Fall 11-4-2015

Quality systems for continuous manufacturing

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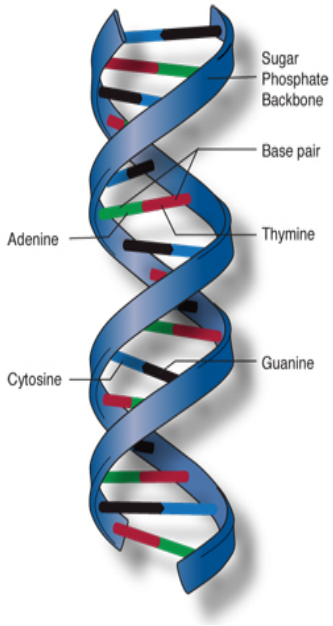
Continuous Manufacturing

A Quality System Approach To Process Monitoring and Control



ICB II

November 2015

Ron Branning

President, RBC LLC

Implementing World-Class Production Quality Systems
The Focus of My Career

- J&J – 1968 – Beginning of Modern GMPs
- 45 years of practical, world wide, science and compliance solution implementation :

  J&J, Searle, Boehringer Ingelheim, Serono, Genetics Institute, Aventis Behring, Somatogen, Genentech, Gilead, Genzyme

- VP, SVP Quality and Compliance Issues Experience:
  - Quality Organization and Operational Performance
  - FDA 483s and WW Regulatory Inspection Observations
  - FDA CRLs, WLs, CDs and DOJ Investigations
  - MHRA, IMB, TGA, ANVISA, JMOH, SFDA, PICS Commitments
  - CHMP Oral Presentation:Commitments and Implementation

FDA's (World Regulator's) Expectations : Production Quality Systems

"We rely upon the manufacturing controls and standards to ensure that time and time again, lot after lot, year after year the same clinical profile will be delivered because the product will be the same in its quality…We have to think of the primary customers as people consuming that medicine and we have to think of the statute and what we are guaranteeing in there, that the drug will continue to be safe and effective and perform as described in the label"

Janet Woodcock, M.D.

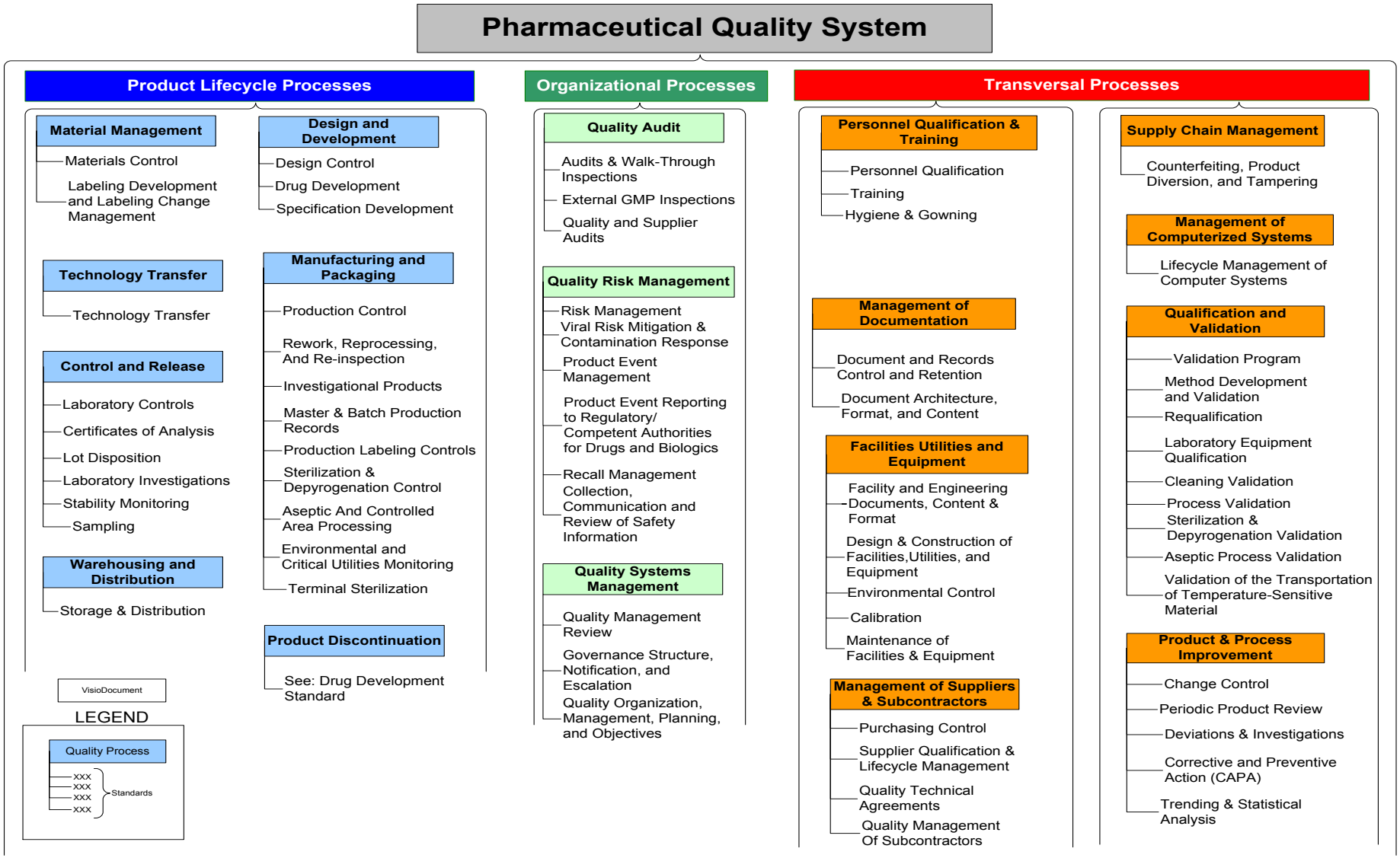
Presentation Outline

- Continuous Manufacturing
- Quality System
- Process Development
- Technology Transfer
- Manufacturing
- Process Monitoring and Control
- Quality Control
- Quality Assurance

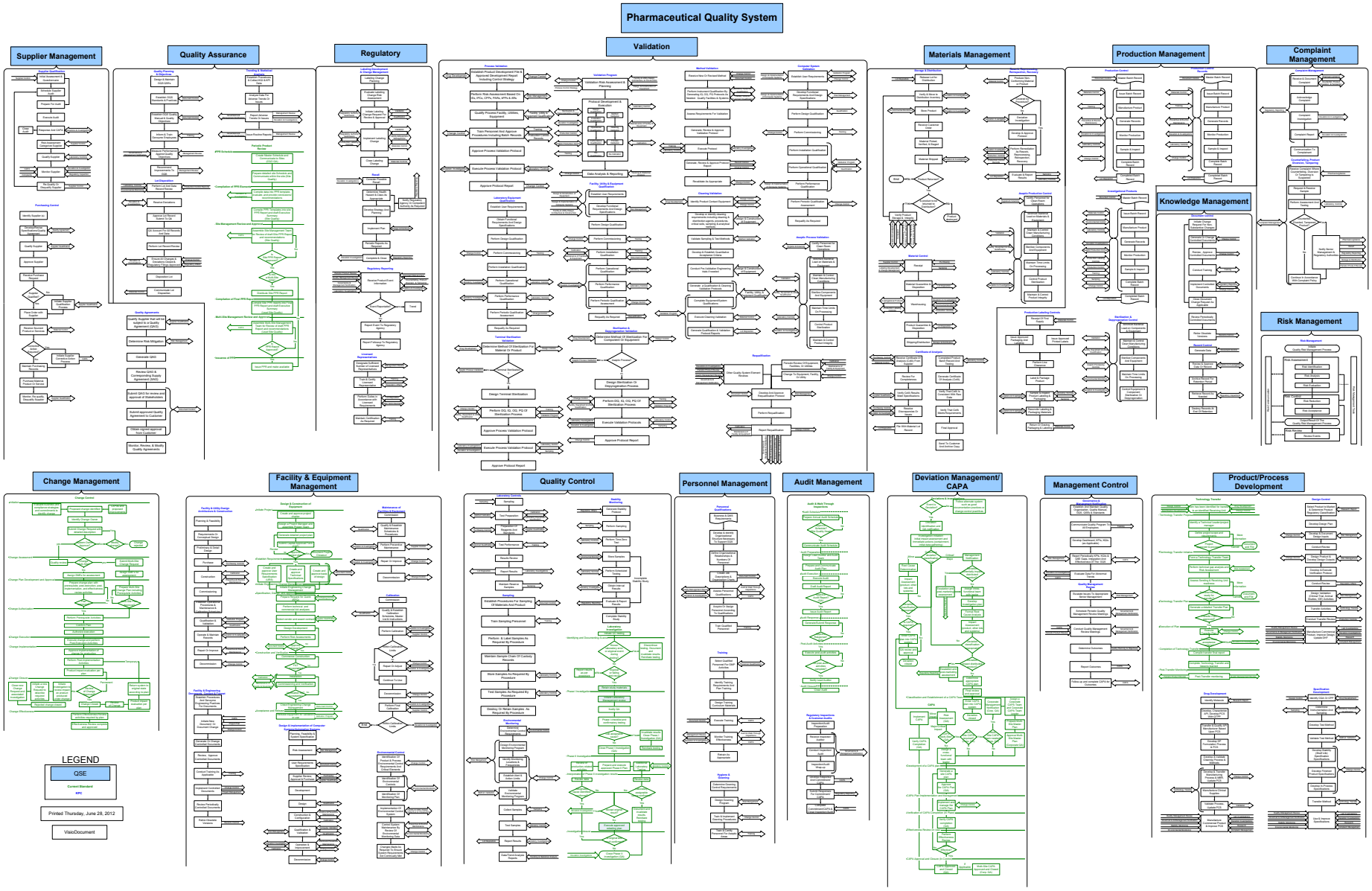
Continuous Manufacturing

- Glass, Plastic Manufacturing
- Radiation Sterilization
- McNeil Tylenol Response
- Serono – Perfusion Disks
- GI – Batch Harvest / Re-Feed
- Continuus - MIT / Novartis Collaboration
- DARPA – Tractor / Trailer Sized BioManufacturing
- Genzyme – Integrated Continuous BioMFG Platform

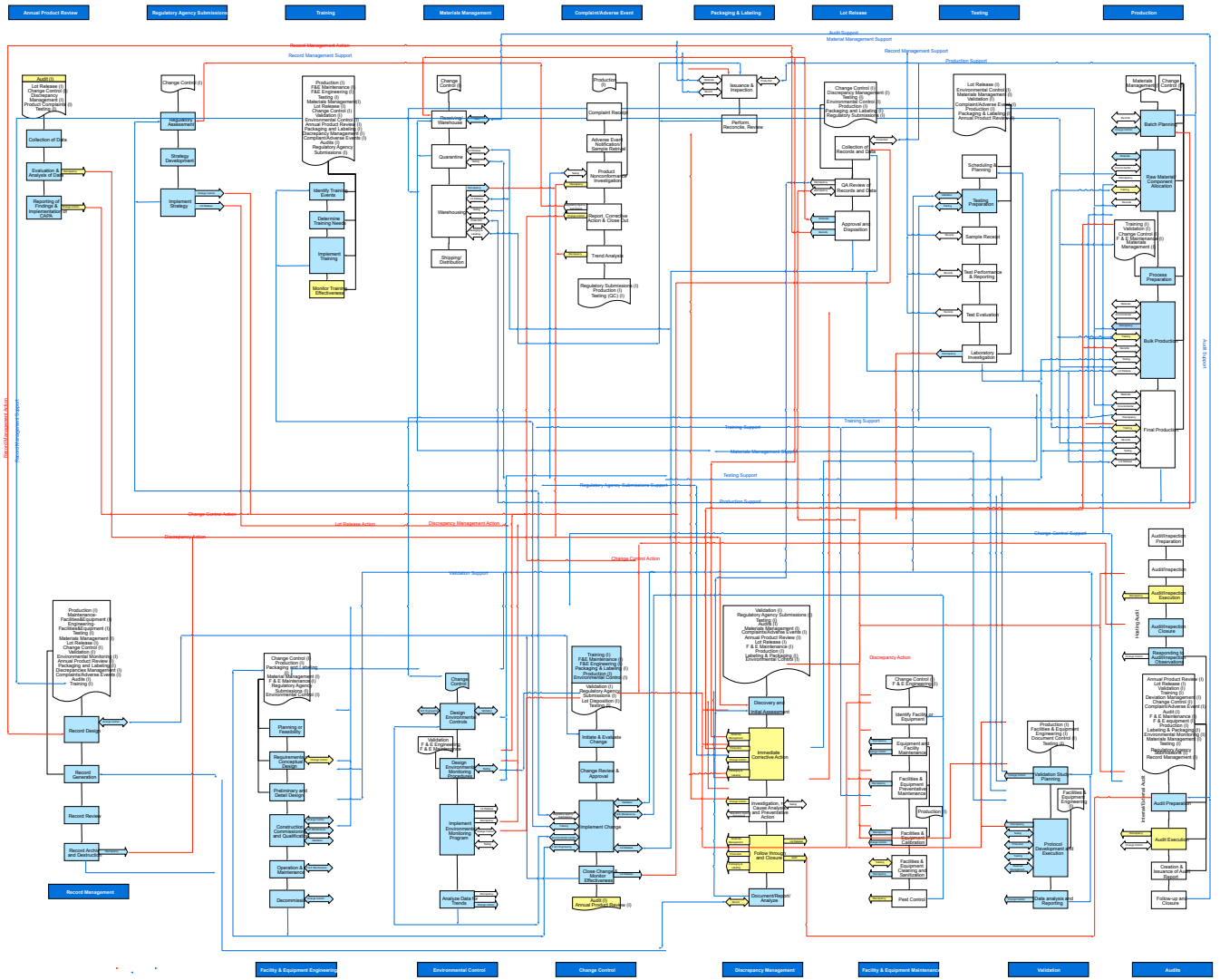
Integrated Product / Process Quality System
Organization Chart – SME's, Risk Assessment, Culture Building



Quality System – Process Map

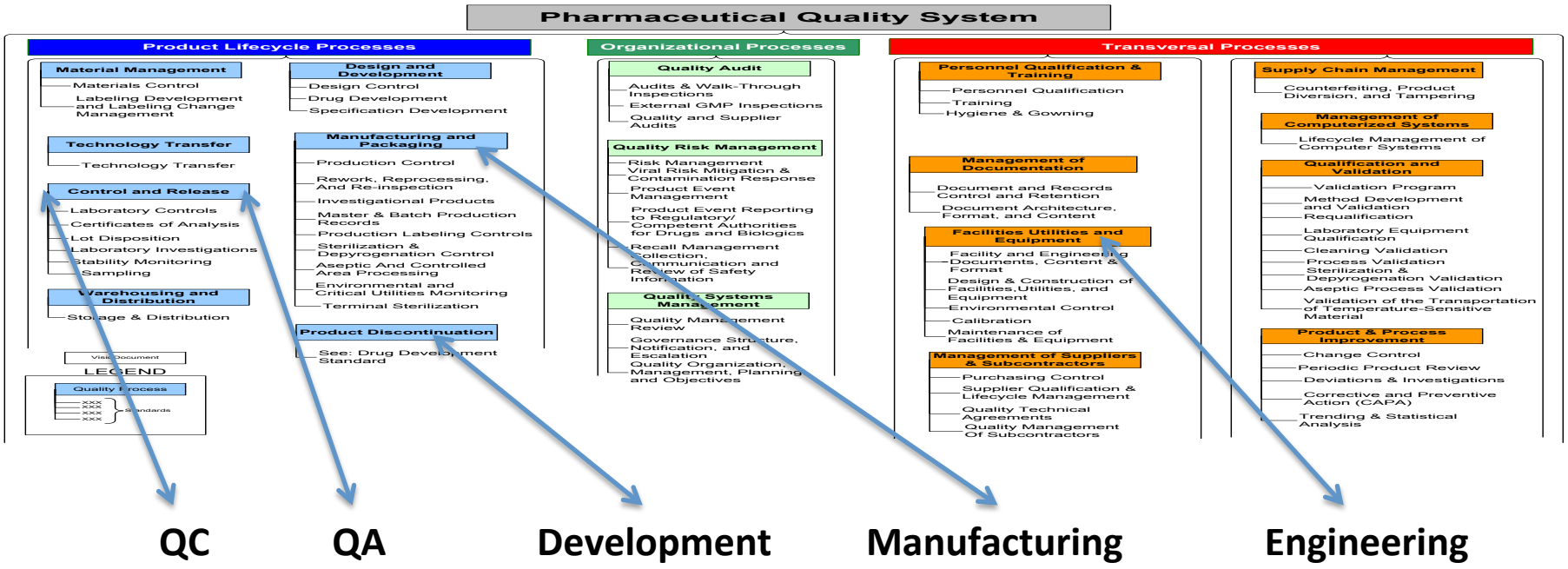


Criticality Assessment : Quality System Map



Blue Lines Are Good; Red Lines … Not So Much

ICH Q10 Quality System – Organization Chart



Core Quality System Elements ™

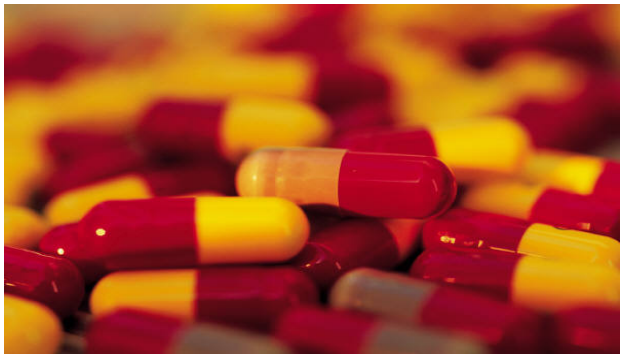
Development	Engineering & Maintenance	Manufacturing	Q C	Q A

Core Quality System Elements

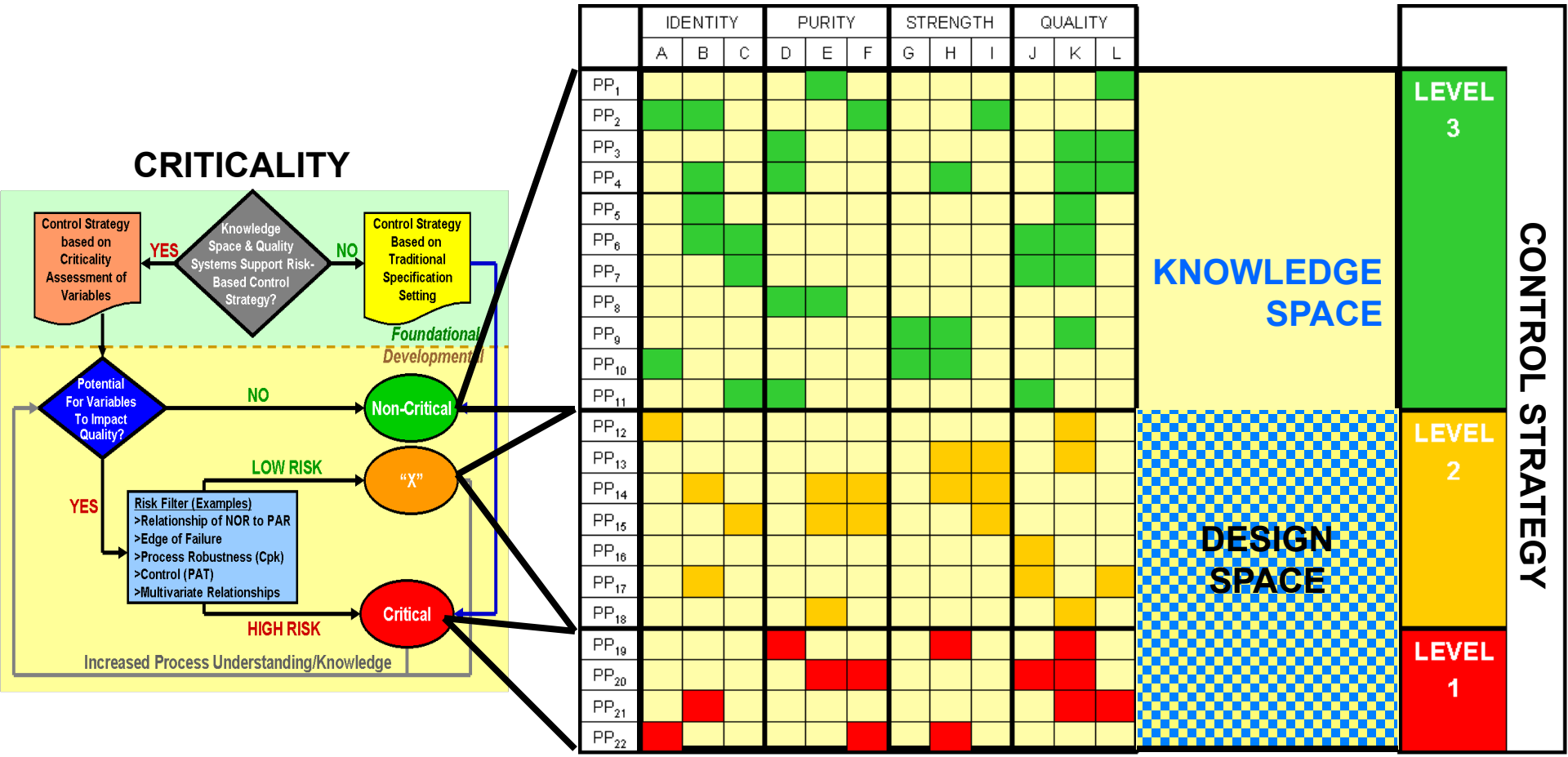
	Development	Engineering & Maintenance (FEUM)	Manufacturing	Quality Control	Quality Assurance
Process development	PD experiments define process CQAs, CPPs	Design FEU based on PD CQAs CPPs data	BR development based on CPP data	CQA initial IP TM development	CQA's and CPP's review and assessment
Test methods	CQA TM development	Design IP&QC TMs sampling capability into FEU	Develop operator training for IP & QC sampling and testing	Initial CQA QC TM review & assessment	IP, QC TM review and assessment with QC
Facility, utilities, equipment	Conduct FEU unit operations risk assessment (RA)	Refine FEU design & Maintenance Program based on PD RA	Verify FEU design incorporates PD RA + Rev & app FEU design	Define initial EM sampling & test requirements	Review & approve Engineering FEU design
Personnel	Verify CQAs and CPP's are included in E,M,QC, QA training material	Include PD RA into FEUM SOPs & training material	Include PD RA into MFG SOPs & training material	Include PD RA into FEU testing QC training material	E, M, M, QA, QC training material review and approval
Tech transfer	Process Development Report (PDR) includes final CQAs & CPP's	FEU completion, install, control sys and maintain based on PDR	Assess final MFG process based on PDR data from RA	IP, QC TM transfer	Maintenance Program, MGG BR & SOP's, IP QC TM review & approval
Process validation	Verify CQAs & CPP's are in validation protocols	Facility certification, Equipment qual, Utility qualification	Execute validation protocols during MFG qual, validation runs	TM validation + testing process validation (PV) samples	PV protocol and executed PV review & approval
Routine manufacturing	Verify CQAs & CPP's are in batch records, ongoing process and test method support	Engineering Maintenance and Calibration support for routine manufacturing	Routine manufacturing	Routine IP, QC sampling and testing	MFG monitoring and verification of CPPs and critical unit operations
In process testing	Monitoring and review of in process data	In process sampling capability support	IP sampling, MFG BR process adjustments	IP sampling and testing	Review IP test results
QC testing	Monitoring and review of QC test data	QC sampling capability support	QC sampling	QC sampling and testing	Review QC test results
Product disposition	MFG data and APR rev & assessment to QA	FEU and Maintenance data to QA	MFG BR, deviation, CAPA data to QA	IP and QC data to QA	QA review of D, M, C, M, QC data for product disposition

Quality System - Development

- PD Experiments Define Process CQAs, CPPs
- CQA Test Method Development
- Production Operations Risk Assessment (RA)
- Process Development Report (PDR)
- Verify CQAs & CPPs – Validation Protocols
- Verify CQAs & CPPs – Batch Records,
- Ongoing Test Method Support
- Monitor Process Data
- Monitor QC Test Data
- APQR Assessment



Development of Product Attributes, Process Parameters, Design Space & Control Strategy



Quality System – Engineering
Basis : Process Development Report

- Design Facilities, Equipment, Instruments, Utilities
- Develop Engineering, Cal/ Maintenance Program
- Install Control System
- Qualification

- Routine Manufacturing Support
- Engineering, Cal/ Maintenance data to QA

Quality System – Manufacturing Basis : Process Development Report

- Drive Process Validation
- Finalize Process Monitoring and Control
- Complete Production Batch Record
- Deviations
- Investigations
- Corrective and Preventive Action (CAPA)
- Manufacturing
- Data to QA

Quality System - Quality Control Basis : Process Development Report

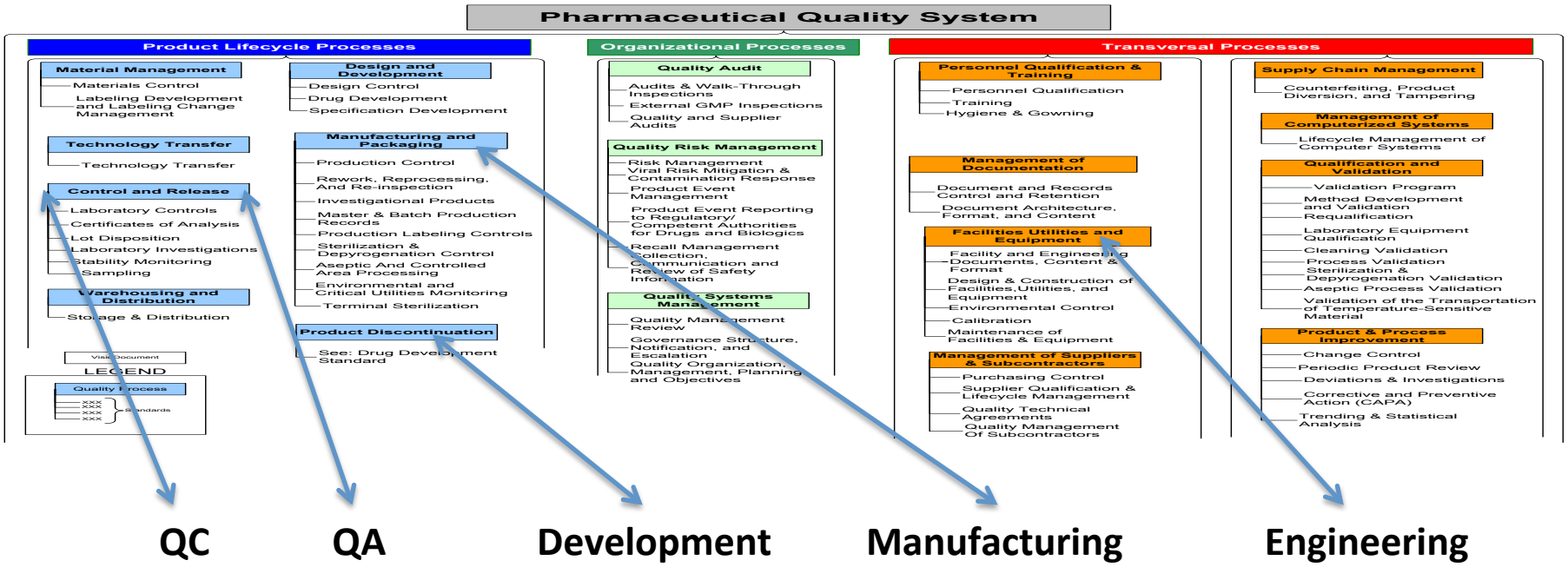
- Define Environmental Monitoring Requirements
- Test Method Transfer Validation

- Routine IP, QC Sampling and Testing
- IP and QC data to QA

Quality System - Quality Assurance Oversight Basis : Process Development Report

- Engineering Design
- Training Materials
- Calibration and Maintenance Program,
- Manufacturing BR & SOPs
- In-Process and QC Test Methods
- Process Validation
- CPPs and Critical Unit Operations
- Review IP and QC Test Results
- QA Production Data Review – Product Disposition

ICH Q10 Quality System – Organization Chart



Core Quality System Elements ™

Development	Engineering & Maintenance	Manufacturing	Q C	Q A

FDA Quality Metrics - Reporting

- Lots Attempted
- Rejected Lots
- Attempted Batches
- OOS (Including Stability)
- Lot Release Tests
- Stability Tests
- Invalid OOS (Including Stability)
- Product Quality Complaints
- Lots Attempted
- APR (QPR) On Time Completion
- AQRs (PQRs) Required

Management Governance

- Corporate Product Quality & Compliance Goals
- Routine Production Monitoring and Control
- Deviations, Investigations
- Rejected Materials / Products
- Product Complaints
- Adverse Events
- Recalls
- Annual/Periodic Product Quality Reviews
- Corrective and Preventive Actions
- Continuous Improvement
- Periodic Management Reviews – Goals / Progress

Final Thoughts

- Put in Place an ICH Q 10 Based QS
- Understand the Product (CQAs)
- Understand the Process and its Impact on the Product (CPPs, QbD and Control Strategy)
- Validate QC Test Methods
- Validate, Monitor and Control the Process
- Investigate and CAPA all Deviations
- Continuously Improve all Operations

Thank You

Questions ?

Comments?