk Management]
Patient & Consumer Safety
Better Informed Customers
Counterterrorism
A Strong FDA
4) Guidance Manual for FDA Staff
Systems-Based Inspections
Quality Assurance
Facilities & Equipment
Materials
Production
Packaging & Labeling
Laboratory Control
2) cGMPs for 21st Century
A Risk-Based Approach
Part 11 ER/ES
Formal Dispute Resolution
Aseptic Processing
Comparability Protocols
[Process Analytical Technology]
3) Process Analytical Technology
A Guidance for Innovative Pharmaceutical Manufacturing And Quality Assurance
Quality cannot be tested into products
It should be built-in, or should be by design

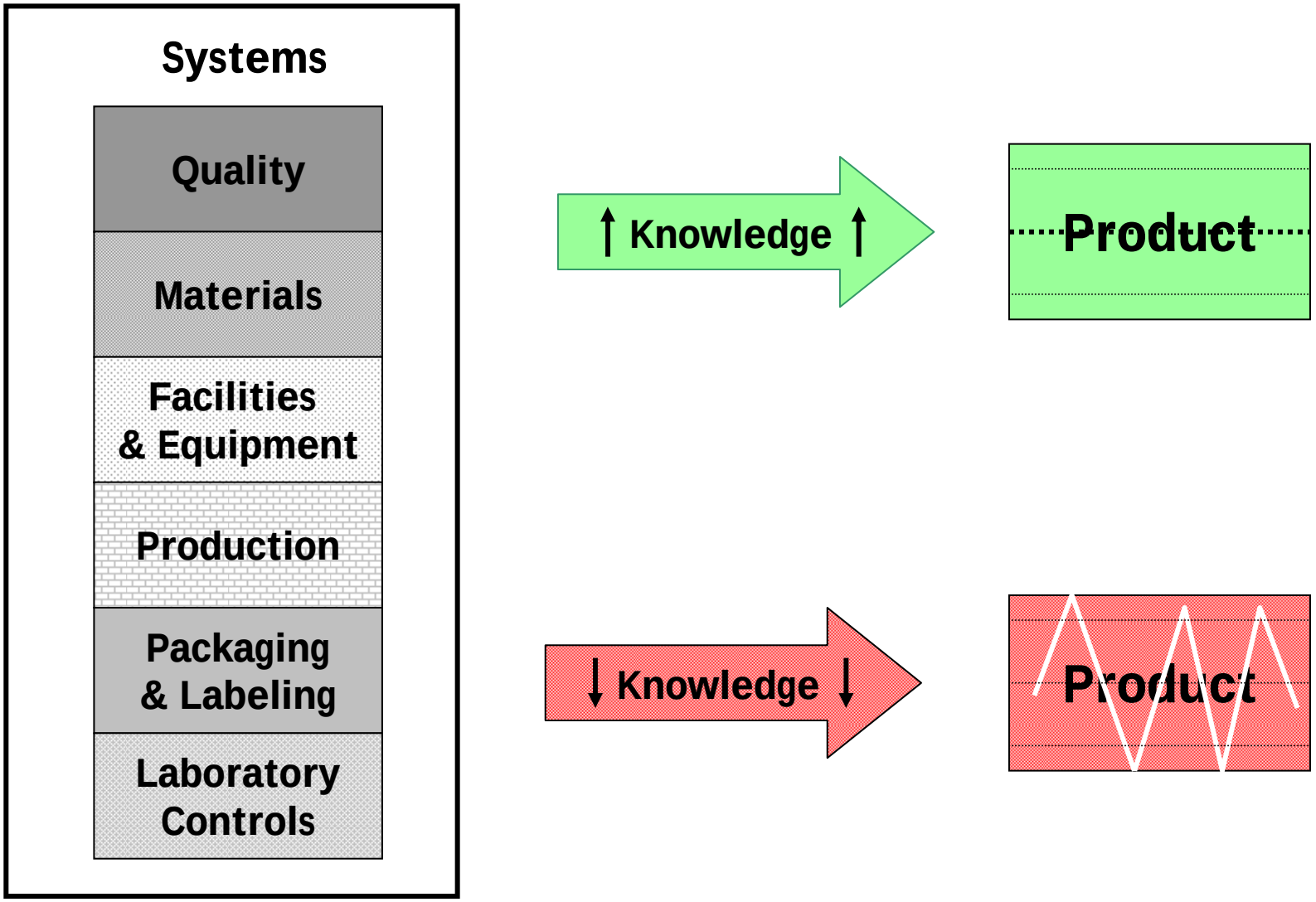
FDA: Sept. 2004

FINAL GUIDANCES
• Sterile Drug Products by Aseptic Processing • PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance
DRAFT GUIDANCES
• Industry Quality Systems Approach to cGMPs • Industry Computerized Systems Used in Clinical Trials
OTHER DOCUMENTS
• White Paper: Innovation and Continuous Improvement in Pharmaceutical Manufacturing • Risk-Based Method for Prioritizing cGMP inspections of Pharmaceutical Manufacturing Sites

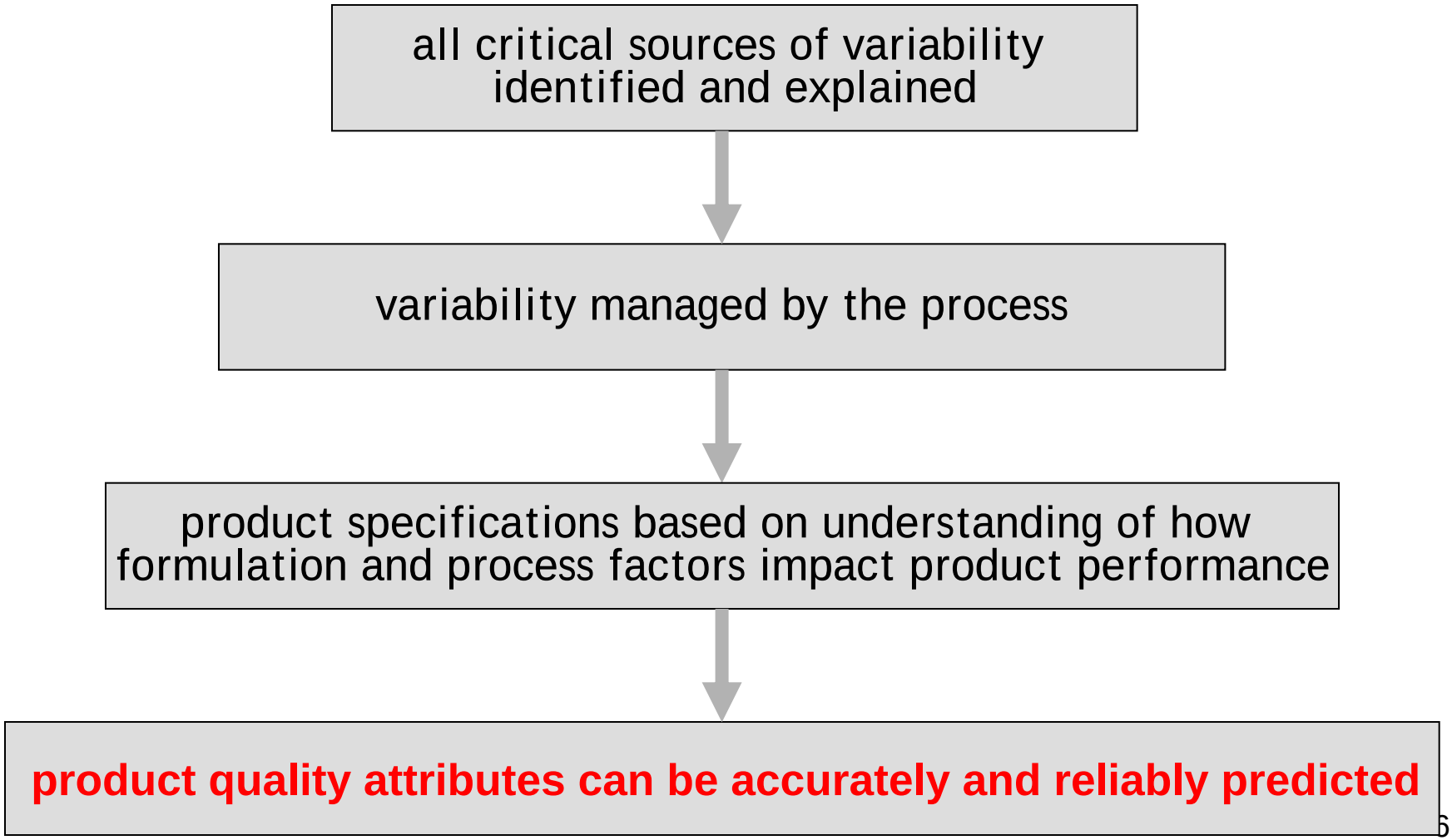
FDA's SRP Hierarchy (Sept. 04)



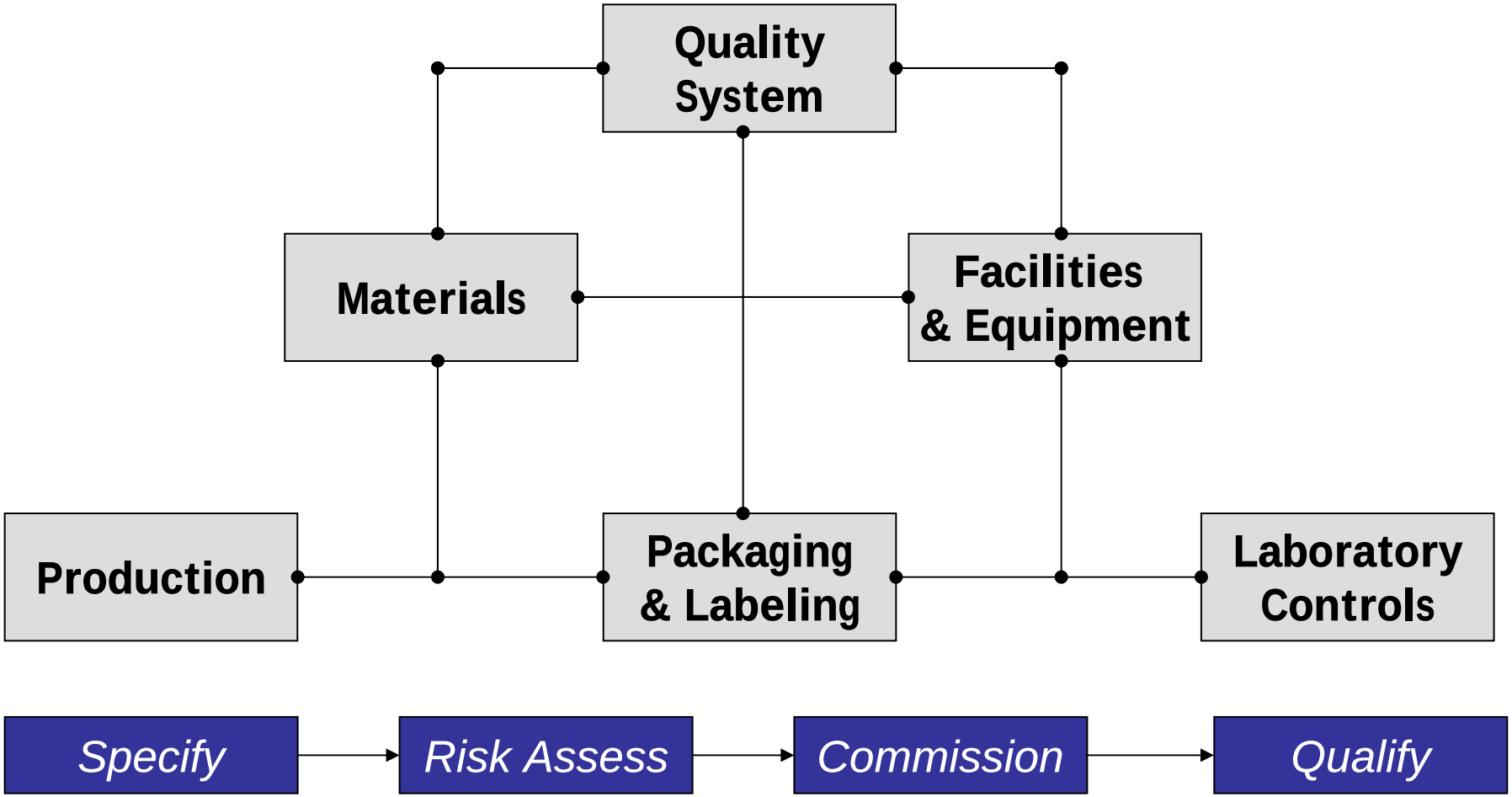
Industry Response



Know Your Process



Know Your Systems



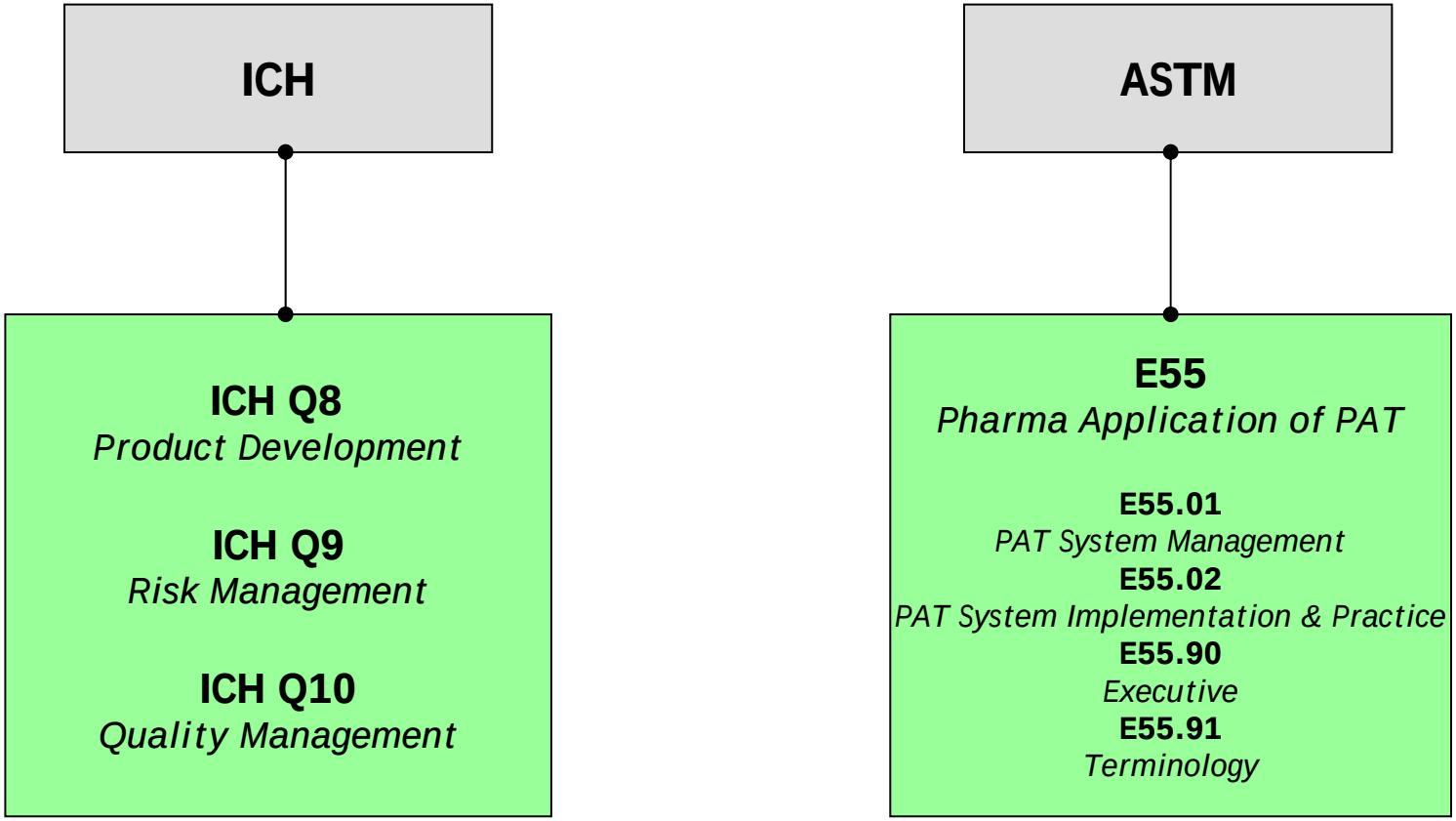
Know the Regs

Materials System

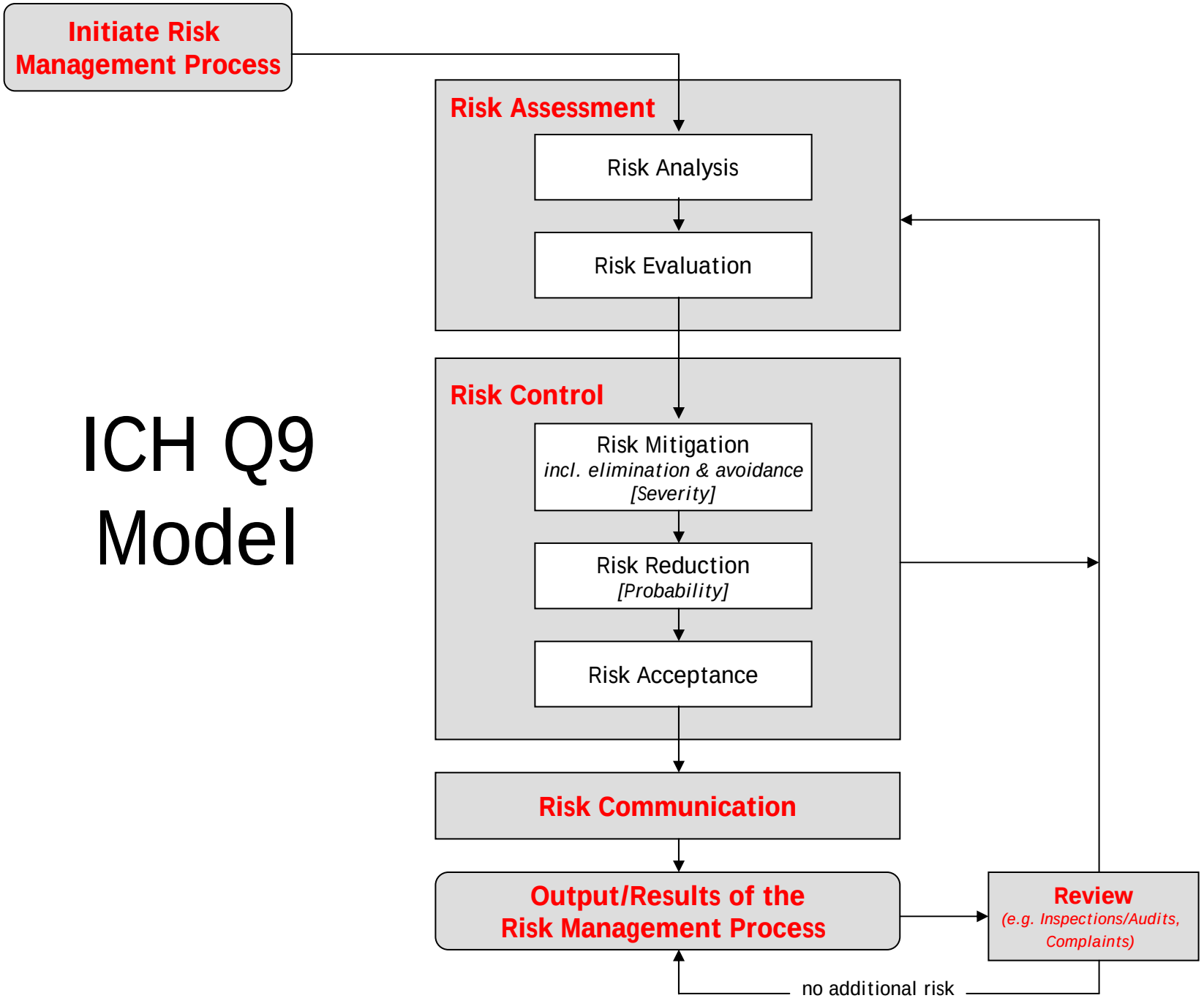
Scope
This system includes measures and activities to control finished products, components, including water or gases, that are incorporated into the product, containers and closures. It includes validation of computerized inventory control processes, drug storage, distribution controls, and records. See the CGMP regulation, 21 CFR 211 Subparts B, E, H, and J.

Hotspots
Release of materials for use or distribution that do not conform to established specifications.
Pattern of failure to conduct one specific identity test for components.
Pattern of failure to document investigation of discrepancies.
Pattern of failure to establish/follow a control system for implementing changes in the materials handling operations.
Lack of validation of water systems as required depending upon the intended use of the water.
Lack of validation of computerized processes.

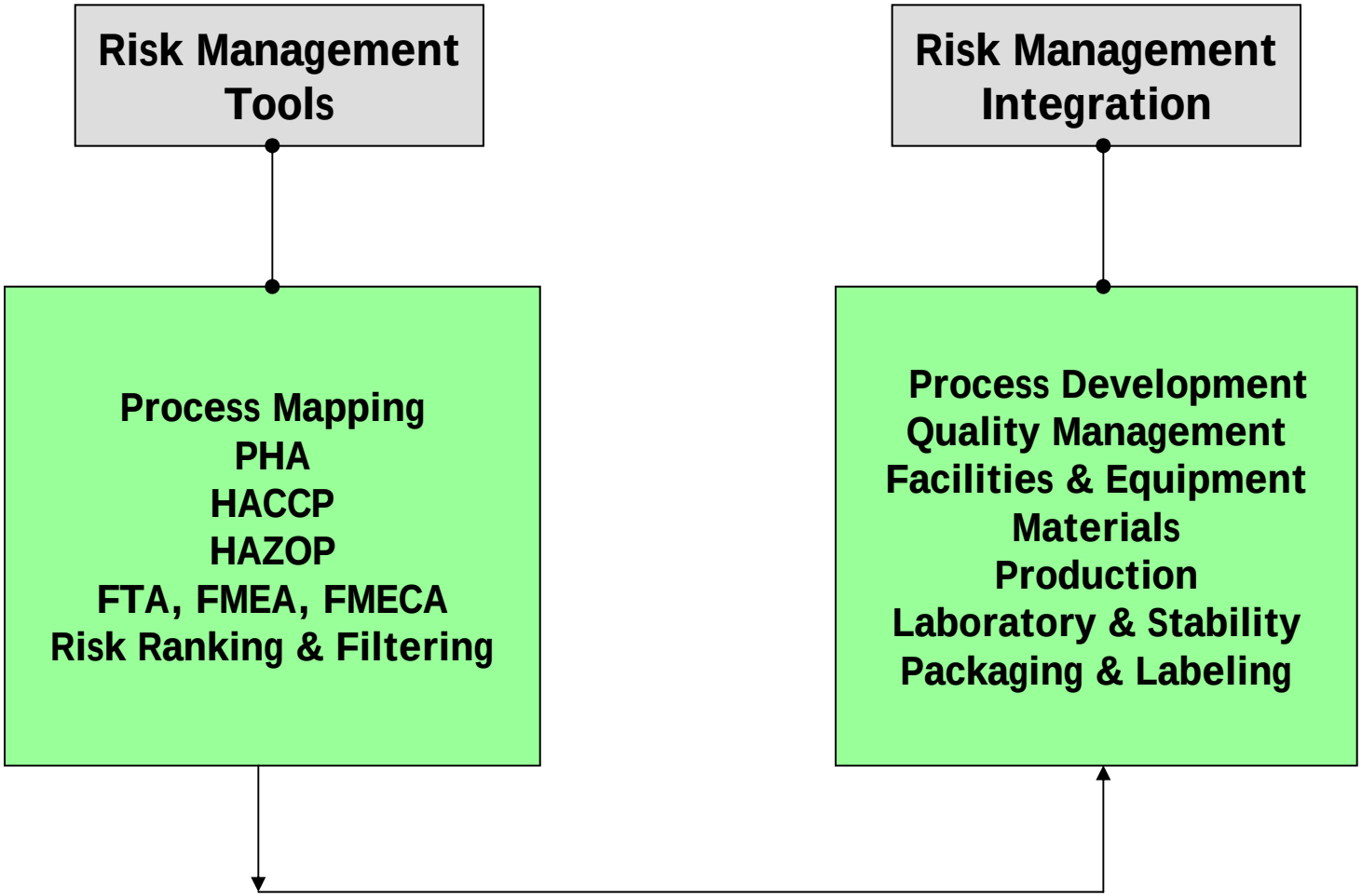
Standards & Guidances



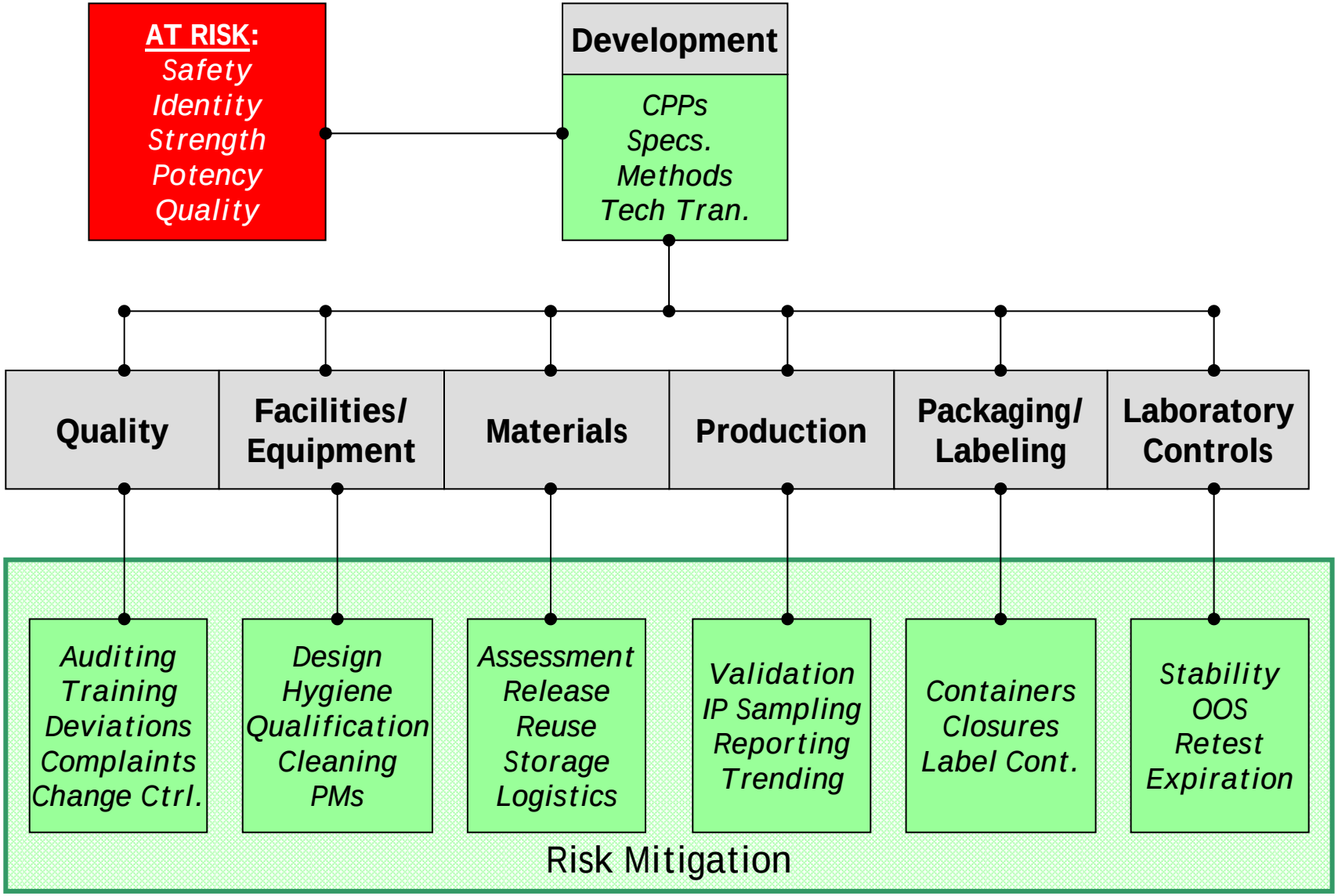
ICH Q9 Model


Initiate Risk Management Process
Risk Assessment
Risk Analysis
Risk Evaluation
Risk Control
Risk Mitigation
incl. elimination & avoidance
[Severity]
Risk Reduction
[Probability]
Risk Acceptance
Risk Communication
Output/Results of the Risk Management Process
Review
(e.g. Inspections/Audits, Complaints)
no additional risk

ICH Q9 Procedure



ICH Q9 : Systems



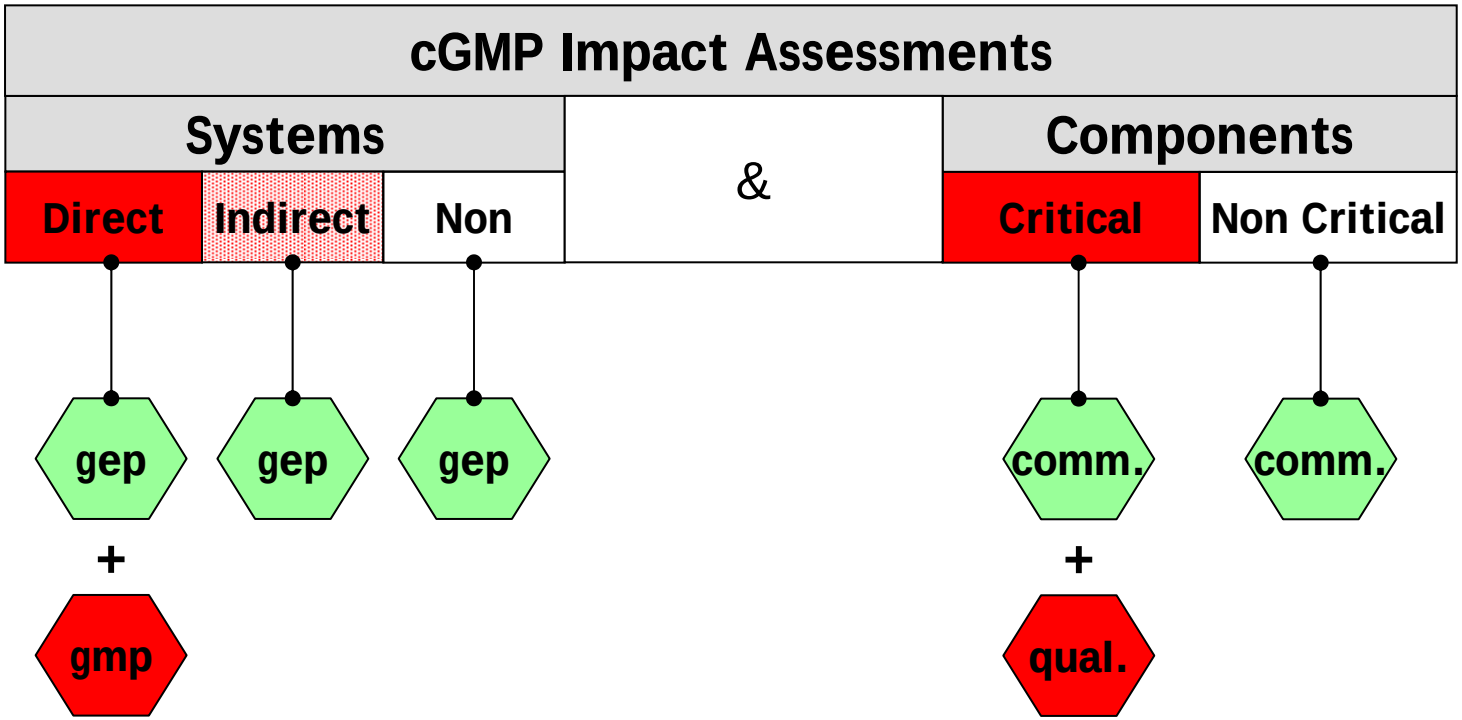
HACCP

Seven Steps

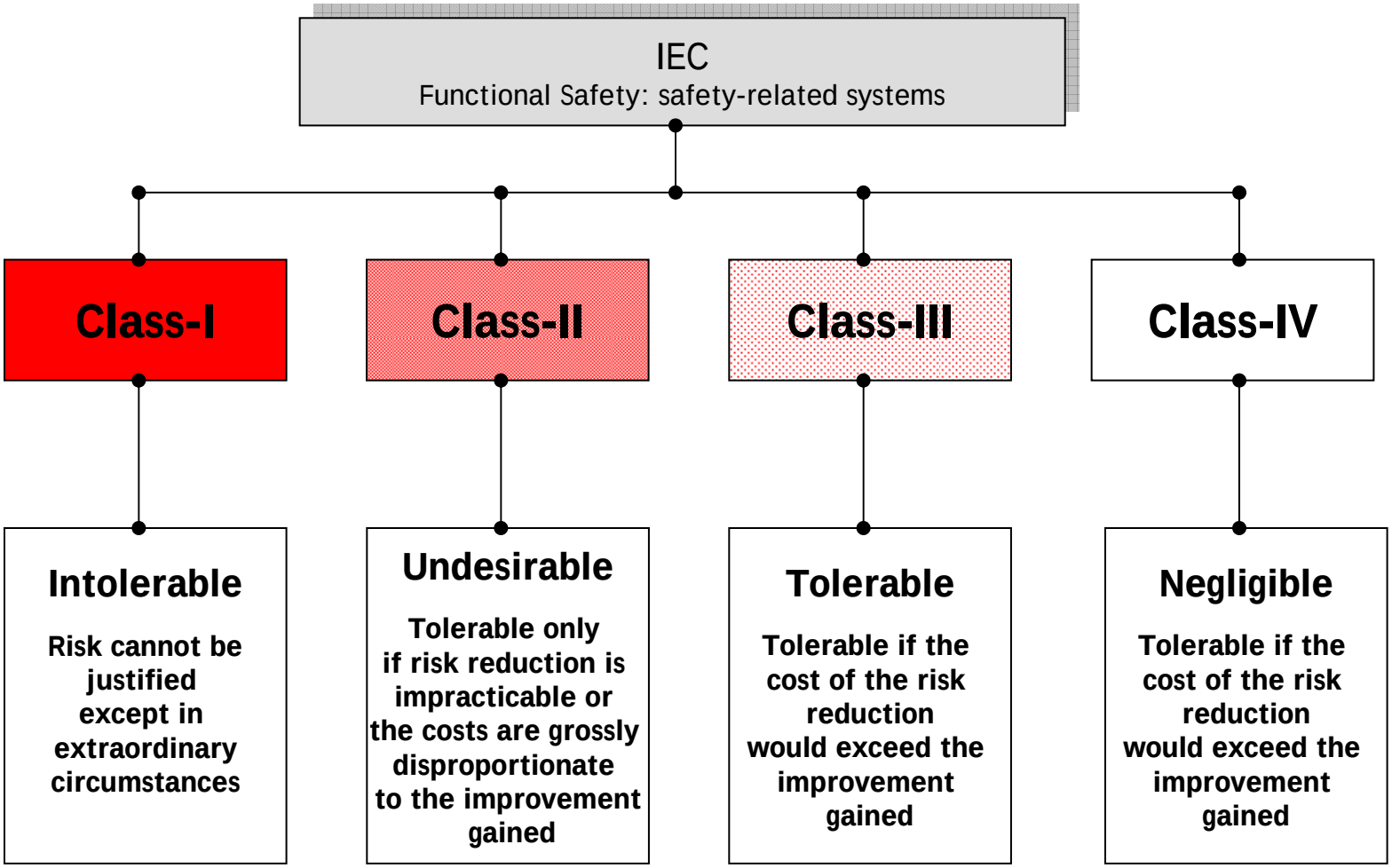
0. **Prepare Process Map**
1. **Conduct hazard analysis (HA) & identify preventive measures**
2. **Determine critical control points (CCP)**
3. **Establish critical limits**
4. **Monitor each critical control point**
5. **Establish corrective action to be taken when deviation occurs**
6. **Establish verification procedures**
7. **Establish record-keeping system**

Generic HACCP via Matrix

Physical Risk



Functional Risk



Process Risk

Probability	Risk Class		
	High Impact	Medium Impact	Low Impact
High	3	3	2
Medium	3	2	1
Low	2	1	1

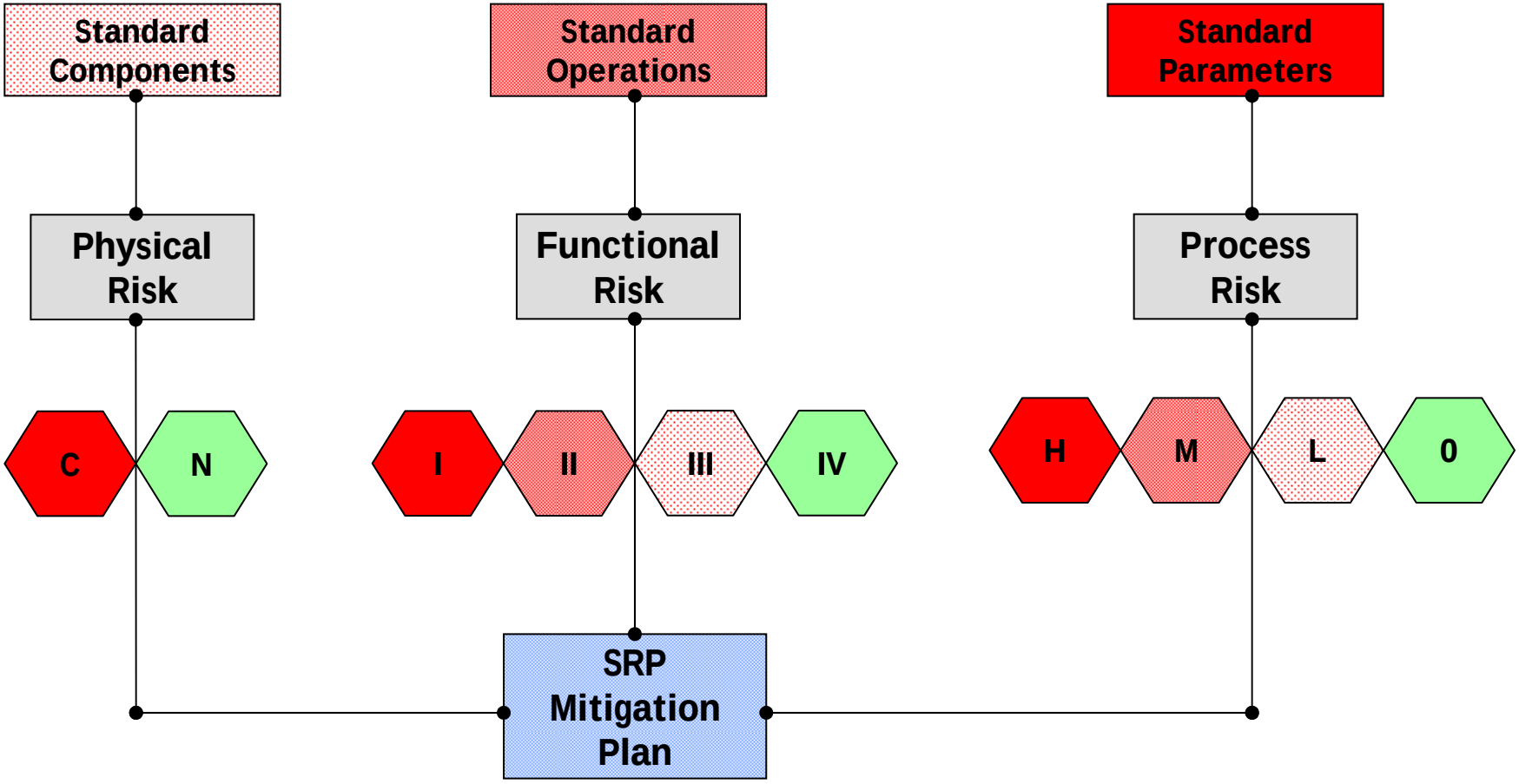
Class *f* (probability, impact)

Risk Class	Risk Priority		
	High Detection	Medium Detection	Low Detection
3	M	H	H
2	L	M	H
1	L	L	M

Priority *f* (class, detection)

Is risk a function of surveillance?

Risk Integration



Risk Dividend

		DQ	IQ	OQ	PQ	PV	PAT	QA	FDA
Physical Risk	C	X	X					X	X
	N								
Functional Risk	I			X	X			X	X
	II			X					
	III								
Process Risk	H					X	X	X	X
	M					X			
	L								

Regulatory Relief ?

Limits of Detection

pH 6-8 does not affect our product but we always hit 6.9-7.1 and the regulator demanded 6.5-7.5

Scientific basis ?

Particle Size

Spec. on API particle size, when size is irrelevant to bioavailability - because it is processed in the final product via a wet granulation

Scientific basis ?

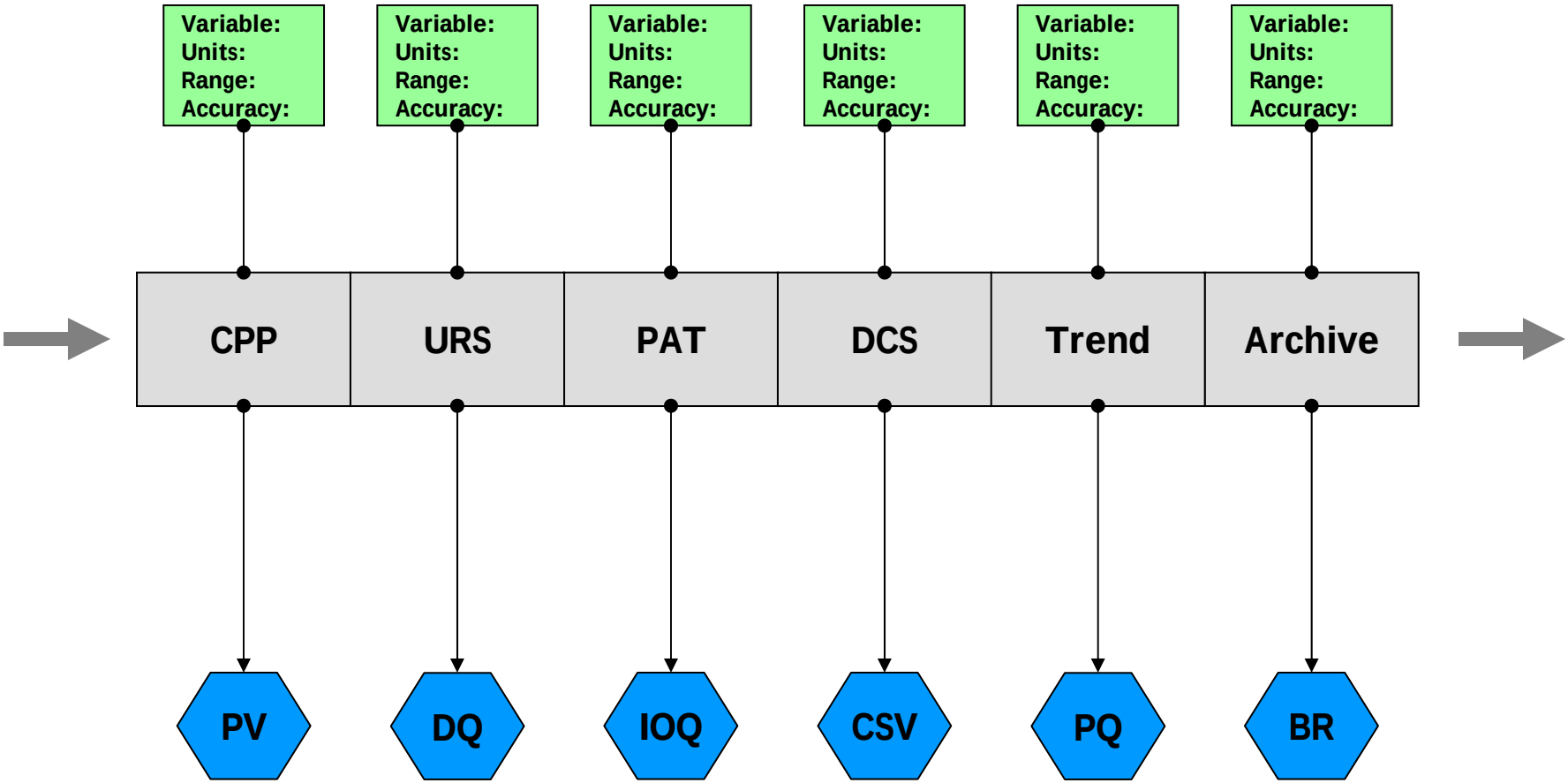
Final Formulation

API must be +/-10% of the nominal value at release and +/-5% at the end of shelf-life

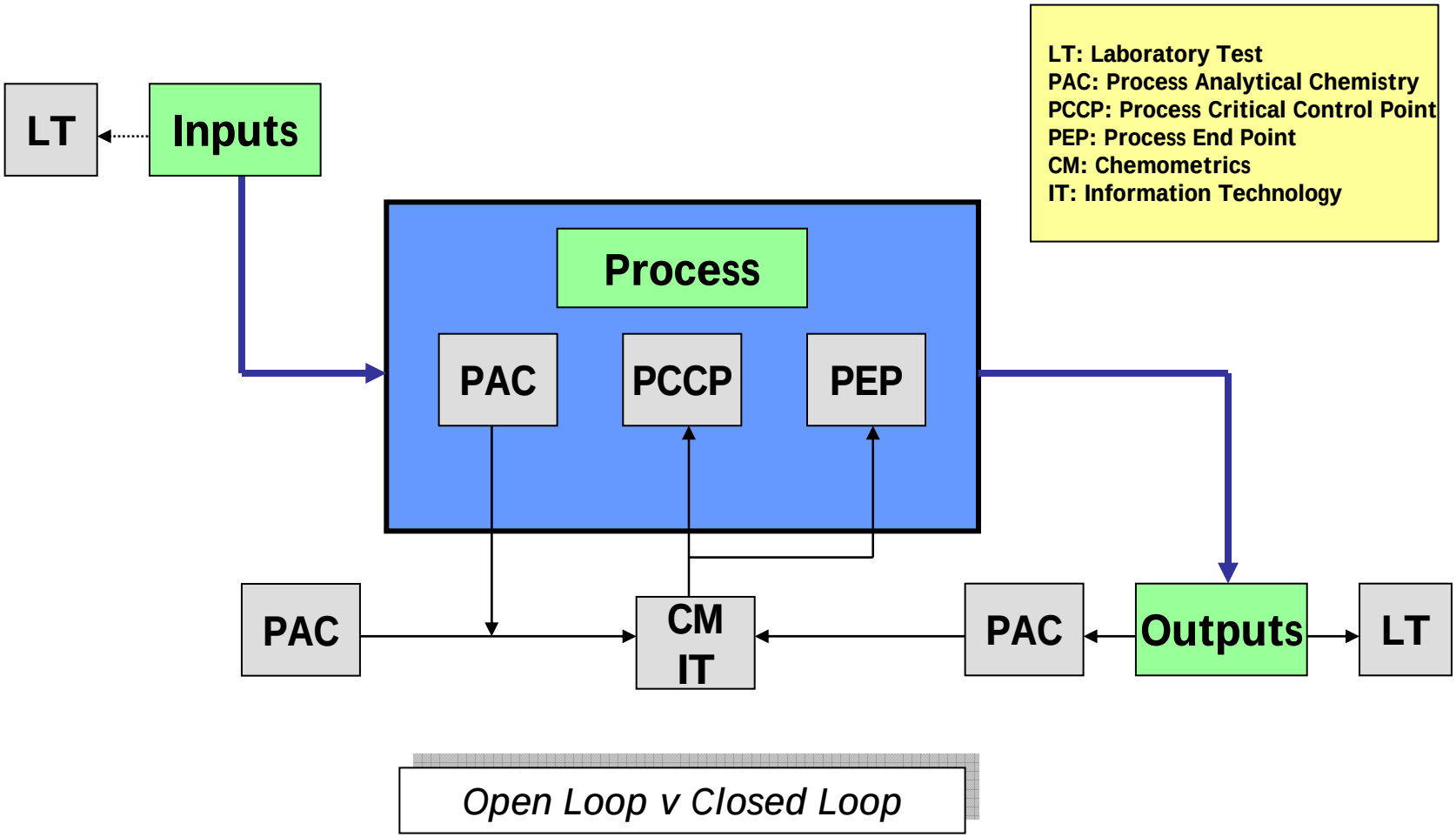
Scientific basis ?

"Also, the aspect of risk management carried out be the authorities has to be addressed. At the moment, it is all give by industry and no relief on regulatory scrutiny from the authorities, which was supposed to be the deal."

Risk ‘Conveyor’

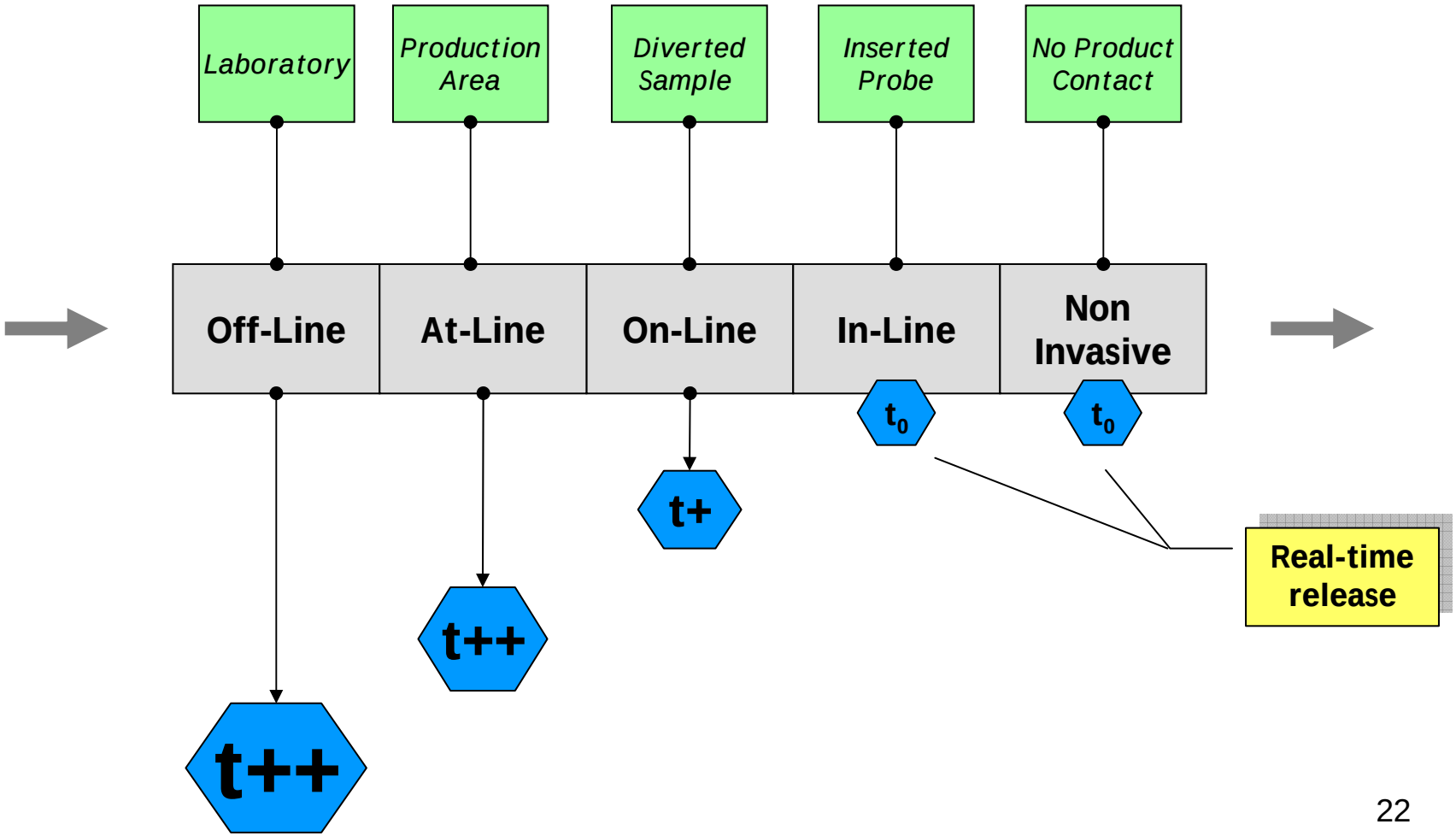


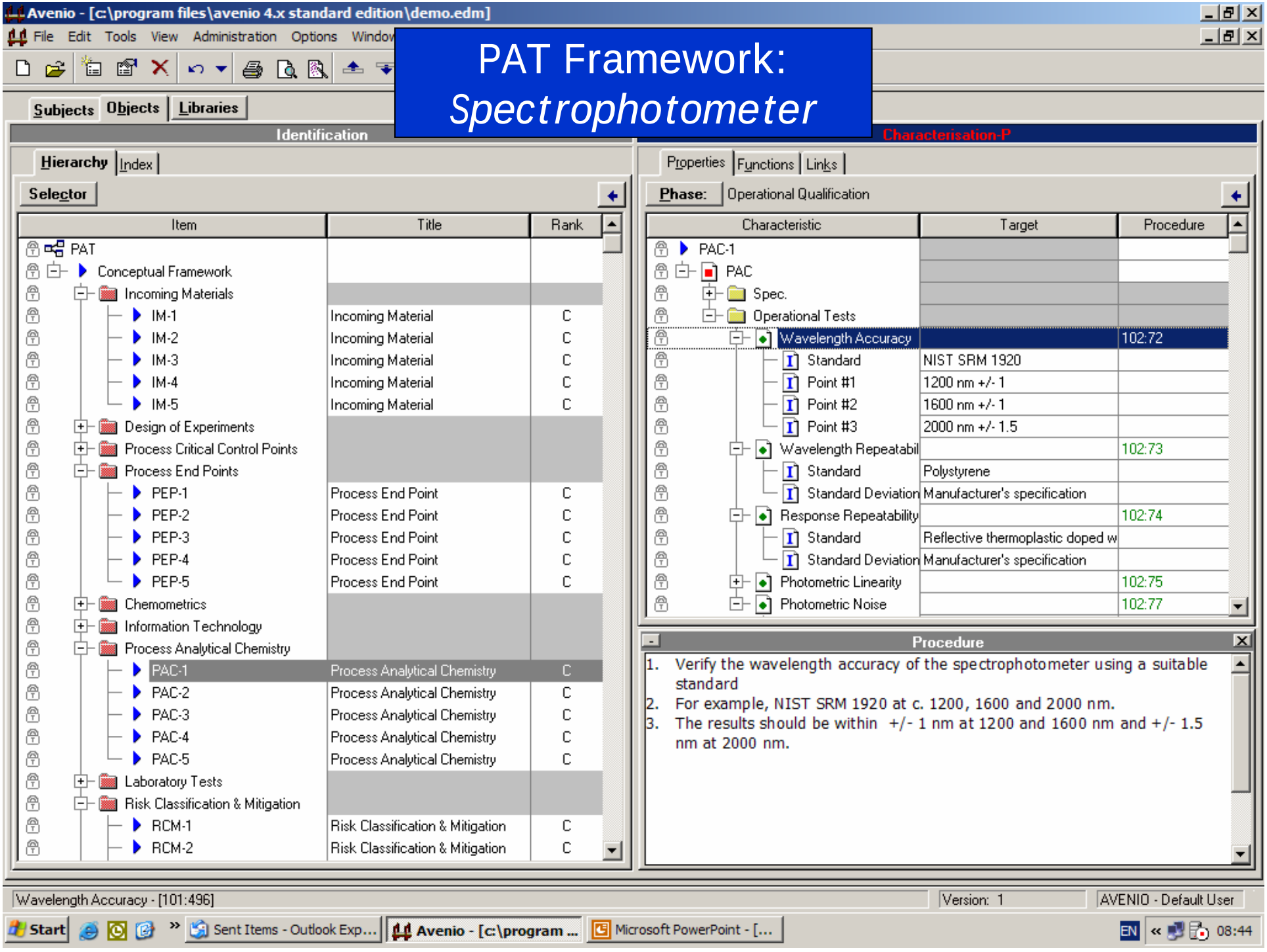
PAT: Vocabulary



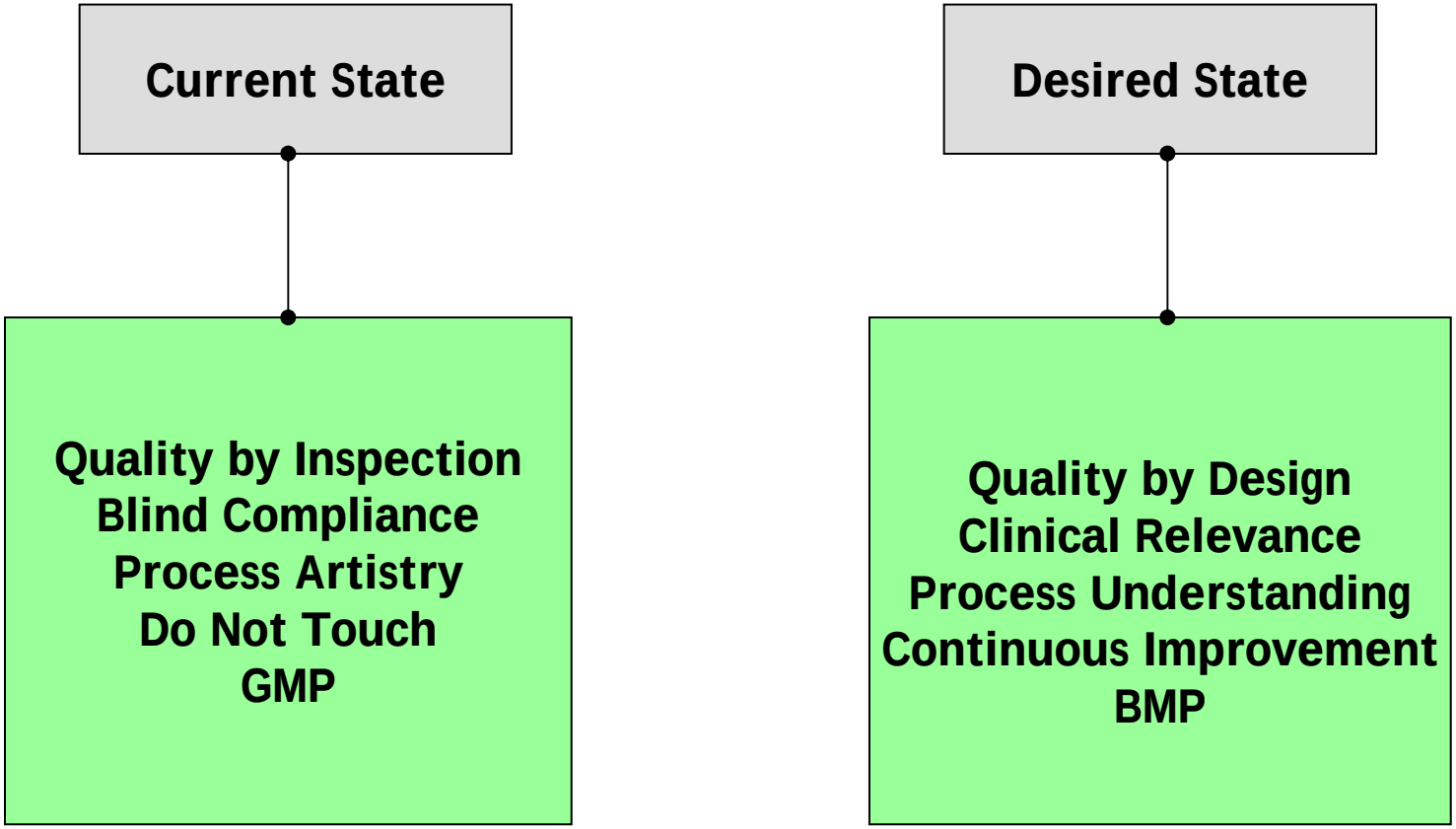
For PAT examples, see http://www.fda.gov/cder/OPS/cooley/

PAT: Measurement




Avenio - [c:\program files\avenio 4.x standard edition\demo.edm]
File Edit Tools View Administration Options Window
PAT Framework:
Spectrophotometer
Subjects Objects Libraries
Identification
Characterisation-P
Hierarchy Index
Selector
Item
Title
Rank
PAT
Conceptual Framework
Incoming Materials
IM-1 Incoming Material C
IM-2 Incoming Material C
IM-3 Incoming Material C
IM-4 Incoming Material C
IM-5 Incoming Material C
Design of Experiments
Process Critical Control Points
Process End Points
PEP-1 Process End Point C
PEP-2 Process End Point C
PEP-3 Process End Point C
PEP-4 Process End Point C
PEP-5 Process End Point C
Chemometrics
Information Technology
Process Analytical Chemistry
PAC-1 Process Analytical Chemistry C
PAC-2 Process Analytical Chemistry C
PAC-3 Process Analytical Chemistry C
PAC-4 Process Analytical Chemistry C
PAC-5 Process Analytical Chemistry C
Laboratory Tests
Risk Classification & Mitigation
RCM-1 Risk Classification & Mitigation C
RCM-2 Risk Classification & Mitigation C
Properties Functions Links
Phase: Operational Qualification
Characteristic
Target
Procedure
PAC-1
PAC
Spec.
Operational Tests
Wavelength Accuracy 102:72
Standard NIST SRM 1920
Point #1 1200 nm +/- 1
Point #2 1600 nm +/- 1
Point #3 2000 nm +/- 1.5
Wavelength Repeatabil 102:73
Standard Polystyrene
Standard Deviation Manufacturer's specification
Response Repeatability 102:74
Standard Reflective thermoplastic doped w
Standard Deviation Manufacturer's specification
Photometric Linearity 102:75
Photometric Noise 102:77
Procedure
1. Verify the wavelength accuracy of the spectrophotometer using a suitable standard
2. For example, NIST SRM 1920 at c. 1200, 1600 and 2000 nm.
3. The results should be within +/- 1 nm at 1200 and 1600 nm and +/- 1.5 nm at 2000 nm.
Wavelength Accuracy - [101:496]
Version: 1
AVENIO - Default User
Start
Sent Items - Outlook Exp...
Avenio - [c:\program ...
Microsoft PowerPoint - [...
EN
08:44

Wrap Up


Current State
Quality by Inspection
Blind Compliance
Process Artistry
Do Not Touch
GMP
Desired State
Quality by Design
Clinical Relevance
Process Understanding
Continuous Improvement
BMP

Thank You !

Q & A