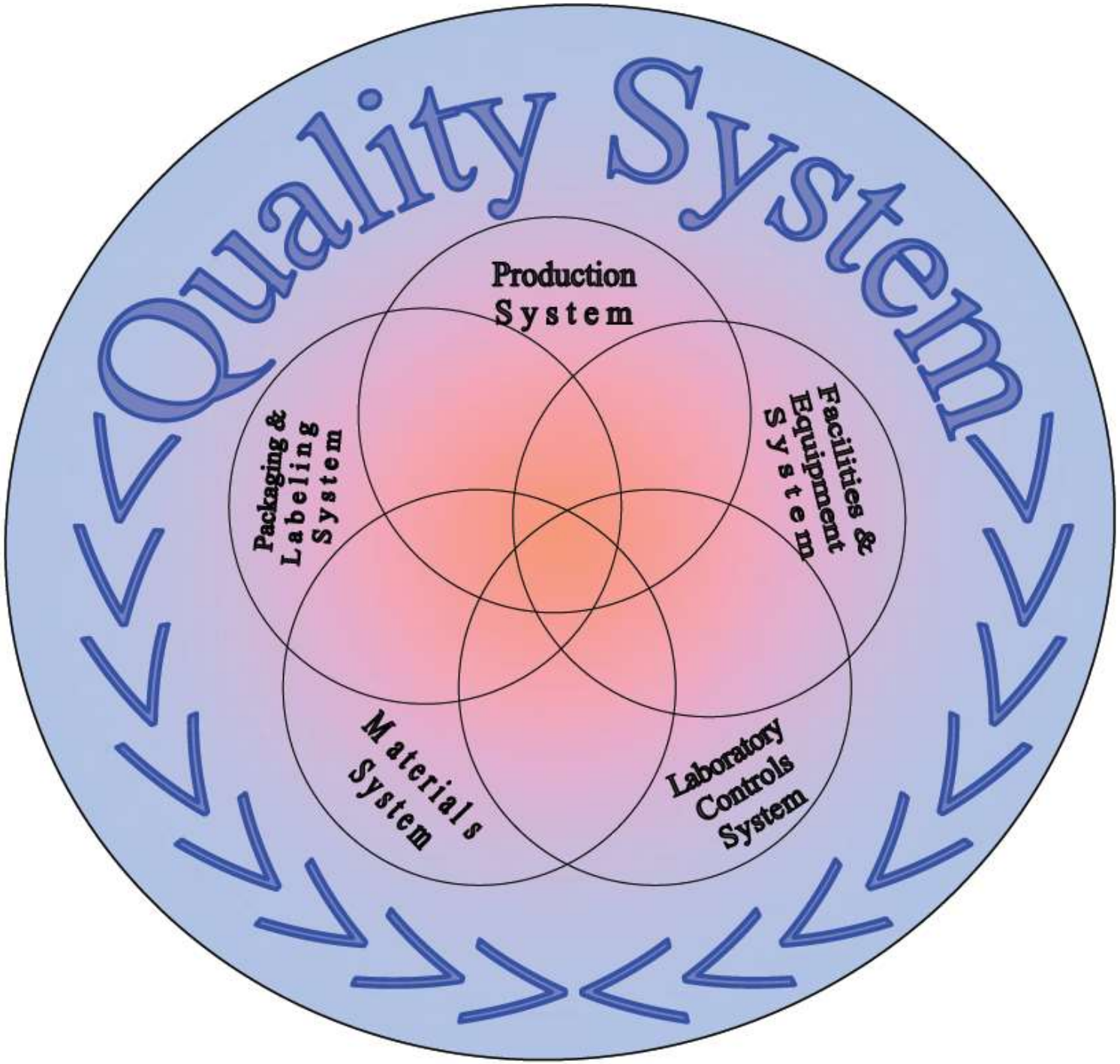
无菌制剂 Aseptic Processing
法规与技术 Compliance & Technology
的 Its
发展趋势 Development Trend

李树德 **Michael Lee**

June 12, 2014

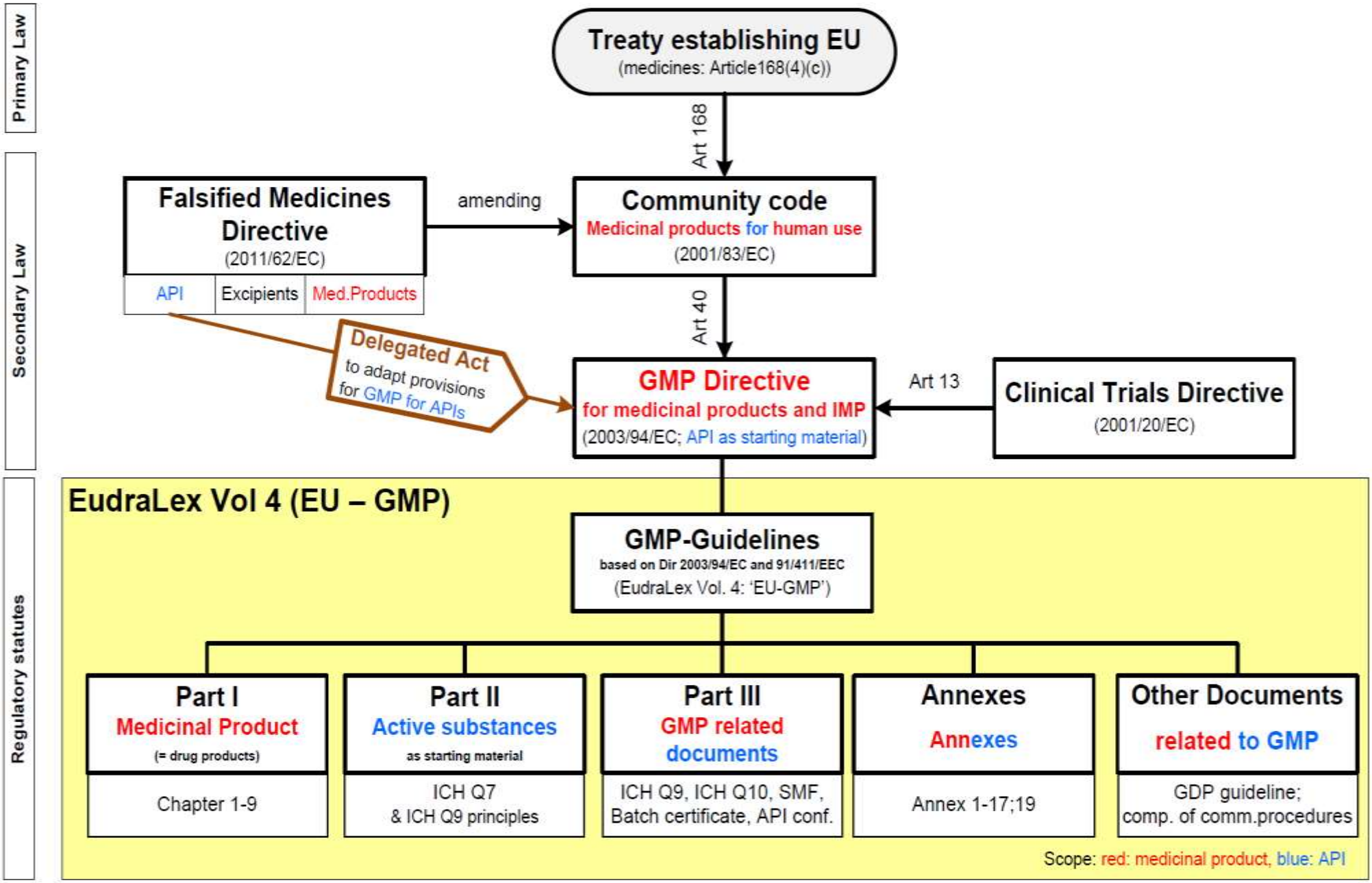
GMP 50 年庆
50th ANNIVERSARY OF GMP

The year of 2013 marks the 50th anniversary of Good Manufacturing Practice (GMP). The first GMP rule was published in 1963 by the FDA to protect the health of drugs' consumers. GMP is the accepted worldwide "gold standard" for the manufacturing and control of medicinal products.


Quality System
Production System
Packaging & Labeling System
Facilities & Equipment System
Materials System
Laboratory Controls System

The idea of building quality into the product instead of ensuring quality by testing is not new. It has been practiced for years in the field of sterilization processes.

The Legal Basis of the GMPs in Europe

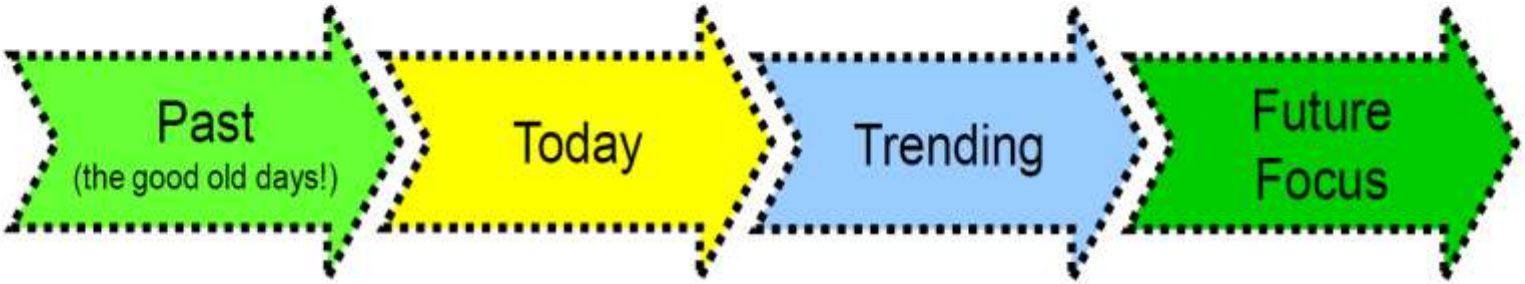


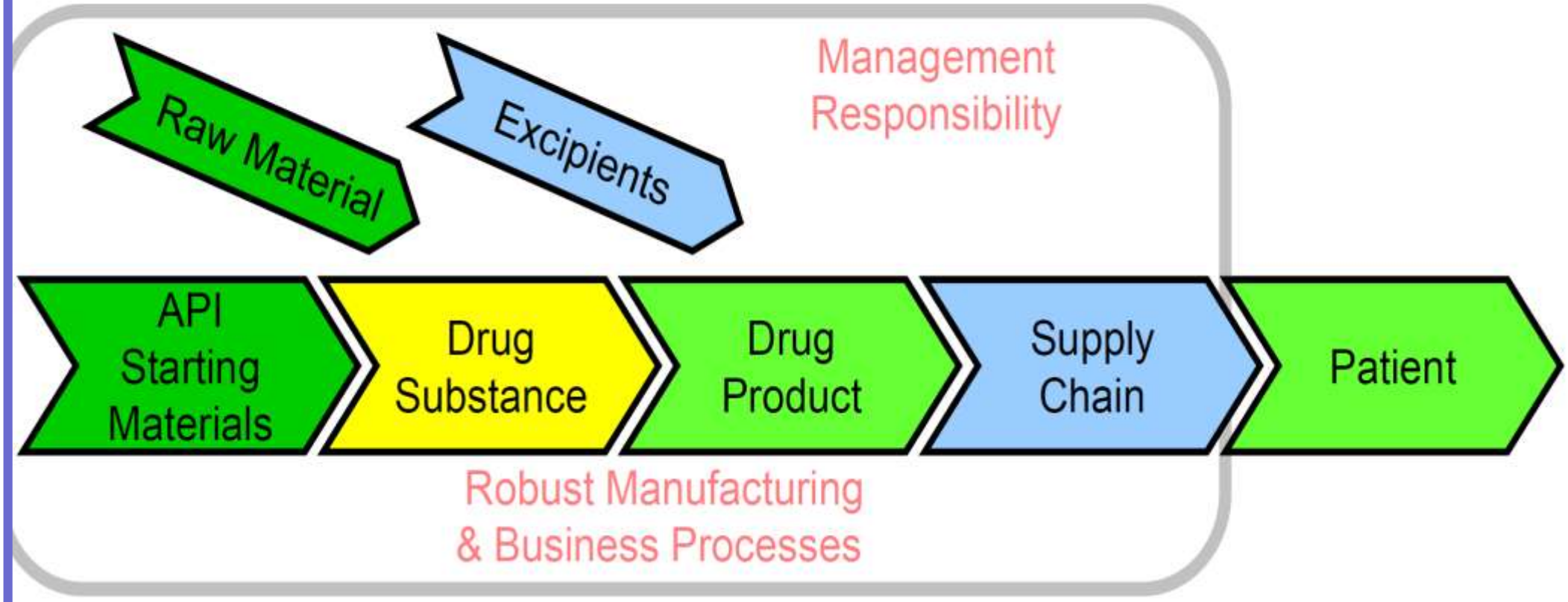
Aim of the Inspections
Make a 'CASE'

- **Inspections are essential to evaluate**
  - **C**apability,
  - **A**dequacy of production and control procedures,
  - **S**uitability of equipment and facilities, and
  - **E**ffectiveness of the quality management system

  in assuring the overall state of control
- **Evaluation of authenticity of submitted data and link to the registration dossier (Pre-approval inspections)**

Evolution of Inspection Focus Areas





The High Cost of Non-Compliance

- Remediation Costs
- Recalls
- Plant Closing/Production Halt
- Negative Stock Share Price
- Fines
- Executive Liability

The FDA Hot Buttons

In examining recent 483's and Warning Letters, a pattern emerges of what the FDA is emphasizing. These are the top compliance trends seen most frequently:

- **Quality Systems Approach** - The FDA is fully embracing the Quality System Inspection Technique and their findings reflect this shift.
- **Standardization across Departments and Organizations** - The FDA is holding organizations accountable to standardization and demanding consistency.

The FDA Hot Buttons

- **Proper Use Of Risk Based Approaches** - With the introduction of the GMP's for the 21st Century in 2002, the FDA incented the industry to use risk-based approaches that are based on sound engineering and scientific data.
- **Management of Change Control** - One of the most frequently cited GMP excursions is poor management of change.
- **Corrective Action/ Preventive Action (CAPA)** - One of the first places the FDA looks; it has become a very common GMP issue found in many Warning Letters and 483's.

PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

Contacts with China's Food and Drug Administration (CFDA)

A side-meeting between the PIC/S Executive Bureau and **China's** Food and Drug Administration (CFDA) took place in order to provide any necessary clarifications with regards to a possible future accession or pre-accession, further to a previous indication that accession to PIC/S was a priority for CFDA.

美国无菌制剂协会(Parenteral Drug Association, PDA)与美国食品药物管理局（Food and Drug Administration, FDA）每年共同举办之聯合法规年会，提供了业者与FDA面对面的研讨沟通无菌生物药品制程最新技术专业、药品GMP法规、FDA政策测导向及各国GMP管理趋势等议题进行之平台。

无菌制剂行业正在推动：在全球协调化理念的法规环境下，以药品生命周期管理来推动质量及合规的工作（**Driving Quality and Compliance throughout the Product Life Cycle in a Global Regulatory Environment**）」。

主要的工作将围绕：「建立质量系统」、「持续技术创新」及「产品生命周期管理」。而延伸出的相关重要的议题，如「原料药**GMP**」、「药品优良运销作业（**GDP**）」及法规协调及同步发展的新动向。

在知識进步以及快速全球协作化的环境下，GMP 合规的管理日益复杂，必须以风险管理的精神，并且推动国际法规的协调与同步更新，以扩展国际合作及信息共享，

以便使监管机构在有限的资源下做到最好的合规执法，

并使行业人员能够在渐趋一致的国际法规要求下，做到产品生命周期全过程的GXPs的合规。

2014年2月27日EMA公布的最新工艺验证指南

Guideline on process validation for finished products -information and data to be provided in regulatory submissions （This guideline replaces the previous note for guidance on process validation. The new guideline is brought into line with ICH Q8, Q9 and Q10 documents and the possibility to use continuous process verification in addition to, or instead of, traditional process validation described in the previous guideline has been added and is encouraged.）

2014年4月25日EMA公布的

Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission（Draft）.

「2013年PDA/FDA聯合法规研讨会」在美国华盛顿特区举行，会议主题为「推动药品生命周期于全球化法规环境下之质量提升及法规遵循（Driving Quality and Compliance throughout the Product Life Cycle in a Global Regulatory Environment）」，由主轴议题-「建立质量系统」、「持续技术创新」及「产品生命周期」中延伸出相关重要的议题，如「原料药GMP」、「药品优良运销作业（GDP）」及FDA新动向。在知識进步以及快速全球化的环境下，GMP的管理日益复杂，必须以风险管理的精神，并且有国际调和与更新的法规，扩展国际合作及信息共享层面，以便在有限的资源下做到最好的管理。

大会第一全会专家报告：评估有关质量体系的工业标准、质量源于设计、药品短缺危机。

第一全会的重点是汇集目前制药工业、执法机构、健康事业工作者及患者对药品安全性、可支付性、可及性达成共识。参会者听到来自制药工业和执法人员讲授的为满足现在及未来患者需求的药品质量体系相关成功案例及遇到的障碍。

大会以FDA 专家组对成立的工作组的意见。FDA 专家组代表分别来自CBER(生物学评价及研究中心)、CDER(器械及放射卫生学中心)、CDRH、CVM 和ORA.

第二全会（合作方与质量文化）、第三全会（对GMPs 的理解）。

这些会议讨论[扎实的质量文化]将推动有效的质量体系，以确保第一时间生产出高质量药品。

第三全会将实际问题与通用质量原则结合，突出坚实的质量体系在制药企业实现商业目标（可靠的药品质量和药物可及性）所起的核心作用。

会议参会者可以选择以下三种分会（tracks）：

- 质量与合规
- 技术与创新
- [产品生命周期]管理

“质量与合规”的讨论焦点是一个有效、可持续的质量体系对一家企业商业需求的积极影响。

讨论议题涵盖质量协议，原料药GMP、药用辅料及成分、对药品测量标准的理解，GDPs、监管及合作、检查后的跟踪。“技术与创新”讨论围绕新的及生命周期、实际工艺（virtual process）、法律监管、外包新模式及药物创新这些概念实际应用的未来趋势。

有关新型设备设计选择、远程监管过程、外包创新及创新化合物也是这个部分讲讨论的内容。“产品生命周期”即从产品生产初期到生命周期结束，以此逻辑引导参会者讨论从产品质量到监管所要达到的目标。

来自制药工业、执法人员为提高现阶段药品质量体系，以满足现在及未来患者用药需求所作出的成功案例及面临的挑战。

法律视角：药品质量体系、质量源于设计、药品短缺——我们面做到了什么程度？ Janet Woodcock, MD, Director, CDER, *FDA*

扎实的质量文化将有效提升生产高质量药品的质量体系。探讨如何执行质量文化，质量文化如何影响质量体系的有效性，揭示缺陷质量文化一些特征。

PDA Technical Reports on Cold Chain / GDP

1. Technical Report No. 39, *Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment*, 2007.
2. Technical Report No. 46, *Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User*, 2009.
3. Technical Report No. 52, *Guidance for Good Distribution Practices (GDPs) for the Pharmaceutical Supply Chain*, 2011.
4. Technical Report No. 53, *Guidance for Industry: Stability Testing to Support Distribution of New Drug Products*, 2011.
5. Technical Report No. 58, *Risk Management for Temperature Controlled Distribution*, 2012.

PDA Parenteral Drug Association

Connecting People, Science and Regulation®

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PDA/EMA 2011 Conference

Regulation, Cooperation, Innovation: An Effective Partnership among Authorities and Industry in Europe

PDA Parenteral Drug Association

2011 PDA/EMA Conference

Regulation, Cooperation, Innovation

3-6 May 2011 | London Heathrow, England

Development and Manufacture of a Pharmaceutical Product with Benefit of QRM / ICH Q9 Methodology

The Expanding Role of the Quality Professional in Europe and USA

EU, US GMPs and Responsibilities of QPs in the Supply Chain

Microbiology – Product Lifecycle

- Product Disposition & Solutions' Shelf Life
- Use of Water Activity as a Microbial Growth Predictor for Establishing Hold-Time Expiry of Manufacturing Process Solutions
- Environmental Monitoring
- Statistical Process Control (SPC) Chart for Setting Alert/ Action Limits for Environmental Monitoring Programs or In-process Bioburden Testing Based on Negative Binomial

Single Use Systems

- Producing Vaccines for the Global Marketplace - Flexible Facility Design

Supply Chain

- Securing the Transportation and Storage Supply Chain
- Managing Supply Channel Information in a Global Enterprise System Shared Learnings on Building a New System
- The Art of Managing an Outsourcing Program
- Outsourcing: Challenging the Project Management System at Your Organization

Analytical Methods

- Analysis of Glycoform Characterization within Monoclonal Antibody Regulatory Submissions
- Analytical Method Transfer and Monitoring - Key Elements of the Analytical Method Life Cycle Management

Risk Management

- Integration of Quality Risk Management and Discrepancy Management
- Sterility Assurance Risk Management - One Company's Approach

Quality Science

- Getting Technology Transfer Right the First Time, How to Train and Learn in Day to Day Manufacturing
- Best Practices for an Aseptic Process Technology Transfer and Case Study
- Lessons Learned: Implementation of a Fully Electronic and Compliant Learning Management System for GlaxoSmithKline Biopharmaceuticals R&D

Joint Regulators/Industry QbD Workshop

28-29 January 2014
London, UK

europe.pda.org/EMA2014

Workshop Guide

ORGANIZED BY PDA EUROPE

ISPE Europe Annual Conference 2014

Connecting a World of Pharmaceutical Knowledge

Driving Effectiveness in Pharmaceutical Operations within the New Quality Culture

Sheraton Frankfurt Airport Hotel

Frankfurt am Main, 28-30 April 2014

The Big Challenge for Pharmaceutical Operations in Europe: Managing Compliance and Quality under New Requirements and the Perceived Trade-Off to Lean, Agile and Flexible Production Dr. Paul Rutten, Principal, McKinsey & Co, the Netherlands
Drug Shortages: Update and Request for Input on Initiatives Aimed at Preventing Shortages Introduction to speakers, topics and objectives: Dr. John Berridge, Strategic Advisor, ISPE
EMA initiatives on Drug Shortages Dr. Brendan Cuddy, Scientific Administrator, European Medicines Agency (EMA)
The Inter-Association Shortages Prevention Project Dr. John Berridge, Strategic Advisor, ISPE, and Emma Ramnarine, Senior Director, Head Global Biologics QC Network, Genentech Roche/PDA Task Force Leader for TR54 QRM and TR54 Annex 4 Drug Shortages, PDA

Day 2 AM - 29 April 2014

PLENARY SESSION: Defining the New Quality Culture –

Chairs: Jean-François Duliere (France) and Dr. Gabriele Wanninger (Germany)

8:00	8:50	**Breakfast Networking Reception**
8:50	9:10	Opening of the meeting by the Chair Jean-Francois Duliere, Pharmaceutical Process Technologist, Technip, and Representative from Regierungspraesidium Darmstadt / Regional Council Darmstadt Welcome by Nancy Berg, CEO, ISPE Foreword by Dr. Thomas Zimmer, Vice President, European Operations, ISPE
9:10	9:50	Introduction of the Speakers: Jean-Francois Duliere, Pharmaceutical Process Technologist, Technip **1st Keynote Speech: Regulatory View** Speaker: Dr. Fergus Sweeney, Head of Inspections & Human Medicines Pharmacovigilance Division, EMA
9:50	10:30	**2nd Keynote Speech: Customer View** **Future Challenges in Biopharma** Speaker: Prof. Dr. Wolfram Carius, Senior Vice President Biopharma Strategy and Member of the Global Leadership Team, Sanofi Frankfurt

13:20	14:00	**Quality Efficiency by Design - A Holistic Operator Centric Approach to OPTIMISE Operational Quality Systems and AVOID Human Errors** Speakers: Xavier Duburcq, Group BD Director, Altran Olivier Depardieu , Consulting Partner, Oxo Pharma	13:20	14:00	**The Roles of Quality Culture and Regulatory Relationships in Preventing Shortages** Industry-Regulatory Roundtable Moderator: Bryan Wright, European Regulatory Affairs Advisor, ISPE Panellists: Speaker Line-Up from QRM in the Supply Chain / Managing Shortages	13:20	14:00	**Enterprise Compliance Management (ECOM) Based on Integrated Data Management** Speakers: Dr. Gabriele Schoenberger, Boehringer-Ingelheim, Dr. Tobias Salb, Location Manager Freiburg, Trivadis
14:00	14:40	**Concepts of Quality by Design for Analytical Methods and Opportunities for Post Approval Change Management** Speaker: Dr. Oliver Grosche, Governance & Regulations Lead, Novartis	**Theme 3: Experiences of QRM**			14:00	14:40	**Building Quality into a New Approach to Portable, Continuous and Miniature Manufacturing** Speaker: Brian Henry, Executive Director, Head of Drug Product Design, Pfizer
			14:00	14:40	**Tackling the Hottest Topics in Process Validation** Speaker: Wendy Zwolenski-Lambert, Global Validation Leader, Technical Operations, Novartis			
14:40	15:10	Networking Break	14:40	15:10	Networking Break	14:40	15:10	Networking Break
15:10	15:50	**Round Table** Moderator: Dr. Georges France, Region Head Quality Europe, Novartis	15:10	15:40	**Cross Contamination and QRM – EC GMP Guide Chapter 3 and 5, "Tox Tool"** Speaker: Dr. Thomas Pfister, Occupational Health Officer, Roche	15:10	15:40	**Future Facilities for Biopharmaceutical Processing** Speaker: Niels Guldager, Senior Technology Partner, NNE Pharmaplan
15:50		**Closing Remarks**	15:40	16:10	**New Method for the Implementation of a Process-Risk Analysis** Speakers: Dr. Jan-Peter Spengler, Head of Quality Assurance Operations and Lead Qualified Person, and Hanno Juhnke, Head of Manufacturing, Sanofi-Aventis	15:40	16:20	**Flexible and Highly Efficient – Future Manufacturing of Small Batch Parenterals** Speaker: Dr. Johannes Rauschnabel, Engineering Pharma Processing, Bosch
			1	1	**Panel Discussion - Improving the QRM Approach**	1	1	


Product Knowledge
Product Specifications
Desired Product Performance
Product Quality Attributes
Product Design
Dosage form, stability, formulation, etc.
Process Performance
Cpk, robustness, etc.
Process Controls
Process Understanding
Quality by Design
Process Design
Unit operations, control strategy, etc.
Process Parameters
Continuous Improvement

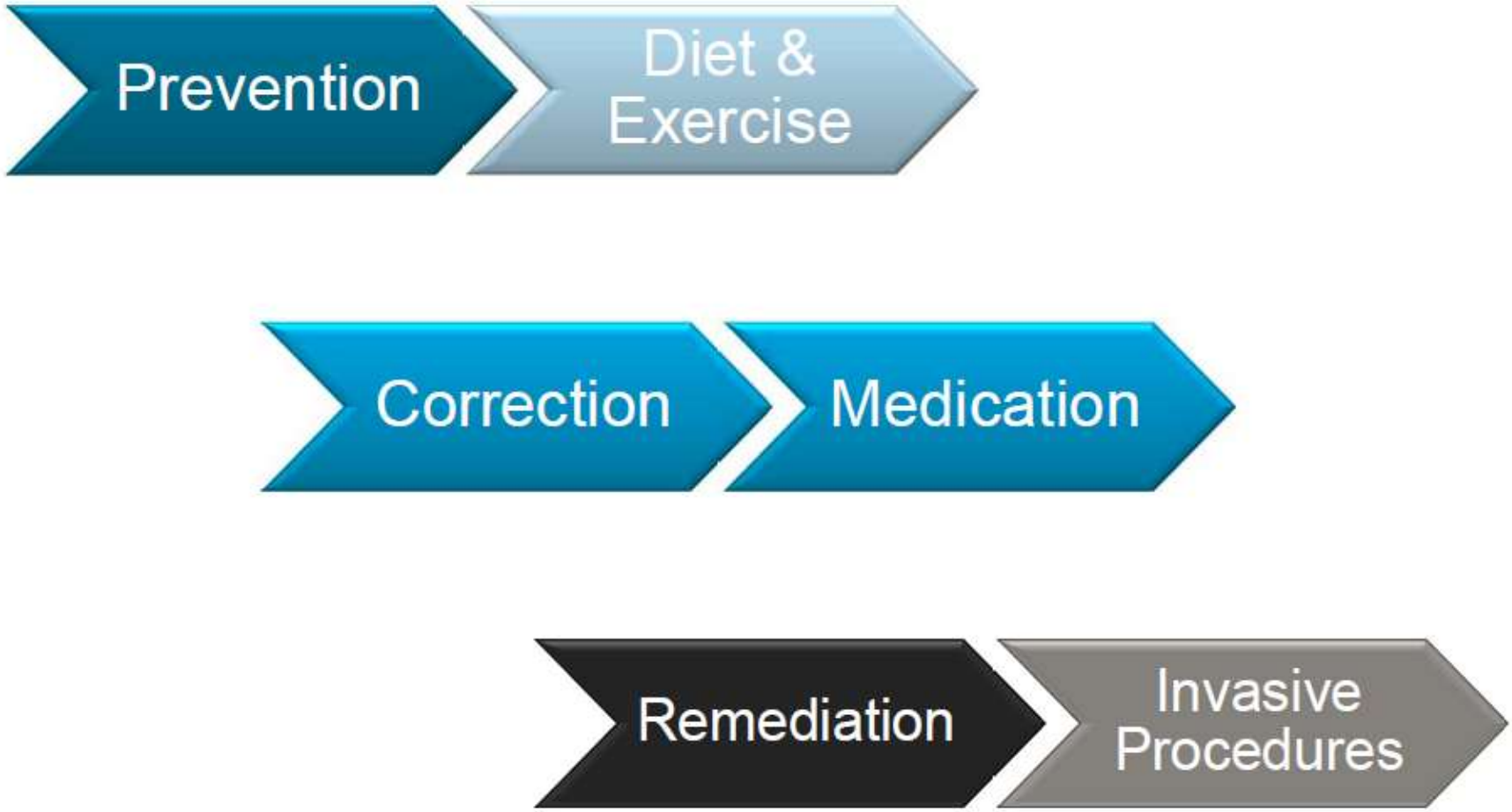
Terminology

- Quality Attributes
  - A physical, chemical, or microbiological property or characteristic of a material that directly or indirectly impacts quality
- Critical Quality Attributes (CQAs)
  - A quality attribute that must be controlled within predefined limits to ensure that the product meets its intended safety, efficacy, stability and performance
- Critical Process Parameters (CPPs)
  - A process parameter that must be controlled within predefined limits to ensure the product meets its pre-defined quality attributes

质量与法规 A1-药品质量协议	技术与创新 B1一新设施设计选择	产品生命周期 C1一生命周期起始阶段［发展］；FDA对递交文件的要求
主持人：Shane Killian, Director, *Johnson & Johnson*	主持人： Stephan Roenninger, PhD, Head External Affairs Europe, International Quality, *Amgen (Europe) GmbH*	主持人：Laurie Norwood, Deputy Director, DMPQ, CBER, *FDA*
会议主题： 随着制药企业逐步将其生产及研发外包，企业需要寻找第三方合作者或管理跨国性复杂的供应链。药品质量协议变得尤为重要。合作双方、关键供应商、服务提供方如不能明确或达到预期标准，将至双方于风险中：为违反法规"破例"、违背合同、关键	会议主题： 会议讨论产品生命再循环的方法包括：质量源于设计的概念，控制方案、只有在原料药及药品生产出来后才能实施的连续生产。本期演讲重点讨论生产设备之间的交叉污染。法规对生产不同产品相同设备的要求。专家会给出实例解释dedication，一次性技术或	会议主题： 任何产品的工艺研发都需投入大量的工作及资源。如何帮助制药企业完成药品研发及生产控制全套工作，填写的产品销售申请易于评审及评估而无需返回IND？药品上市申请需要填报哪些信息？企业提交的有关质量源于设计的信息有哪些要求？本期内

质量与法规 A2-原料药、药用辅料及组分GMP管理	技术与创新 B2—FDASIA	产品生命周期 C2—产品生命周期系统措施：研发与技术转移。
主持人：Moderator: Maria Guazzaroni Jacobs,PhD, Director – Quality and Regulatory Policy, Quality Operations, Pfizer, Inc.	主持人：David Cummings, Associate Director for Quality, CDER, FDA	主持人：Renee Kyro, Director, QA Compliance Program Management, Quality Assurance, AbbVie, Inc.
会议主题： 全球多数药品法规监管机构将ICH Q7（原料药的优良制造规范）作为原料药生产商的GMPs管理准则。但药用辅料及组分生产管理规范应当参照哪些规定执行？本期内容将探讨欧洲、美国及世卫组织对药用辅料管理规定，监管机构及制药工业的观点。解决对上述药用组分GMPs管理的风险评估。本期讨论还将呈现ICH执行机构	会议主题： 2012.7.9奥巴马总统签署了食品药品安全与创新法。本法案旨在提升评审过程管理、加强药品持续供应、提高决策机构决策过程透明度。与本法规相对应，框架性的收益风险评估方案已开始实施，提高FDA对会患者收益-风险决策的透明度。FDA及制药工业对本项立法宗旨达成共识。参会人员将了解到： 1、风险评估模型将法规管理	会议主题： 产品生命周期的核心环节是将技术研发转入商业化生产。将ICH Q8与ICH Q9的风险评估办法整合有助于企业成功实现技术转移。应用这些整合的概念将为ICH Q10引入自然生命周期并不断提高企业质量体系。本阶段将结合这些概念探讨企业经验以及监管者对产品生命周期这个核心阶段的法规要求。

How do you know your PQS is a healthy one?

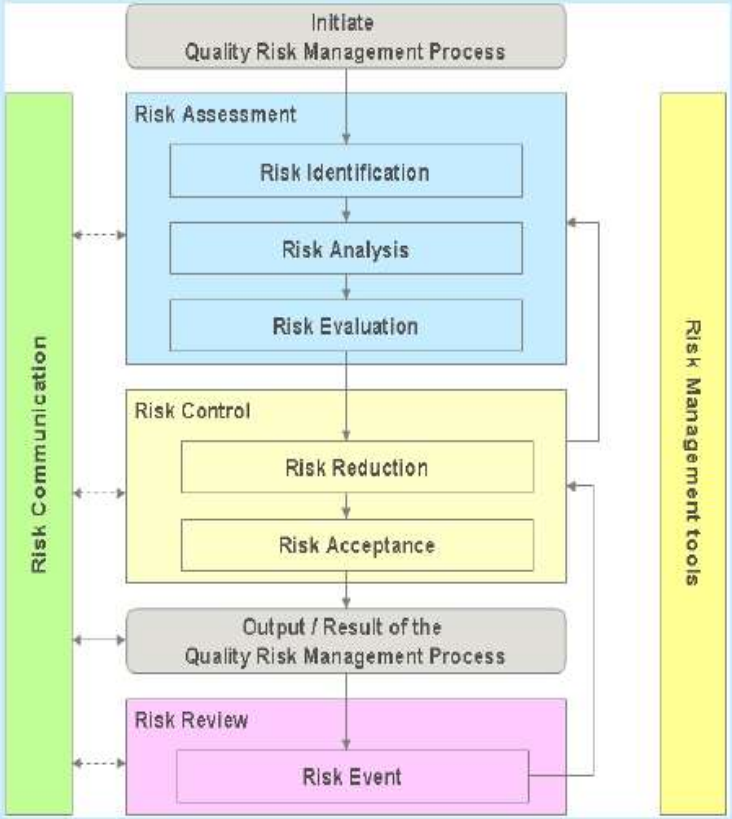


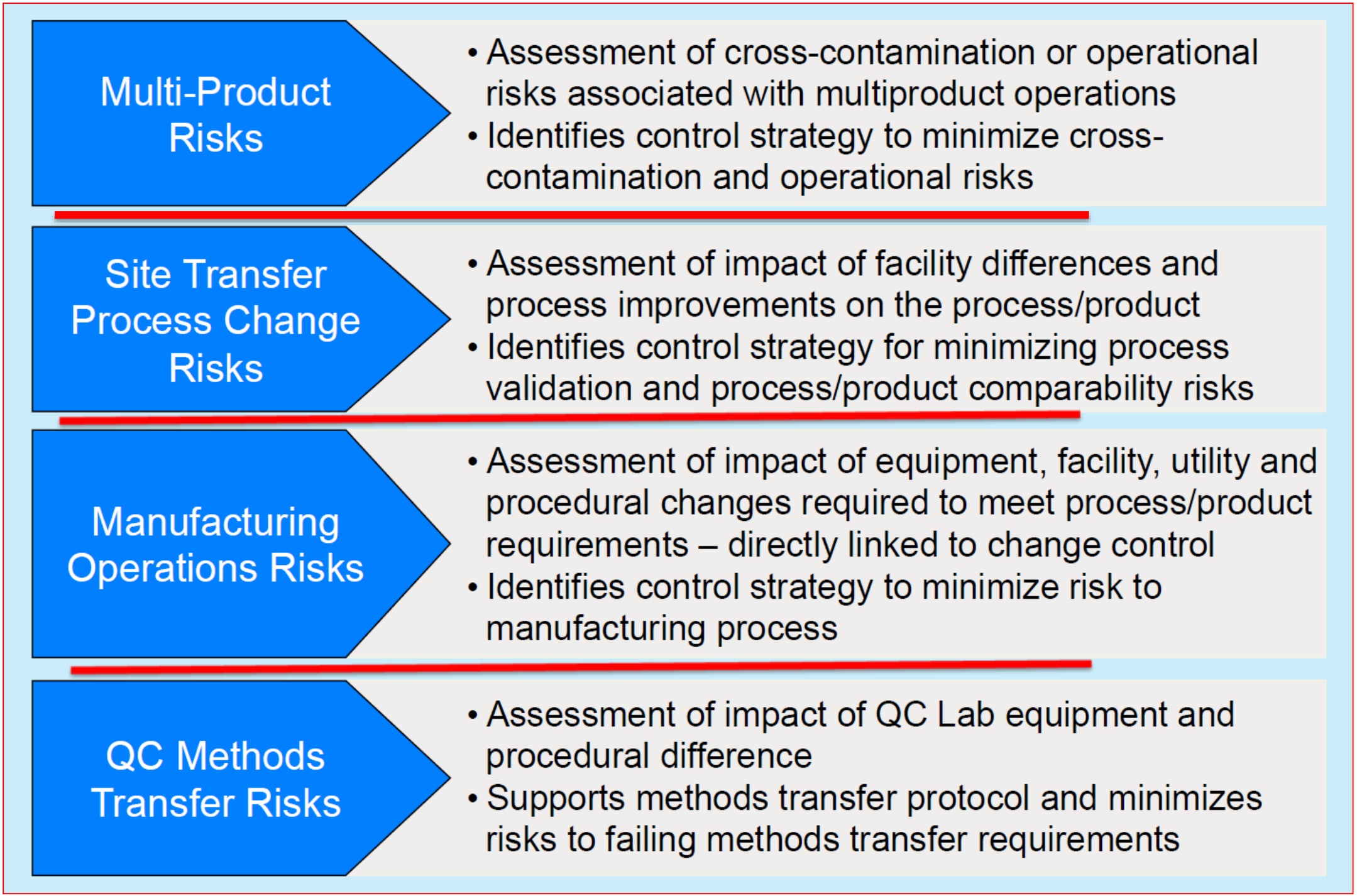
Essential Elements

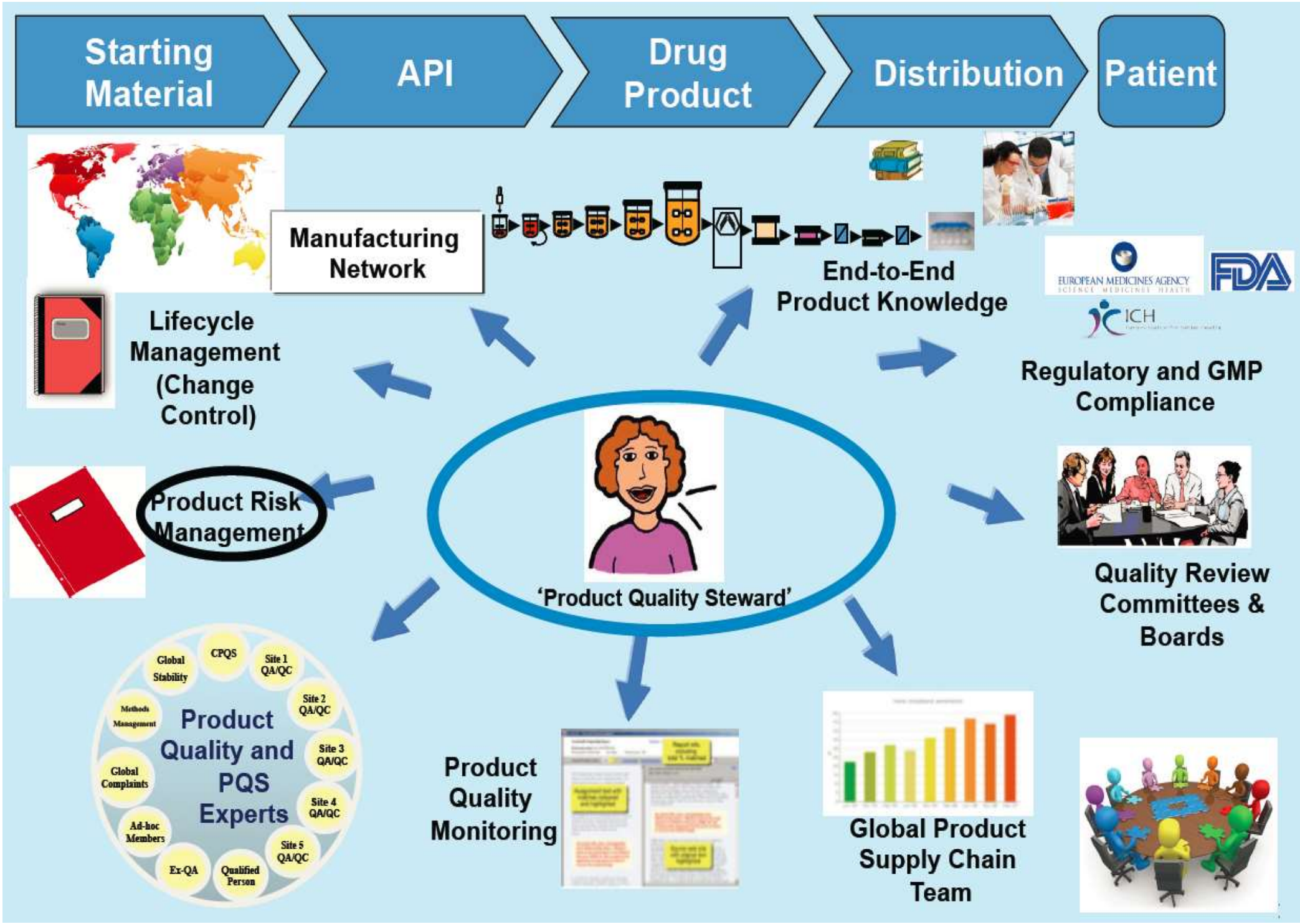
- Science and a Patient Focus
- Metrics
- Management review
- Goals and Initiatives
- Quality Plans
- Trend Monitoring
- Quality Investigations

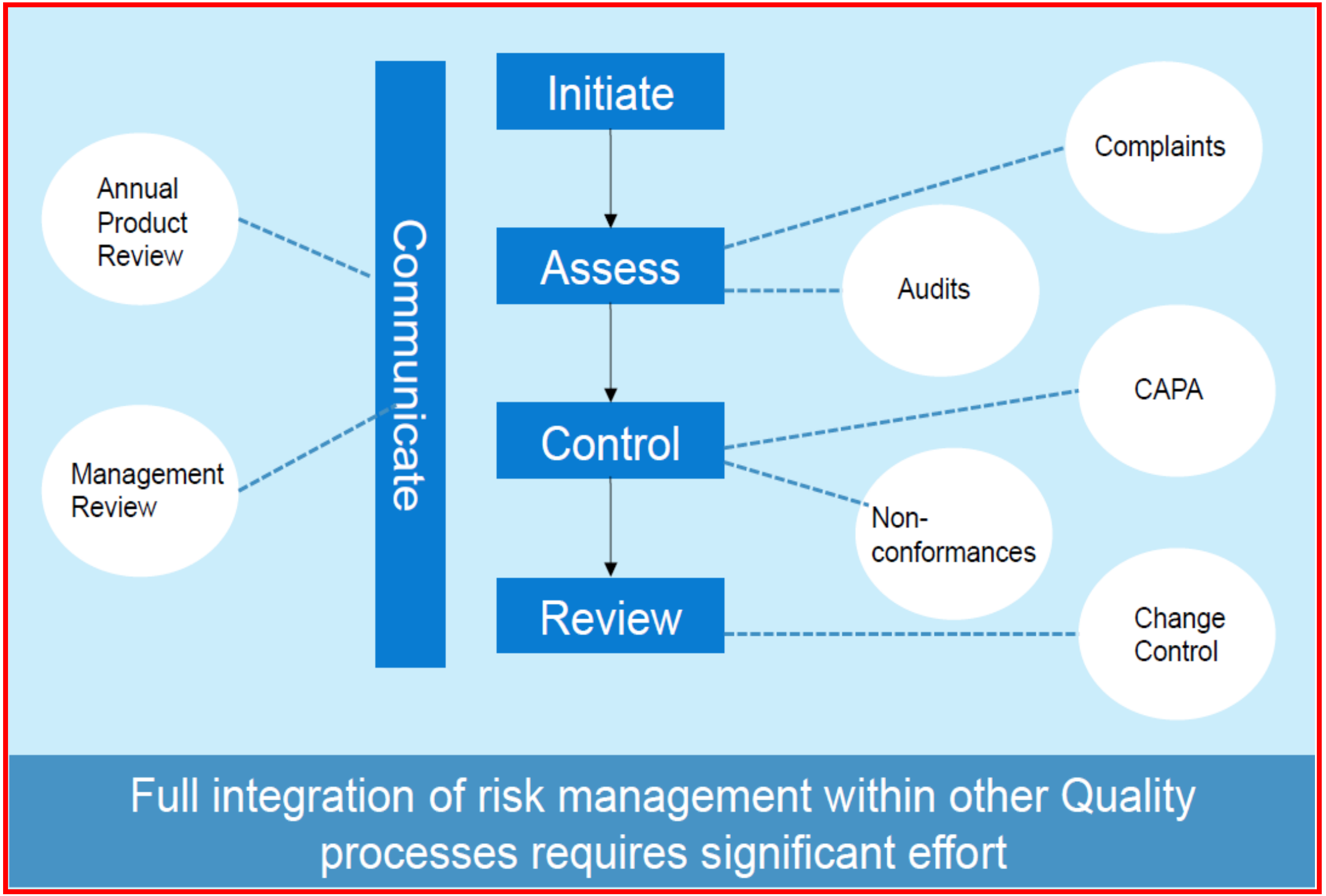
Current Status of QRM in the Industry

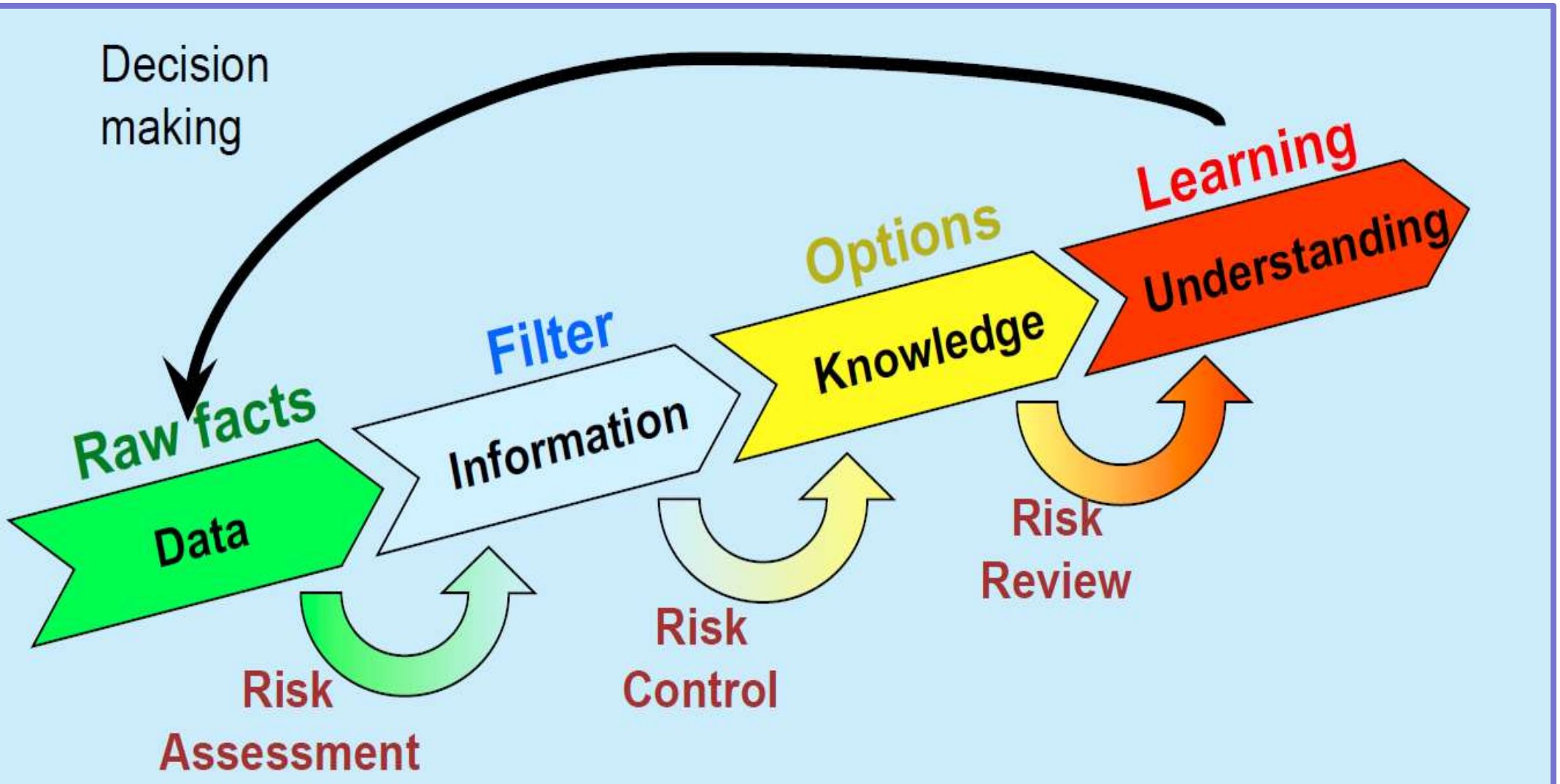
- QRM is legally enforceable (i.e. EU GMPs)
- ICH Q8, Q9 and Q10 expect:
  - QRM application throughout the product and process lifecycle
  - Integration of QRM into the Pharmaceutical Quality System (PQS)
- Regulatory agencies' focus on use of risk assessments has increased significantly
  - Increased use of risk assessments to address inspection observations
  - Inspection observations due to inadequate risk management
  - Regulators are seeking formal training on QRM
  - Increase in risk based regulatory filings (e.g. comparability protocols)




Multi-Product Risks
• Assessment of cross-contamination or operational risks associated with multiproduct operations
• Identifies control strategy to minimize cross-contamination and operational risks
Site Transfer Process Change Risks
• Assessment of impact of facility differences and process improvements on the process/product
• Identifies control strategy for minimizing process validation and process/product comparability risks
Manufacturing Operations Risks
• Assessment of impact of equipment, facility, utility and procedural changes required to meet process/product requirements – directly linked to change control
• Identifies control strategy to minimize risk to manufacturing process
QC Methods Transfer Risks
• Assessment of impact of QC Lab equipment and procedural difference
• Supports methods transfer protocol and minimizes risks to failing methods transfer requirements


Starting Material
API
Drug Product
Distribution
Patient
Manufacturing Network
End-to-End Product Knowledge
EUROPEAN MEDICINES AGENCY
FDA
ICH
Regulatory and GMP Compliance
Lifecycle Management (Change Control)
Product Risk Management
'Product Quality Steward'
Quality Review Committees & Boards
Product Quality and PQS Experts
CPQS
Site 1 QA/QC
Site 2 QA/QC
Site 3 QA/QC
Site 4 QA/QC
Site 5 QA/QC
Qualified Person
Ex-QA
Ad-hoc Members
Global Complaints
Methods Management
Global Stability
Product Quality Monitoring
Global Product Supply Chain Team

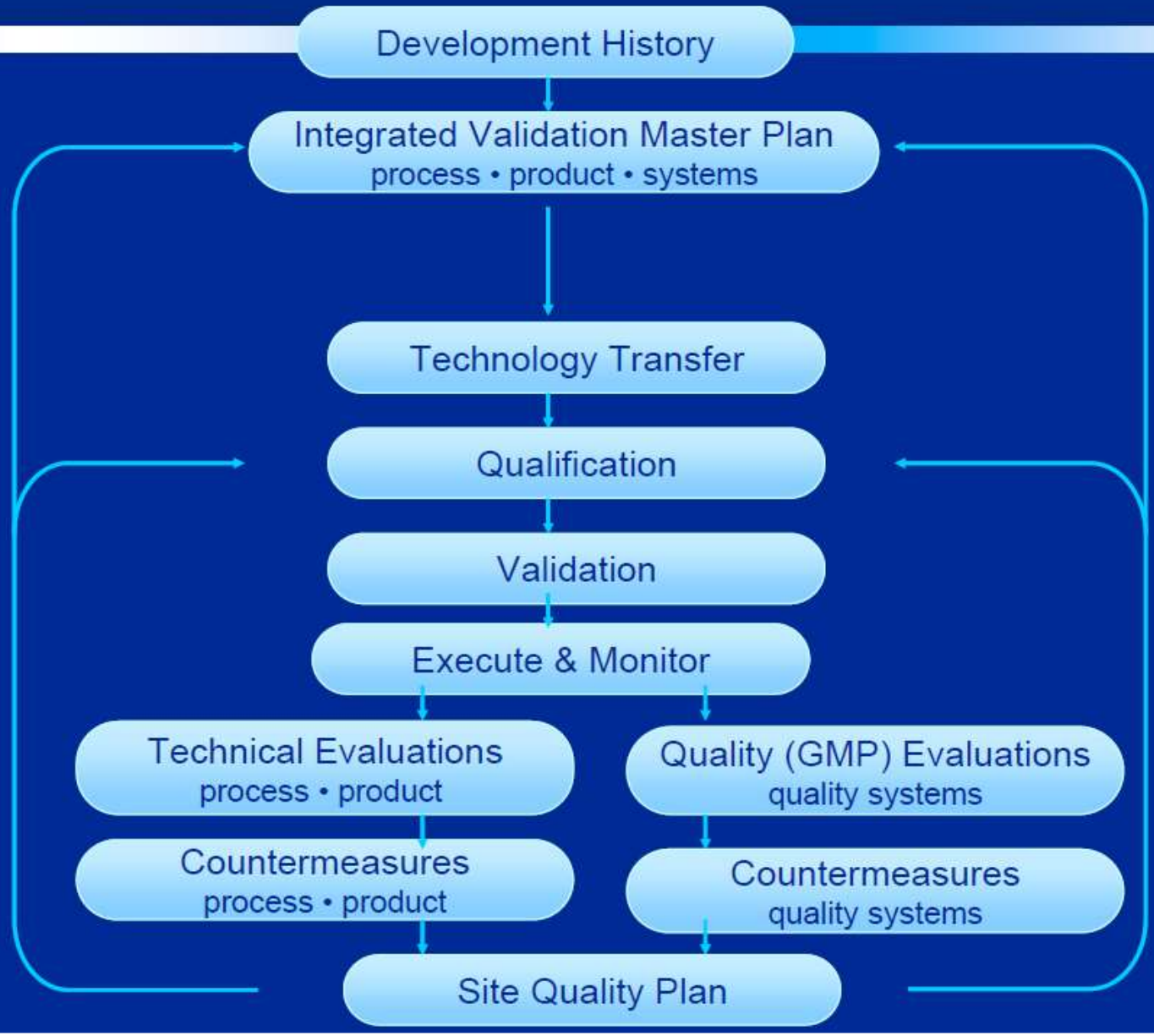

Initiate
Assess
Control
Review
Communicate
Annual Product Review
Management Review
Complaints
Audits
CAPA
Non-conformances
Change Control
Full integration of risk management within other Quality processes requires significant effort



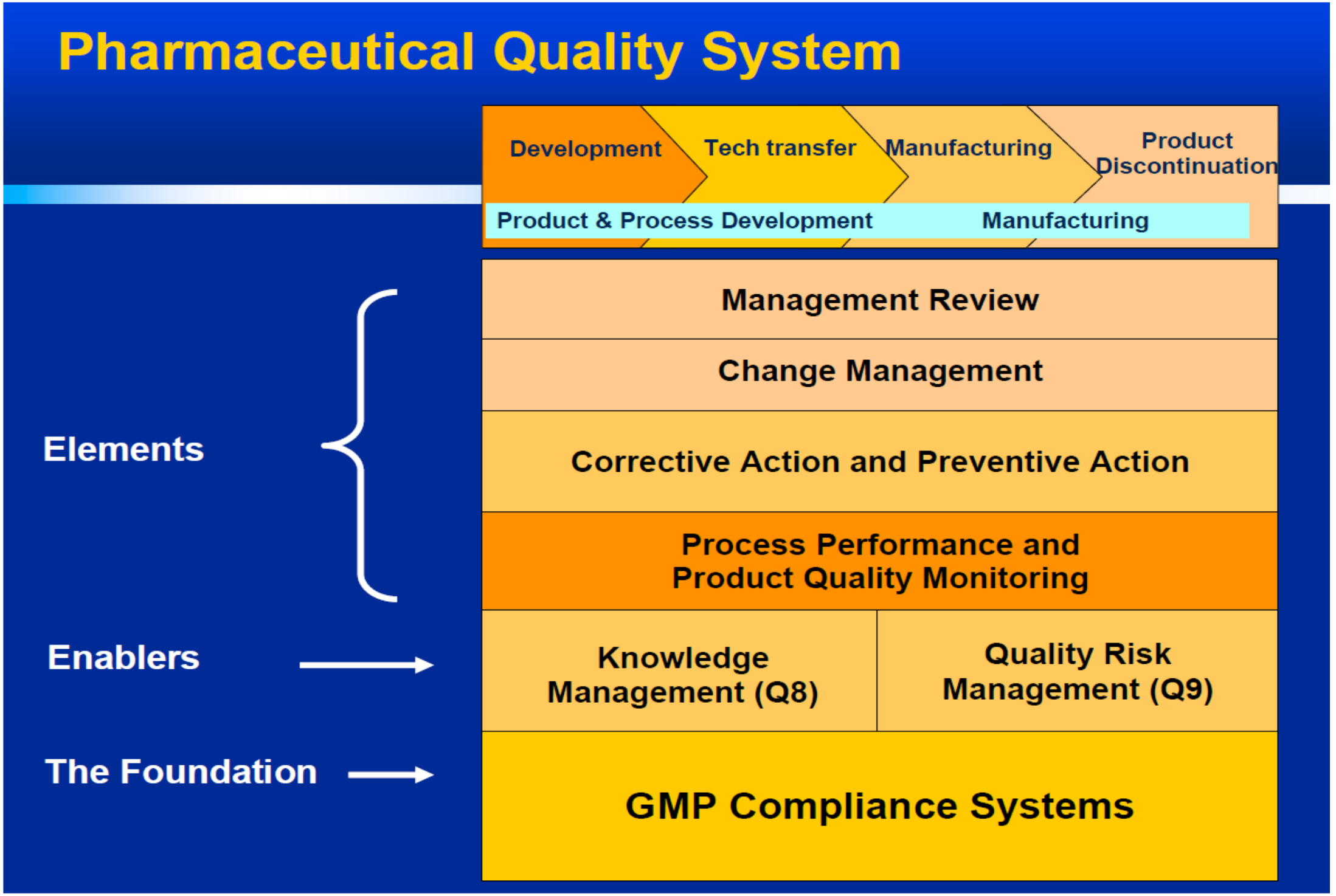
QRM and Knowledge Management as systematic activities can facilitate

- Development, implementation, maintenance of Design Space & Control Strategy
- Technology transfer
- Continual improvement of product and manufacturing processes across the life cycle
- Continual improvement of Quality System elements (including documentation)

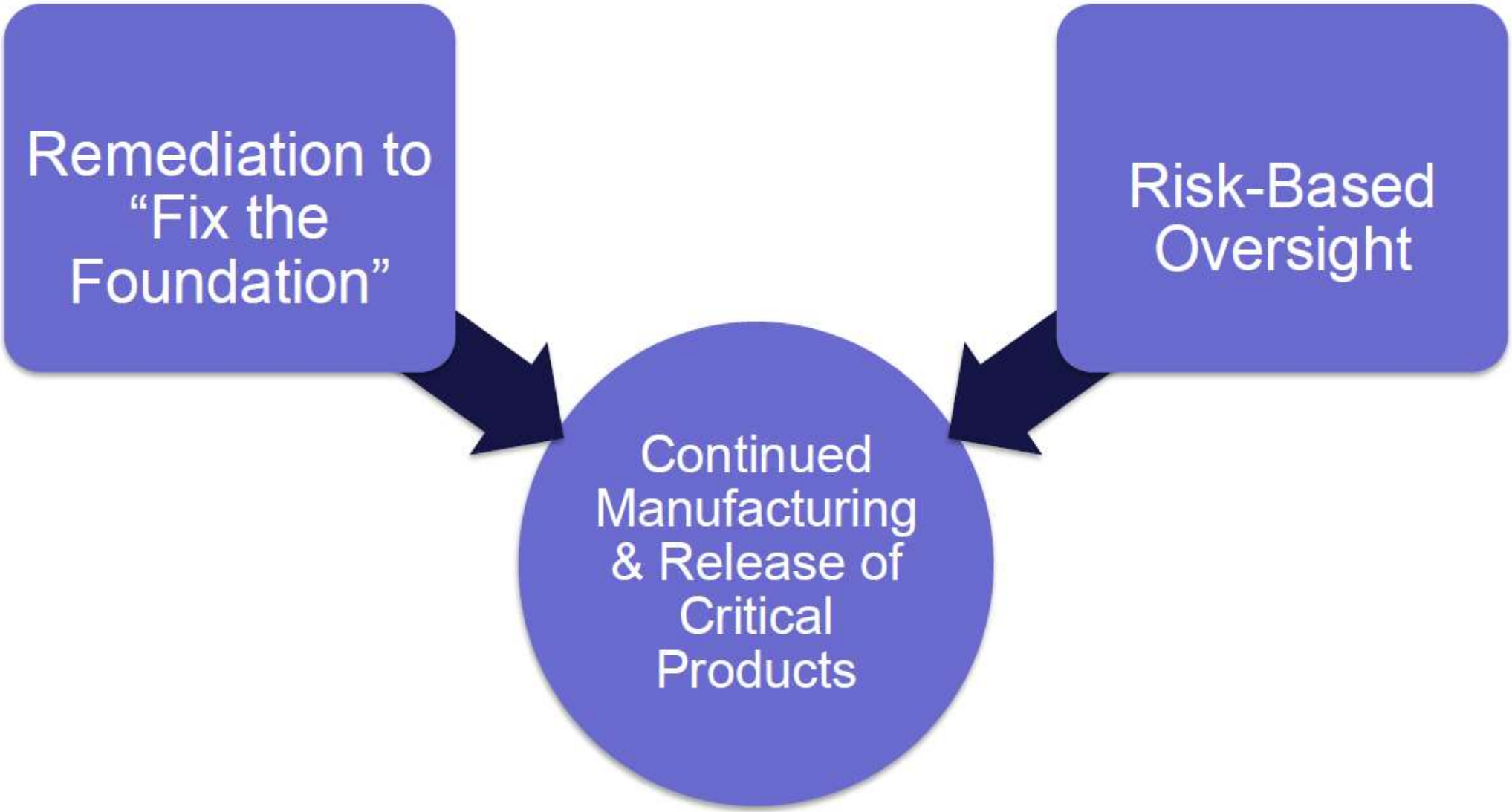
Process Control and Capability Cycle



Pharmaceutical Quality System



Integrated Design to Achieve Short- and Long-Term Quality and Compliance



Quality Strategy Plan

Objective - Ensure Sustainable Compliance as We Move Towards Quality Lifecycle Optimization

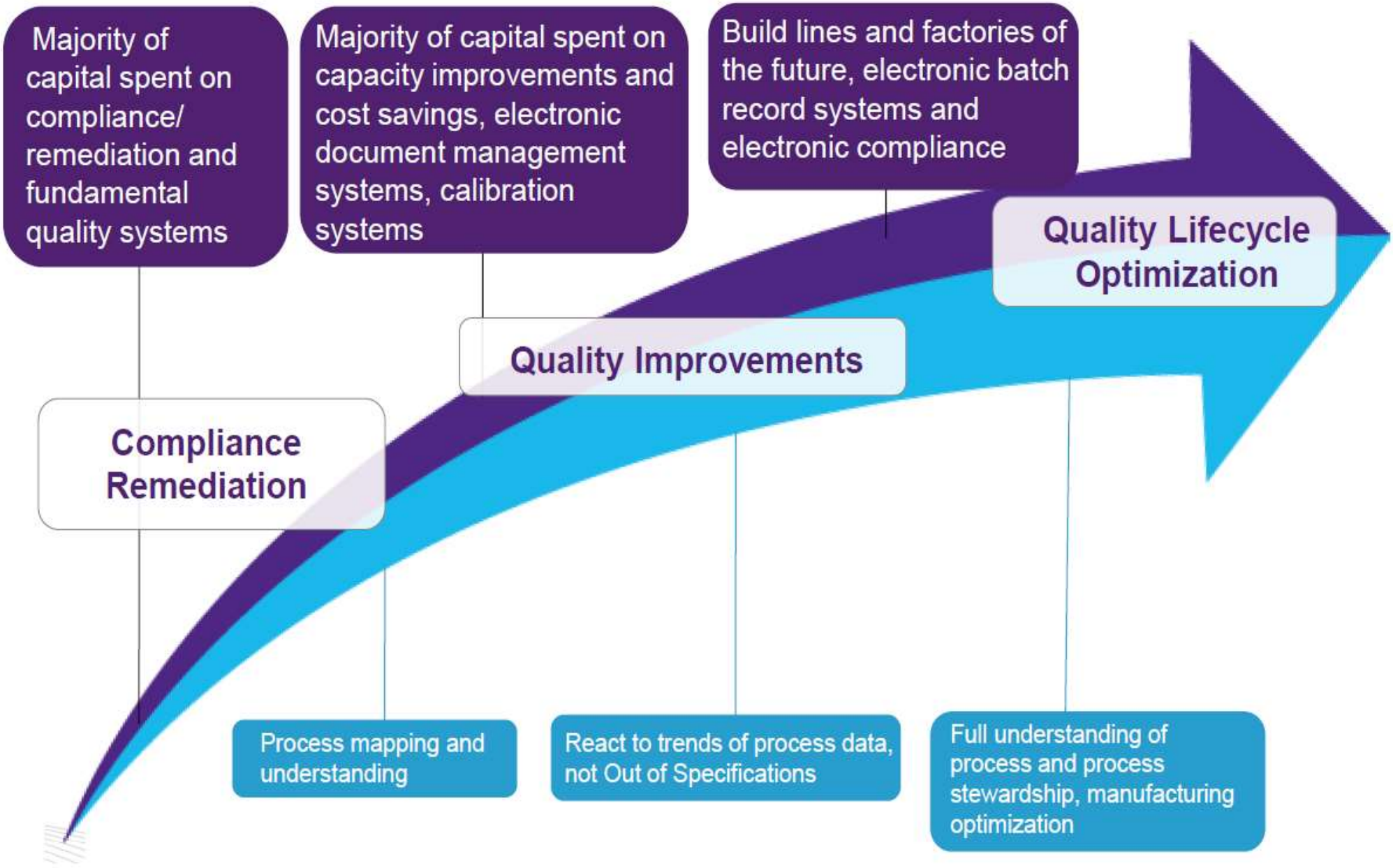
Compliance Remediation

- Ensure field compliance
- Enhance management oversight
- Strengthen
  - Global Quality Systems
  - Quality capabilities and culture
  - Supplier qualification and maintenance program

Quality Improvement

- Effective investigations assuring elimination of issues
- Supplier relationship management
- Continuous improvement management
- Strategic risk program launch

Where are we going? Quality Strategy Alignment

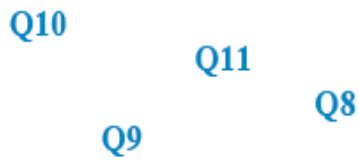


ICH Quality Guideline Q11

Development and Manufacture of APIs

Why Q11?

- New ICH Guidelines
  - Q8 Pharmaceutical Development
  - Q9 Quality Risk Management
  - Q10 Pharmaceutical Quality System



- **Concepts** of these guidelines **apply** to Drug Substance as well as Drug Product
- **Process** for manufacture of Drug Substance very **different** from Drug Product - **purification**
- Need Q11 to **clarify principles** of Q8, Q9, and Q10 as they relate to Drug Substance and provide **examples**

1. Introduction
2. Scope
3. Manufacturing Process Development
4. Description of Manufacturing Process
5. Selection of Starting Material
6. Control Strategy
7. Process Validation/Evaluation
8. Submission in CTD Format
9. Lifecycle Management
10. Illustrative Examples
11. Glossary

Regulatory Requirements and Expectations

Pharmaceutical Quality Systems

- Deviations and Failure Investigation
- CAPA
- Batch Record Review
- Change Control
- PQR / APR (Product Quality Review and Annual Product Review)
- Documentation Systems
- Risk Analysis

Current Regulatory Developments and their Impact on Quality Assurance: Challenges and Opprtunities

- ICH Q8 & Q9 – approach and implementation
- ICH Q10 - integration of the Quality Management System
- Chapter 1 of the EU-GMP Guide – implications of recent updates
- The Falsified Medicines Directive – new requirements for the Quality Management System

Documentation Systems and their Compliance with the Marketing Authorisation

- Regulatory requirements on batch documentation
- Document change management: maintaining compliance
- Records retention
- Archiving
- How to keep track of raw data/GMP relevant documentation
- Language: local language vs. English; quality of translation
- Issue/training/effective date vs. new document version

Deviation and Failure Investigation

- cGMP Requirements/ Expectations
- Deviation management - Best industry practice
- Performing Failure Investigations – practical approaches (interdisciplinary teams, differential diagnose, visualisation, mind mapping)
- Recommendations for a good report
- Business Process Failure Investigation – What to define in the local procedure?

CAPA System

- Philosophy and background
- cGMP requirements and expectations
- CAPA Subsystems
- Success factors for an integrated system
- Industry approaches for CAPA Systems

Batch Record Review

- Steps to consider for a successful BRR
- Responsibilities: manufacturer vs. supplier vs. contractor and QA vs. production vs. lab
- KPIs: examples and possible improvements to reduce review cycles times
- Deviations: how to handle during BRR/ transfer into CAPA system/ impact on batch release

Change Control

- What is affected by Change Control?
- The process of Change Control
- Emergency changes
- Change Management in a global environment

Product Quality Review and Annual Product Review as Quality Enhancement Tools

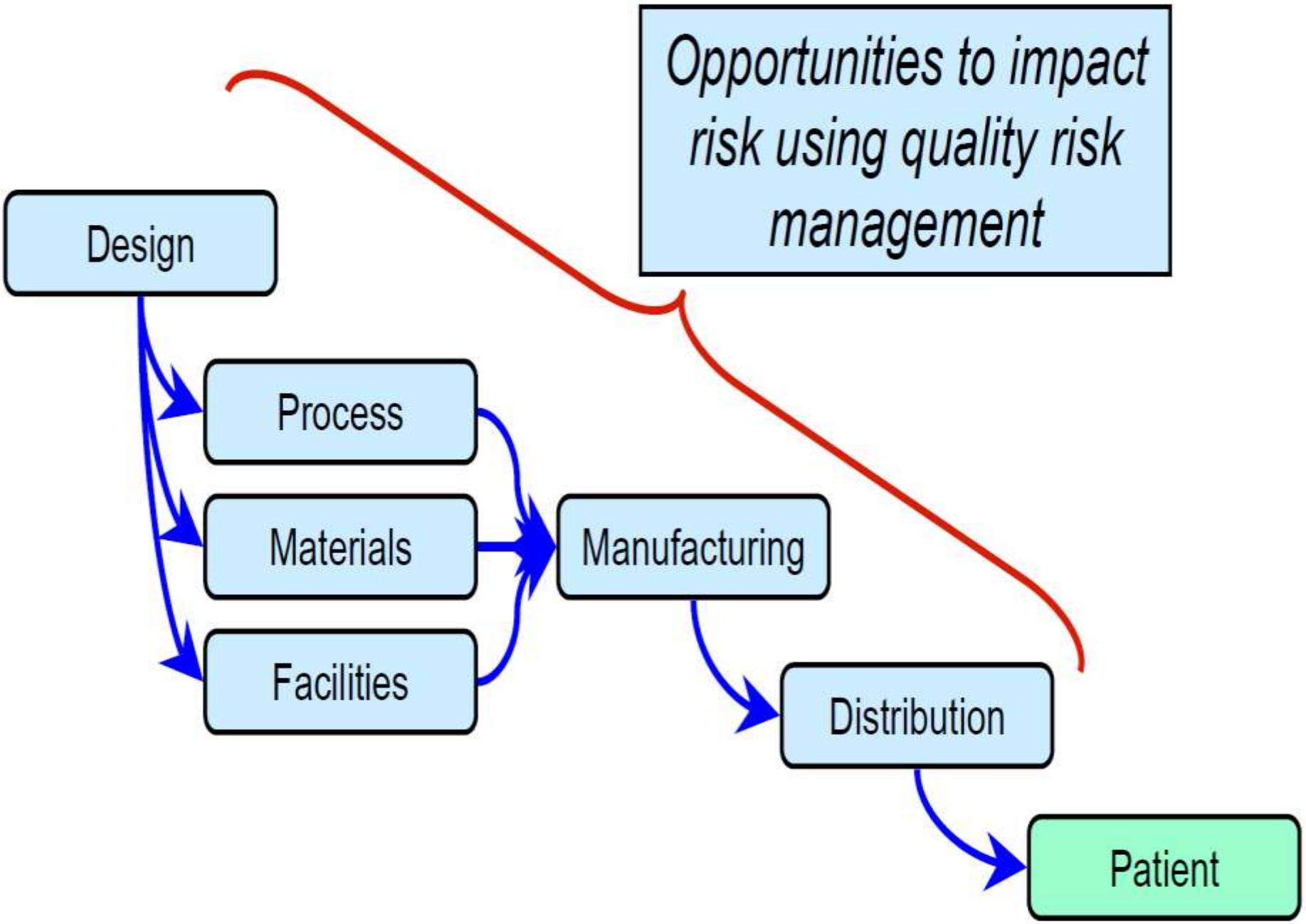
- Best practices in combining the two reviews
- Statistical background and trending
- Timing of PQRs with discussion around product groupings
- Responsibilities: who is responsible for generation of particular parts of the report, analysis and final conclusion
- Site specific versus product specific PQR
- Challenges and recommendations to overcome challenges
- Examples and case studies

Risk Analysis and Management

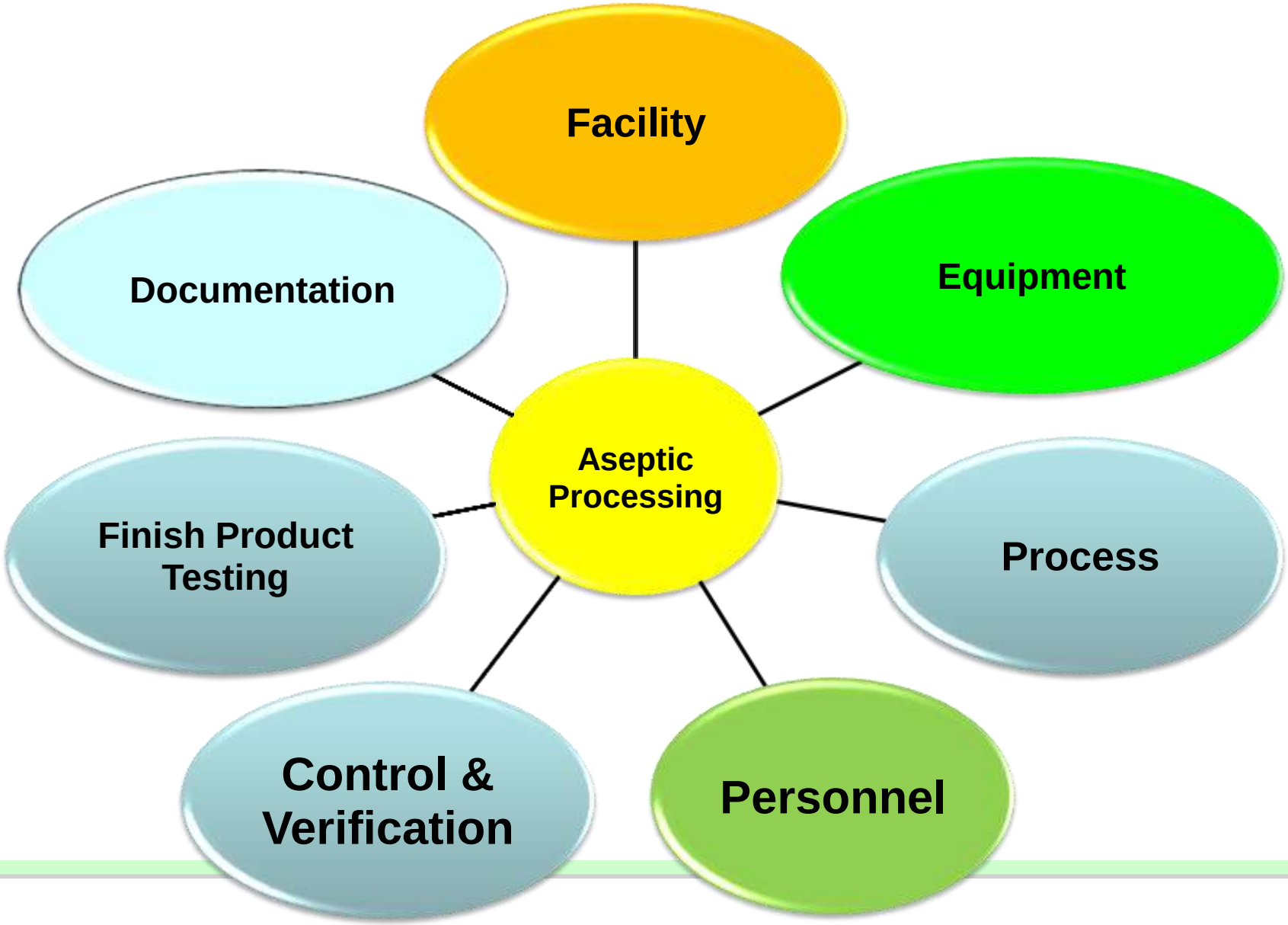
- The Principles of Risk Analysis
- A detailed look at FMEA and HACCP
- How to apply ICH Q9 "Quality Risk Management"
- Process improvement with Risk Analysis

- Deviations and CAPA
- Integration of a Pharmaceutical Quality System
- Risk-based Supplier Qualification

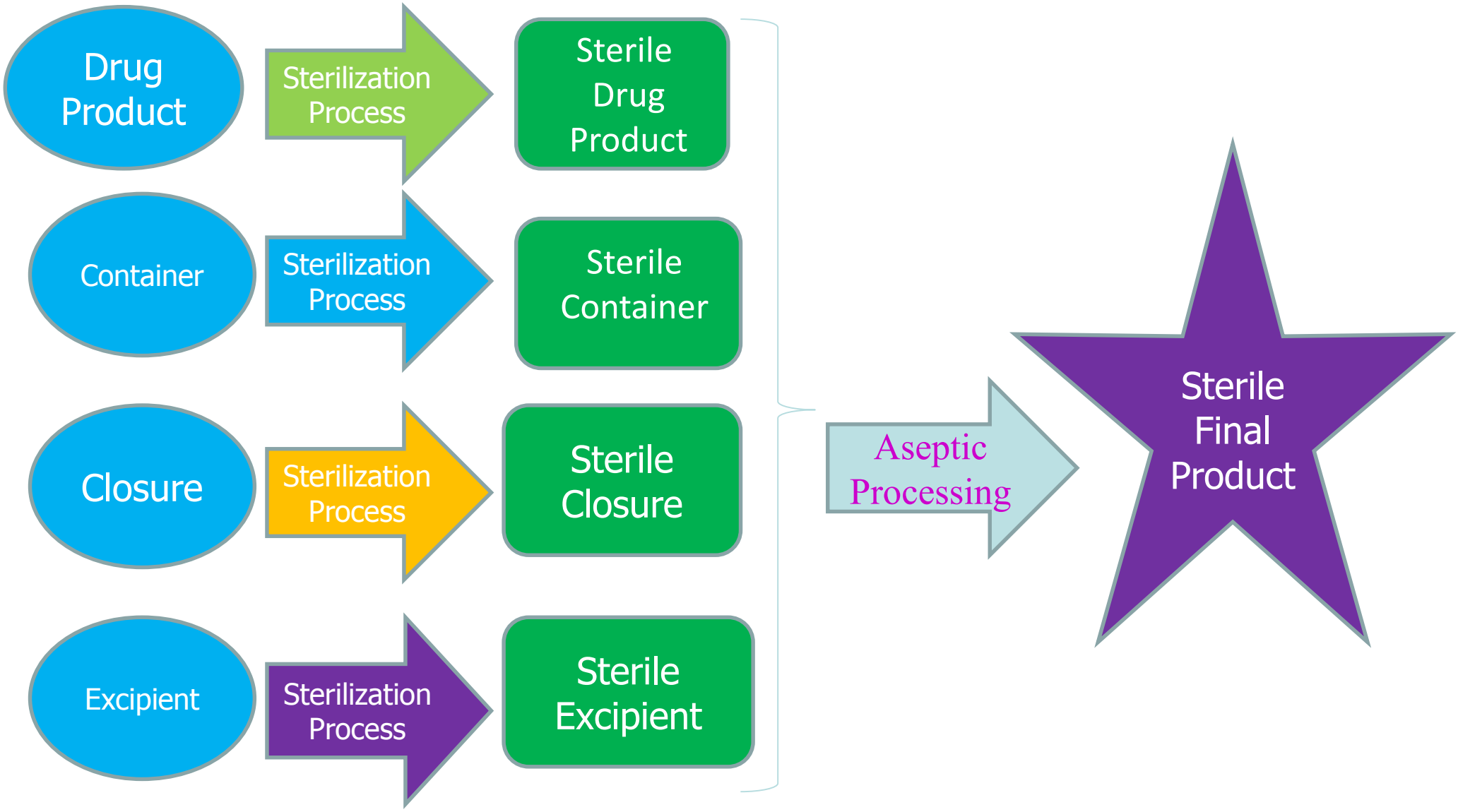
1) **Deviations - Failure Investigation - CAPA**
2) **Integration of a Pharmaceutical Quality System: What does it mean in practice?**
3) **Risk Management in Supplier Qualification:**
   How to reduce the effort of qualification without losing control and become non-compliant


Opportunities to impact risk using quality risk management
Design
Process
Materials
Facilities
Manufacturing
Distribution
Patient

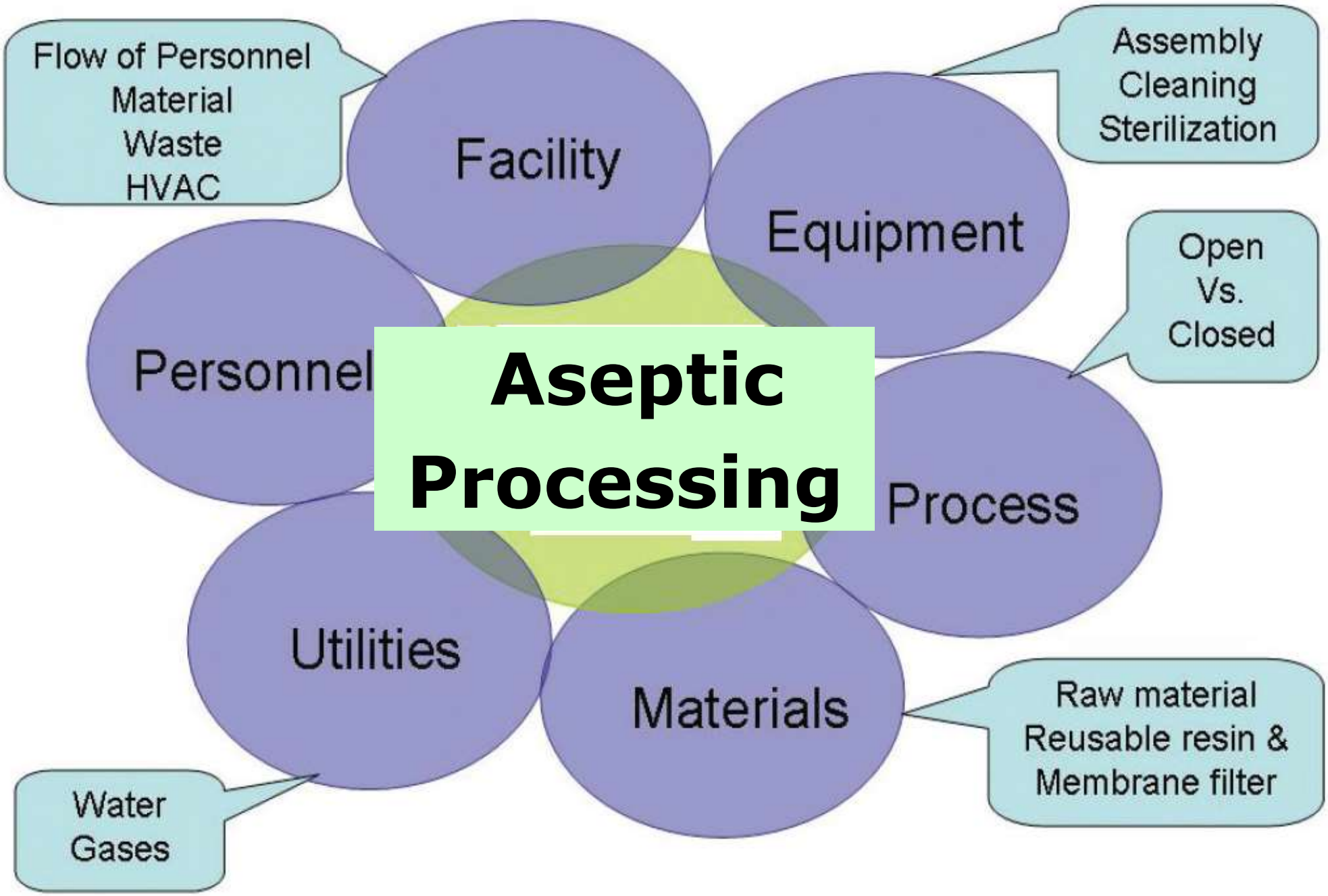
Aseptic Processing: Essential Elements

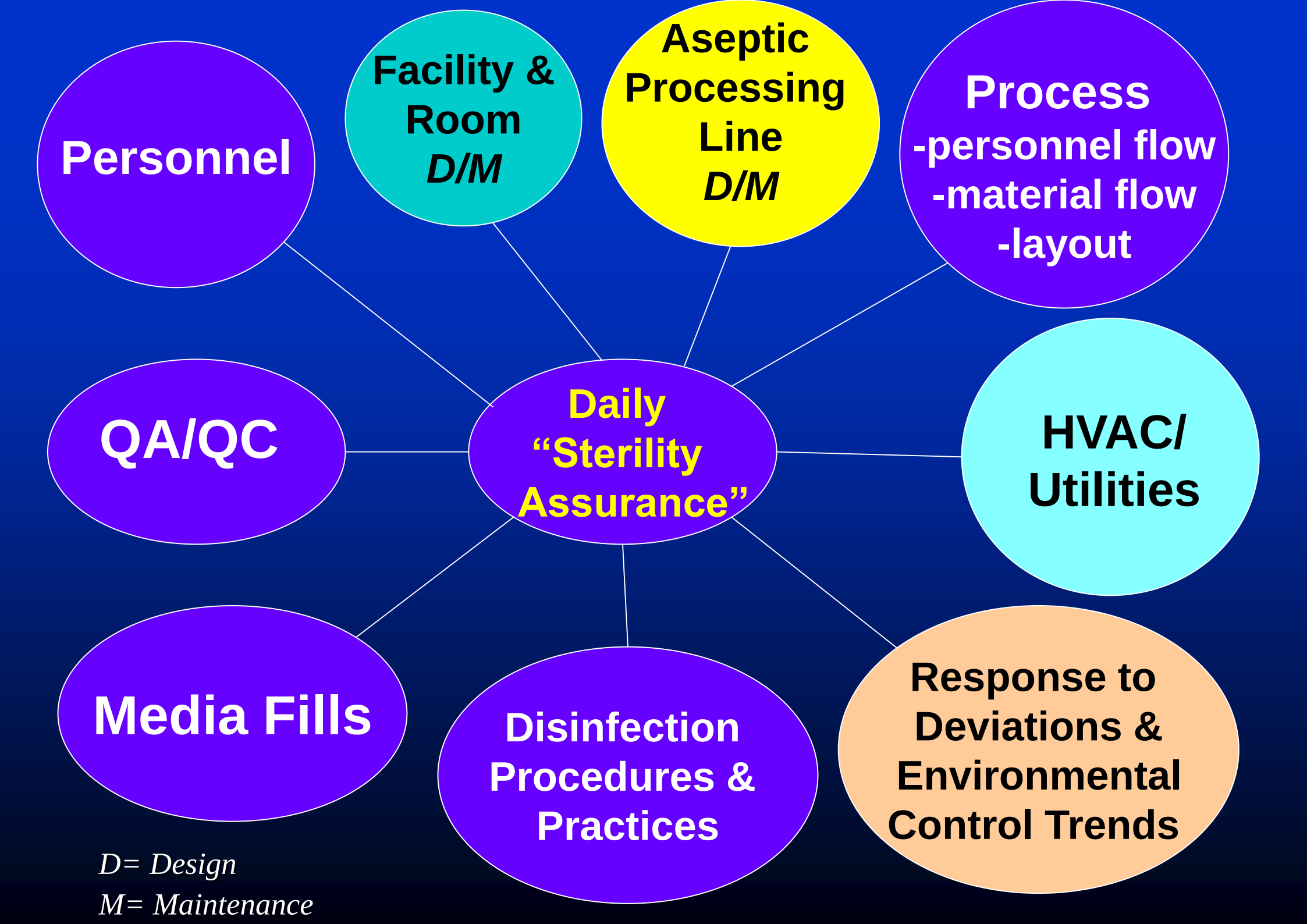


Aseptic Processing



Can use multiple sterilization processes each optimized for the individual component


Flow of Personnel
Material
Waste
HVAC
Facility
Assembly
Cleaning
Sterilization
Equipment
Open
Vs.
Closed
Personnel
Aseptic
Processing
Process
Utilities
Materials
Raw material
Reusable resin &
Membrane filter
Water
Gases


Personnel
Facility & Room D/M
Aseptic Processing Line D/M
Process -personnel flow -material flow -layout
QA/QC
Daily "Sterility Assurance"
HVAC/ Utilities
Media Fills
Disinfection Procedures & Practices
Response to Deviations & Environmental Control Trends
D= Design
M= Maintenance

Pharma Project Lifecycle

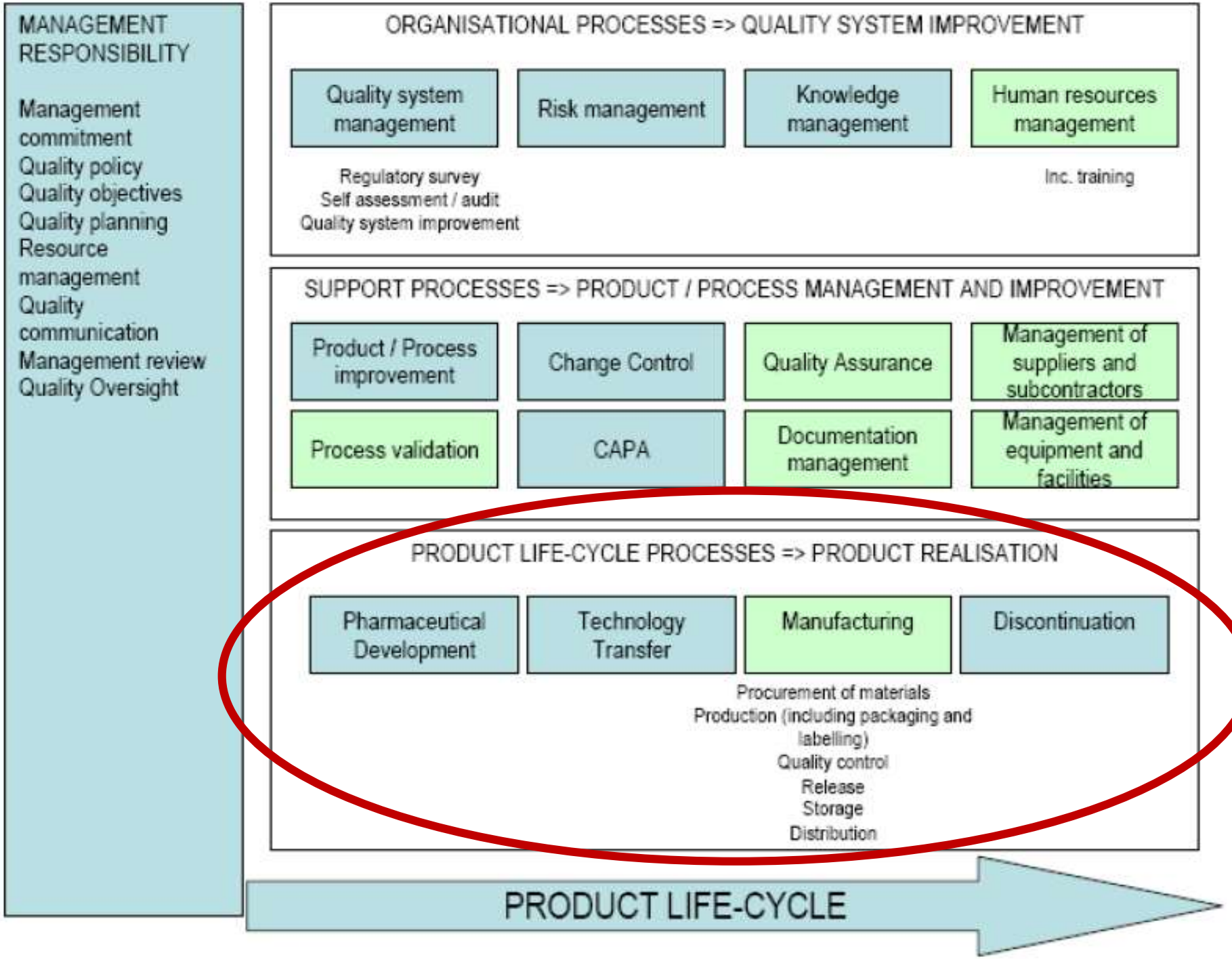
Product

Life Cycle Management

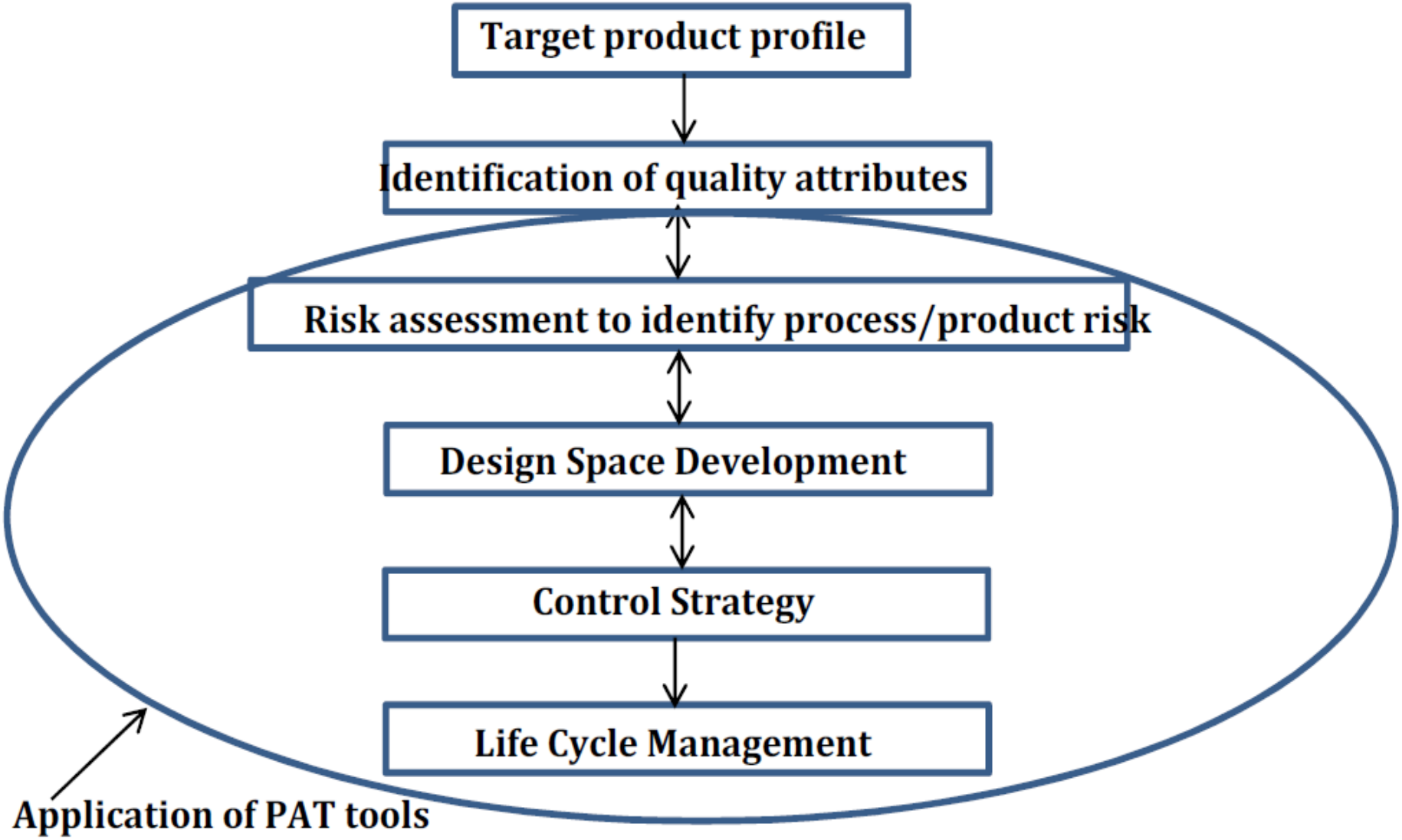
decrease footprint, create opportunities and make value

The pillars of a robust aseptic process

- Facilities design
- HVAC validation
- Material / component transfer
- Process simulation (media fills)
- Personnel training & monitoring
- Environmental monitoring


MANAGEMENT RESPONSIBILITY
Management commitment
Quality policy
Quality objectives
Quality planning
Resource management
Quality communication
Management review
Quality Oversight
ORGANISATIONAL PROCESSES => QUALITY SYSTEM IMPROVEMENT
Quality system management
Risk management
Knowledge management
Human resources management
Regulatory survey
Self assessment / audit
Quality system improvement
Inc. training
SUPPORT PROCESSES => PRODUCT / PROCESS MANAGEMENT AND IMPROVEMENT
Product / Process improvement
Change Control
Quality Assurance
Management of suppliers and subcontractors
Process validation
CAPA
Documentation management
Management of equipment and facilities
PRODUCT LIFE-CYCLE PROCESSES => PRODUCT REALISATION
Pharmaceutical Development
Technology Transfer
Manufacturing
Discontinuation
Procurement of materials
Production (including packaging and labelling)
Quality control
Release
Storage
Distribution
PRODUCT LIFE-CYCLE

QbD (quality by design) as part of Product Life Cycle Management



Life Cycle Approach to Aseptic Process Validation

Process Design		Process Qualification	Process Verification
Parameter or condition	**Control strategy**	**Process Qualification Test**	**Continued Process Verification**
Personnel/interventions	HEPA air positioning and flow, aseptic technique	Unidirectional air velocity, smoke/air flow profile studies, personnel qualifications, aseptic process simulations	Process observation, personnel monitoring, sterility test results
Environmental condition	HEPA air flow, room pressurization, clean room temperature and humidity, sanitization	HVAC qualification, HEPA certification, clean room qualification, disinfection qualification	Environmental monitoring results, differential pressures, periodic clean room certification

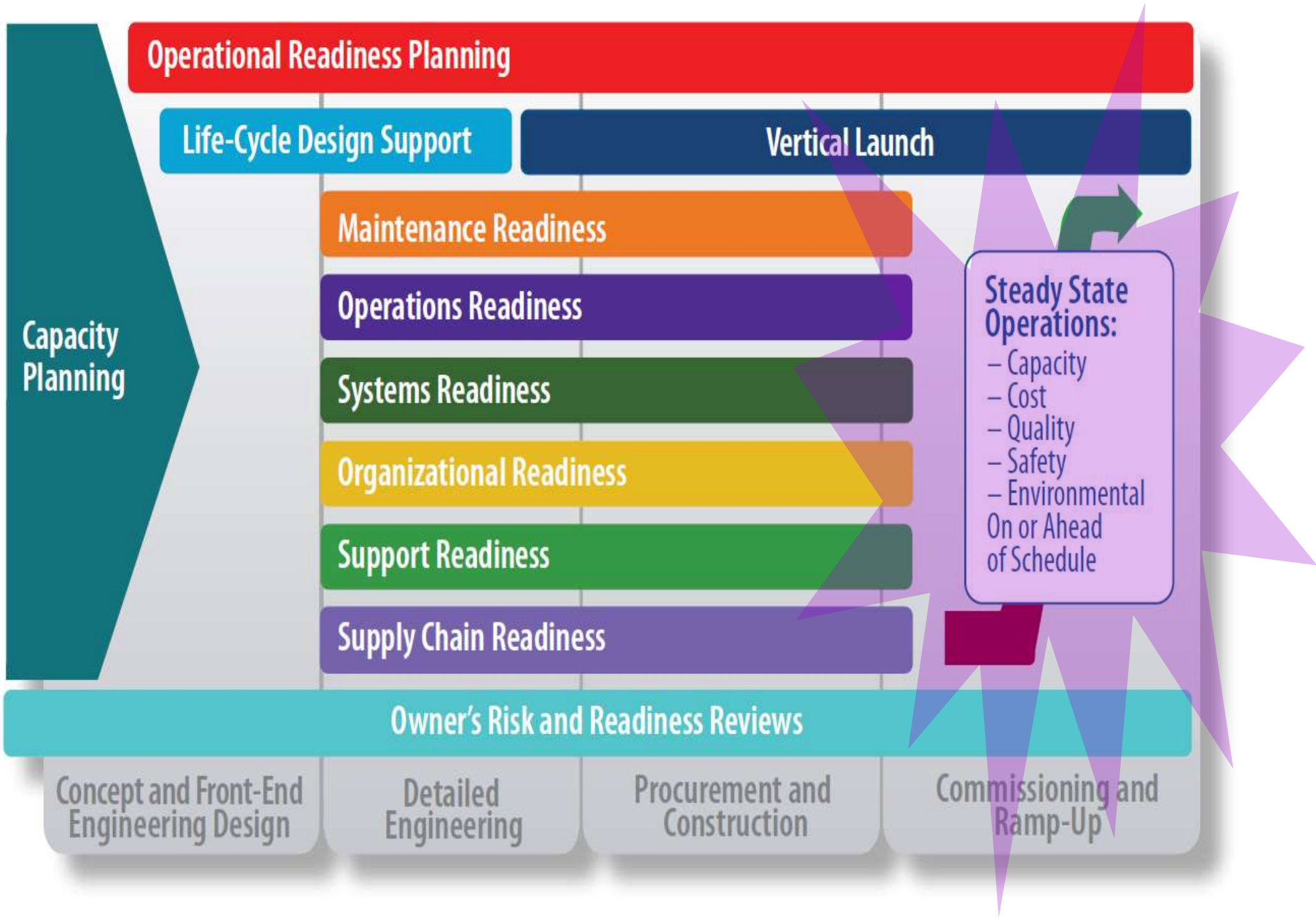
Life Cycle Approach to Aseptic Process Validation

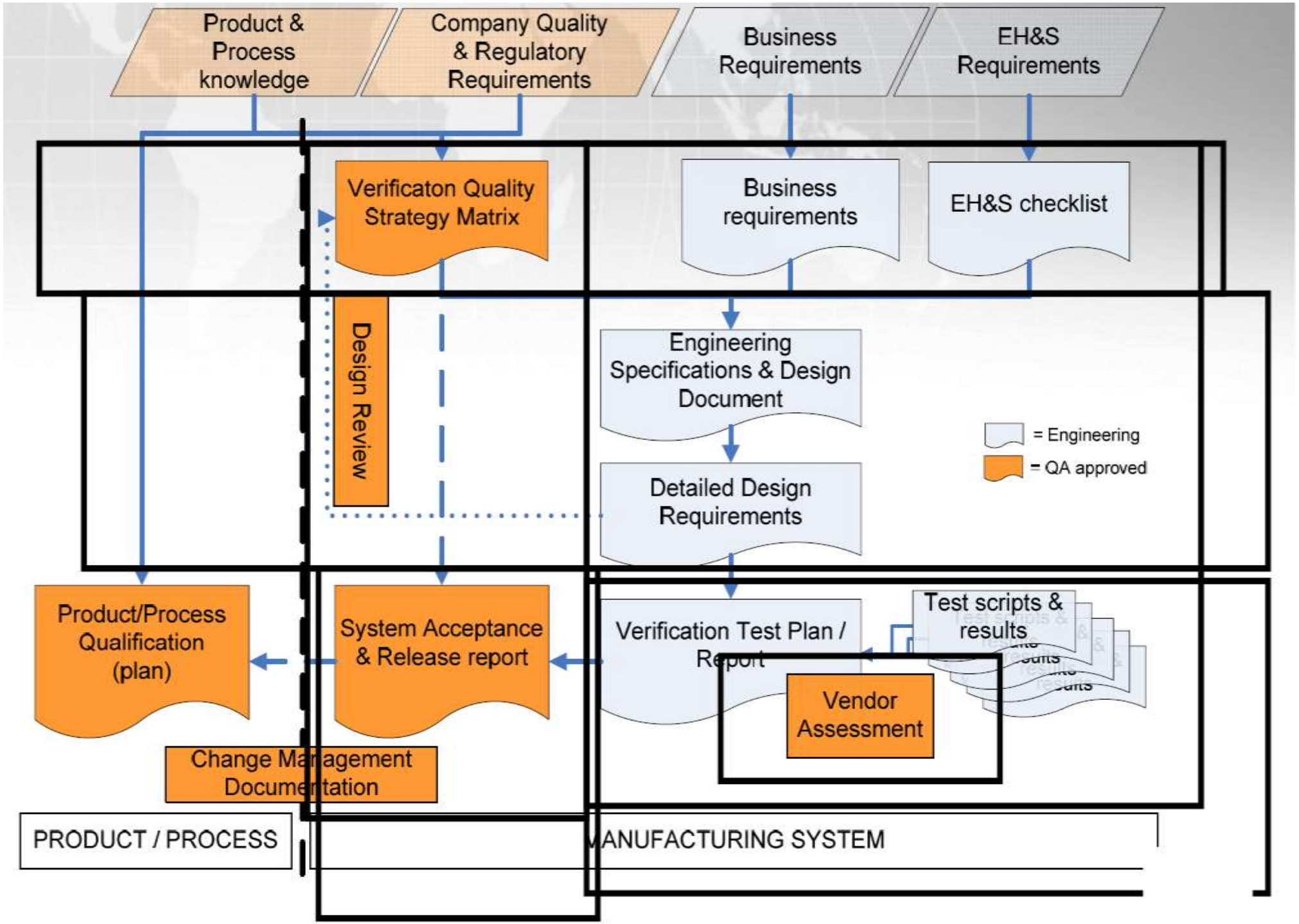
Process Verification

Sterility of product and product contact surfaces/parts/components	Sterilization procedure, bioburden, component wrapping, handling, and holding	Clean Steam system qualification, steam in place qualification, autoclave qualification, sterilized parts hold time studies	Sterility test results, bioburden monitoring, periodic requalification of utilities and equipment
Condition of non-product contact surfaces	Cleaning and sanitization	Disinfectant efficacy, cleaning and sanitization qualification	Environmental monitoring results
Production yields and quality of output	Filling process speed and duration	Fill line qualification, aseptic process simulations	Production yields, analysis of product defects and rejection rates, production downtime, customer feedback/complaints

Process Design

Process Qualification


Operational Readiness Planning
Life-Cycle Design Support
Vertical Launch
Capacity Planning
Maintenance Readiness
Operations Readiness
Systems Readiness
Organizational Readiness
Support Readiness
Supply Chain Readiness
Steady State Operations:
– Capacity
– Cost
– Quality
– Safety
– Environmental
On or Ahead of Schedule
Owner's Risk and Readiness Reviews
Concept and Front-End Engineering Design
Detailed Engineering
Procurement and Construction
Commissioning and Ramp-Up


Product & Process knowledge
Company Quality & Regulatory Requirements
Business Requirements
EH&S Requirements
Verificaton Quality Strategy Matrix
Business requirements
EH&S checklist
Design Review
Engineering Specifications & Design Document
= Engineering
= QA approved
Detailed Design Requirements
Product/Process Qualification (plan)
System Acceptance & Release report
Verification Test Plan / Report
Test scripts & results
Vendor Assessment
Change Management Documentation
PRODUCT / PROCESS
MANUFACTURING SYSTEM

ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification

ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry

ISPE Good Practice Guide: Interactive Response Technology
(electronic format only)

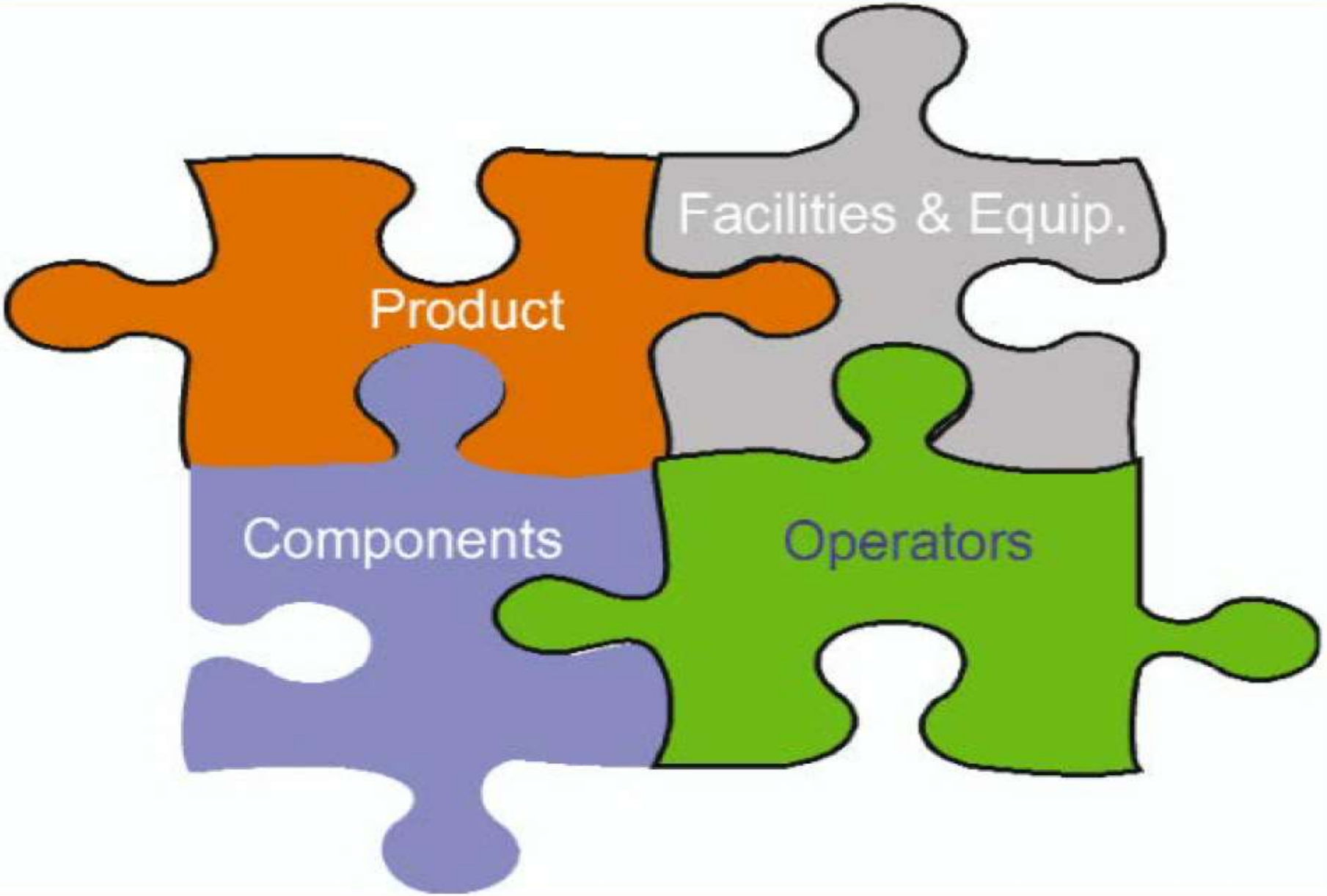
ISPE Baseline® Guide: Sterile Product Manufacturing Facilities (Second Edition)

ISPE Baseline® Guide: Water and Steam Systems Guide (Second Edition)

ISPE Guide Series: (PQLI®)
Part 1 – Product Realization using QbD, Concepts and Principles

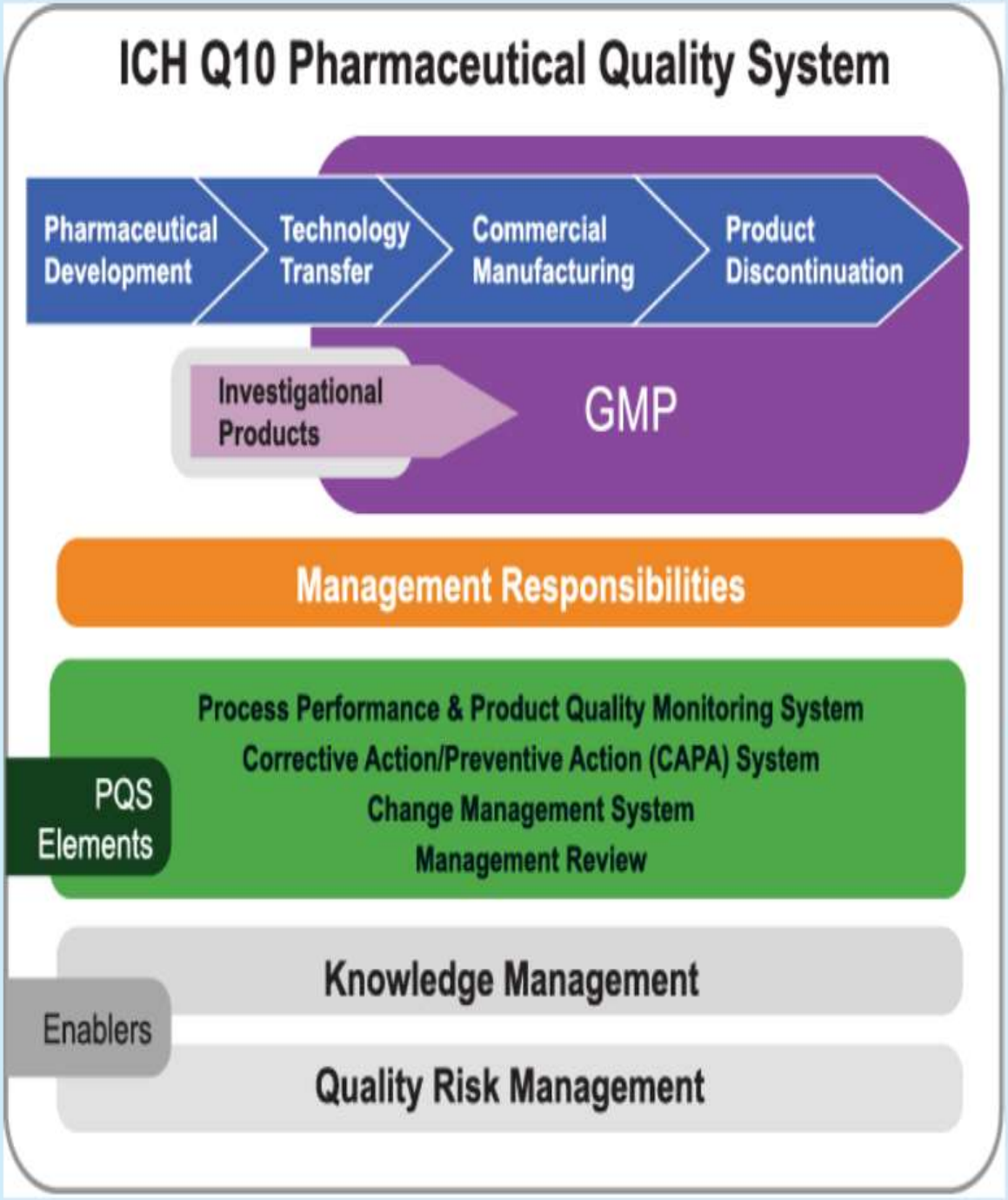
Part 2 – Product Realization using QbD, Illustrative Example

Aseptic process interrelationships



Process Life Cycle Management

	Early Stage Dev	Late Stage Dev	Commercial Mfg
Process Knowledge	Nascent	Evolving	Maturing
Process Performance	Variable	Improving	Robust
Tech Transfer Objectives	Process Definition	Registration/ Commercialization	Replication Across Sites

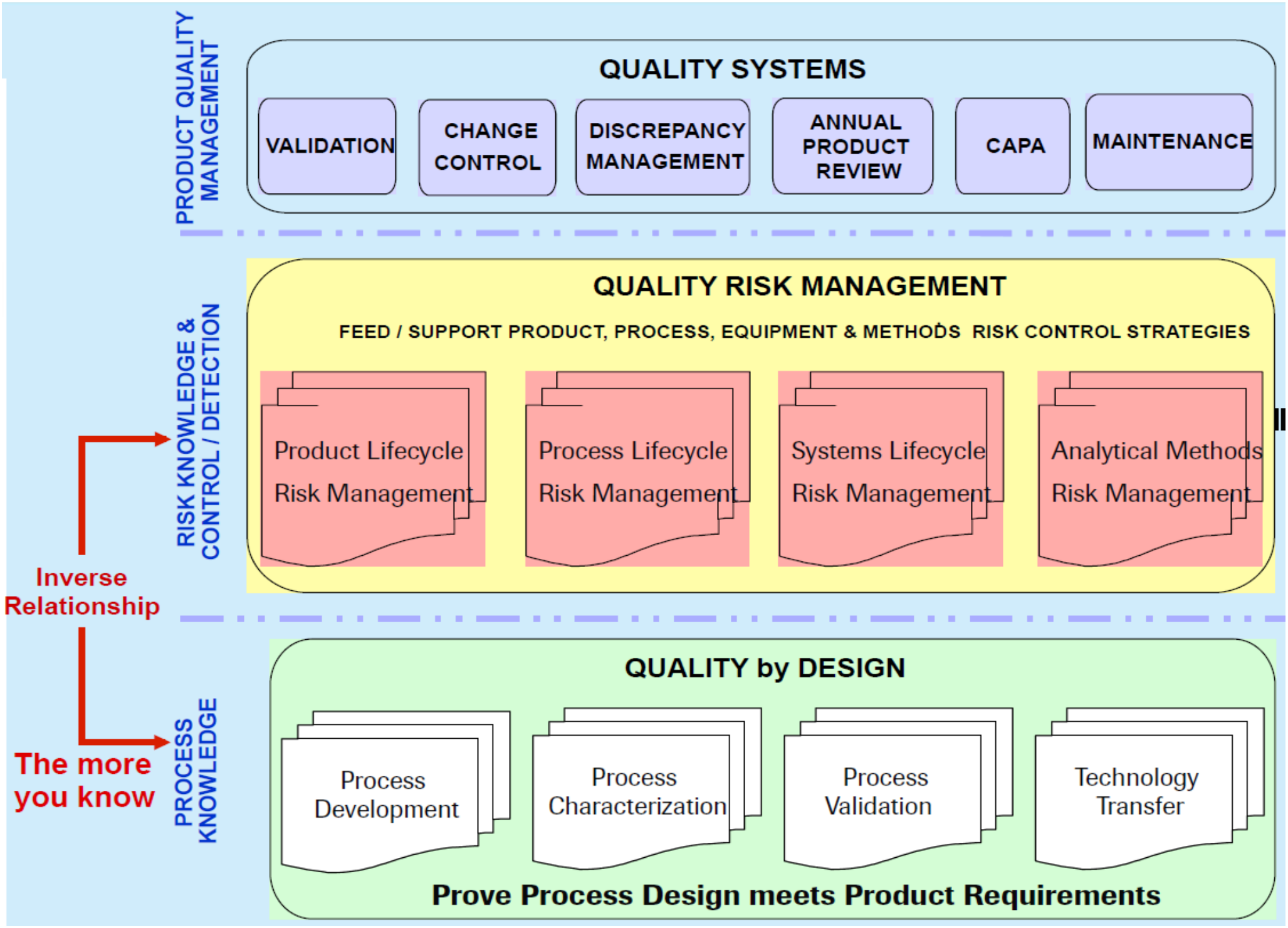


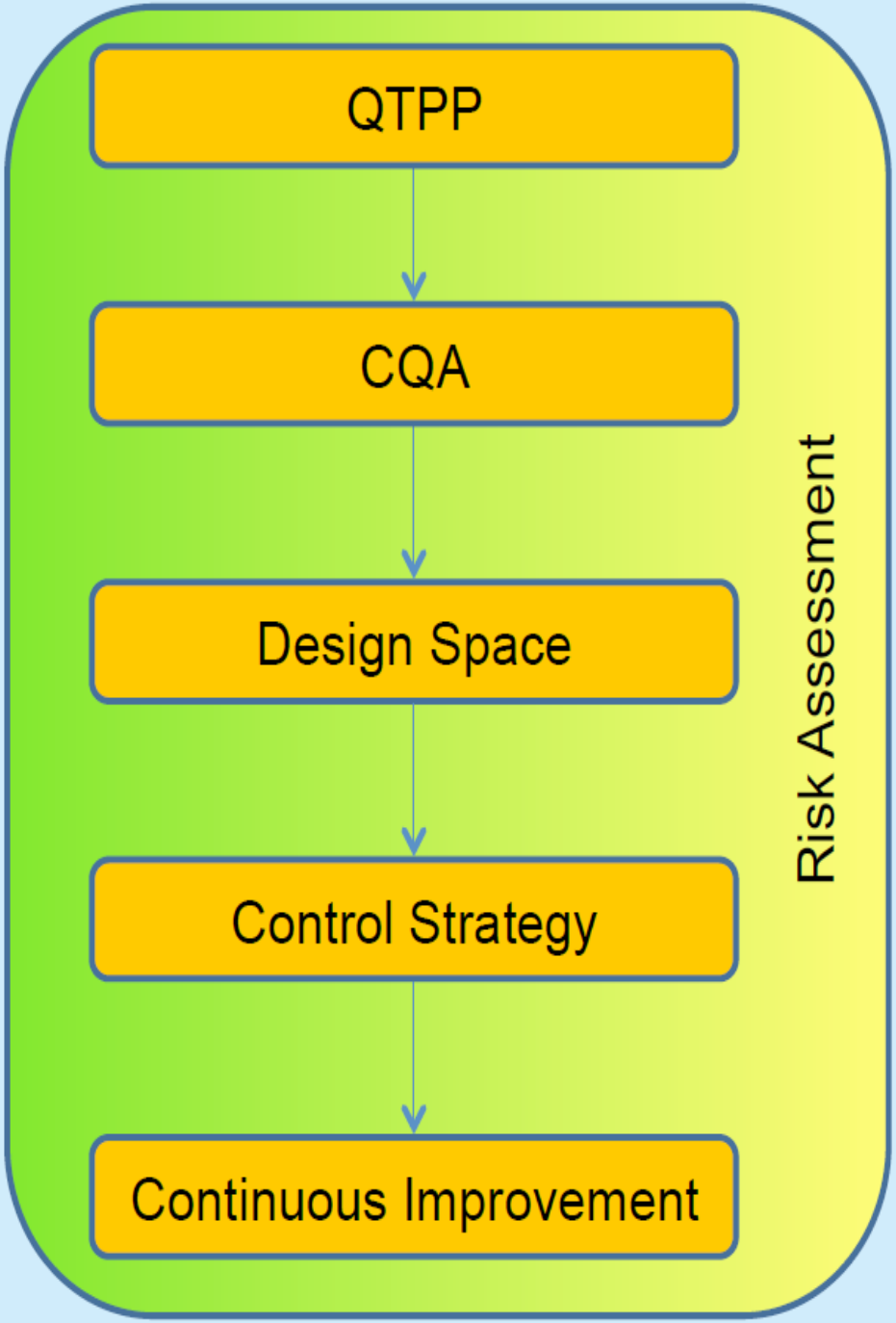
–A comprehensive and effective Pharmaceutical Quality System (PQS) model based on

- ISO quality concepts
- GMP regulations, and
- complements ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management"

–Objectives:

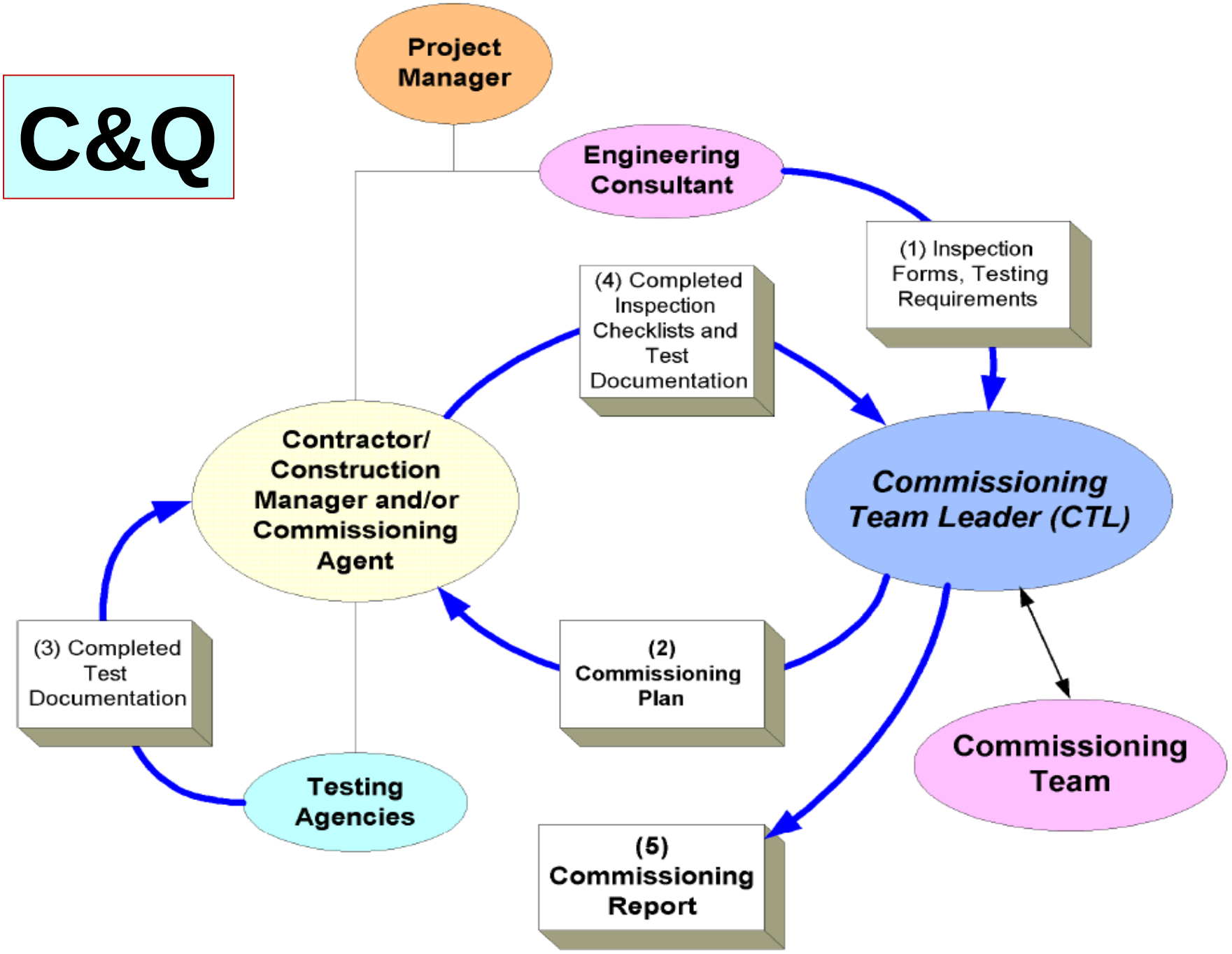
- Achieve Product Realization
- Establish and Maintain a State of Control
- Facilitate Continual Improvement


PRODUCT QUALITY MANAGEMENT
QUALITY SYSTEMS
VALIDATION
CHANGE CONTROL
DISCREPANCY MANAGEMENT
ANNUAL PRODUCT REVIEW
CAPA
MAINTENANCE
RISK KNOWLEDGE & CONTROL / DETECTION
QUALITY RISK MANAGEMENT
FEED / SUPPORT PRODUCT, PROCESS, EQUIPMENT & METHODS
RISK CONTROL STRATEGIES
Product Lifecycle Risk Management
Process Lifecycle Risk Management
Systems Lifecycle Risk Management
Analytical Methods Risk Management
Inverse Relationship
The more you know
PROCESS KNOWLEDGE
QUALITY by DESIGN
Process Development
Process Characterization
Process Validation
Technology Transfer
Prove Process Design meets Product Requirements

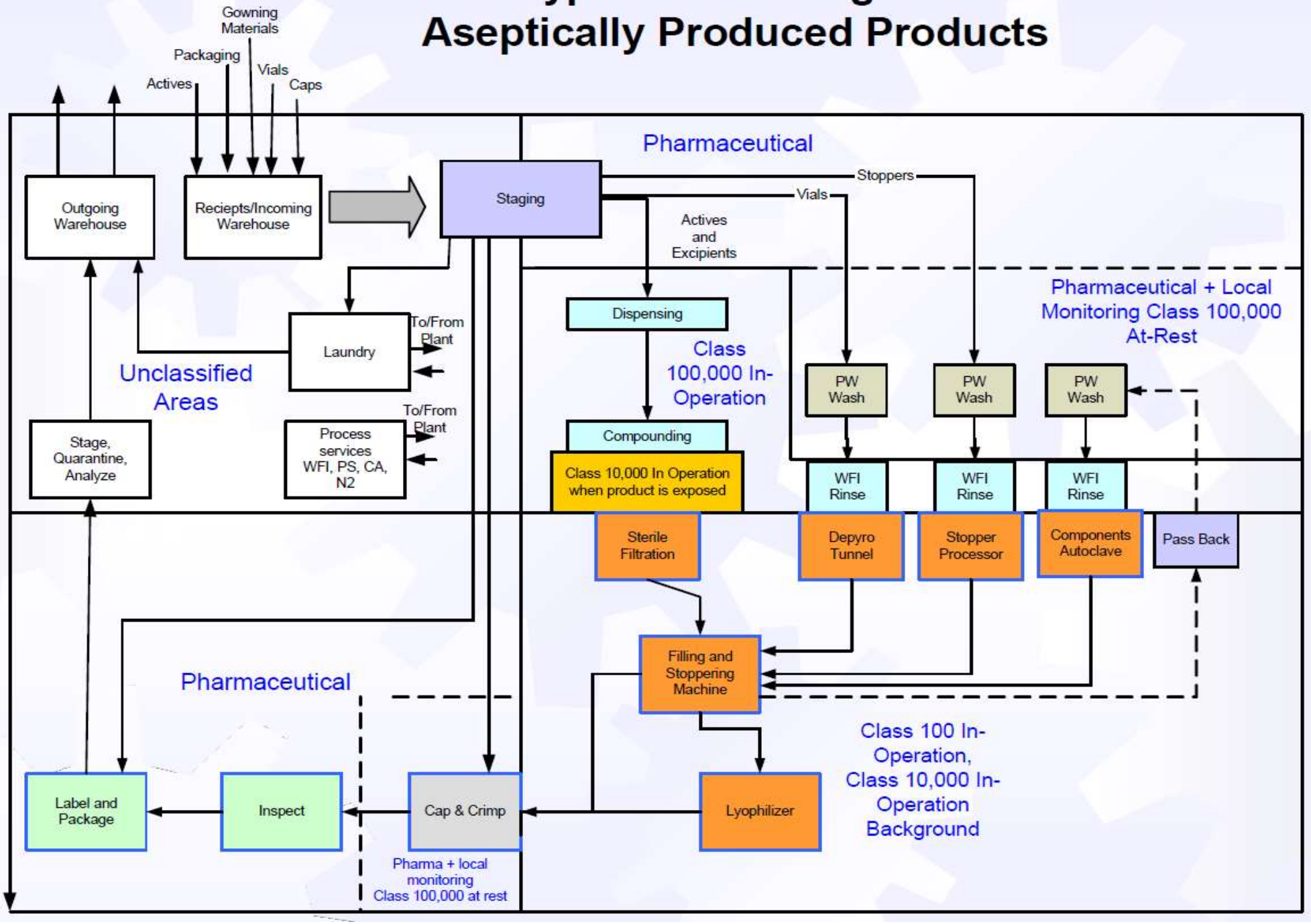


- Target product profile
- Determine Critical Quality Attributes
- Link raw material attributes and process parameters to CQAs
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement
- Risk Assessment is used throughout the development cycle

C&Q


Project Manager
Engineering Consultant
(1) Inspection Forms, Testing Requirements
(4) Completed Inspection Checklists and Test Documentation
Contractor/ Construction Manager and/or Commissioning Agent
Commissioning Team Leader (CTL)
(3) Completed Test Documentation
(2) Commissioning Plan
Commissioning Team
Testing Agencies
(5) Commissioning Report

Typical Flow Diagram
Aseptically Produced Products



Quality Risk Management (Q9)

Pharmaceutical Development (Q8)

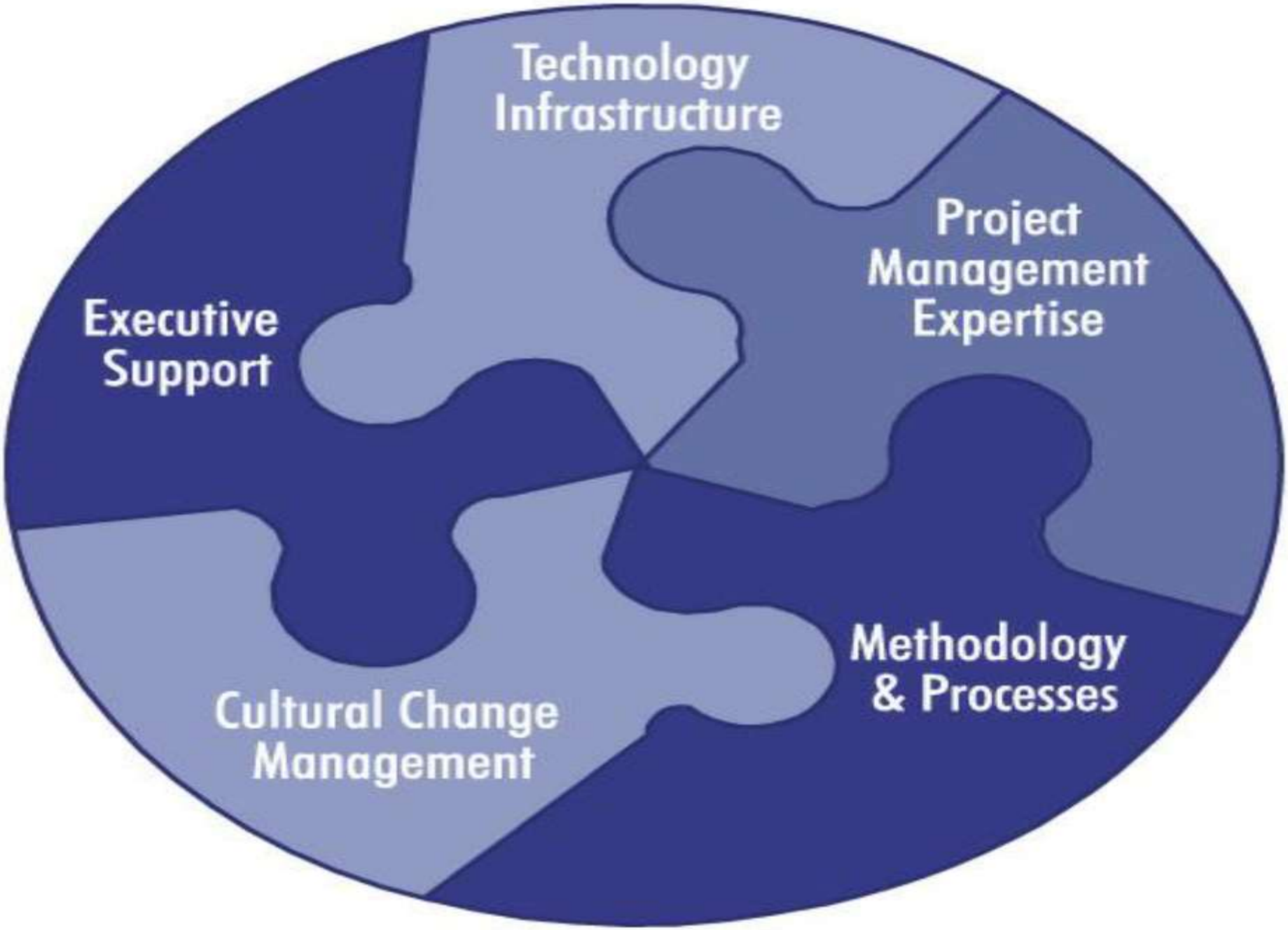
Quality Systems (Q10)

For companies with :

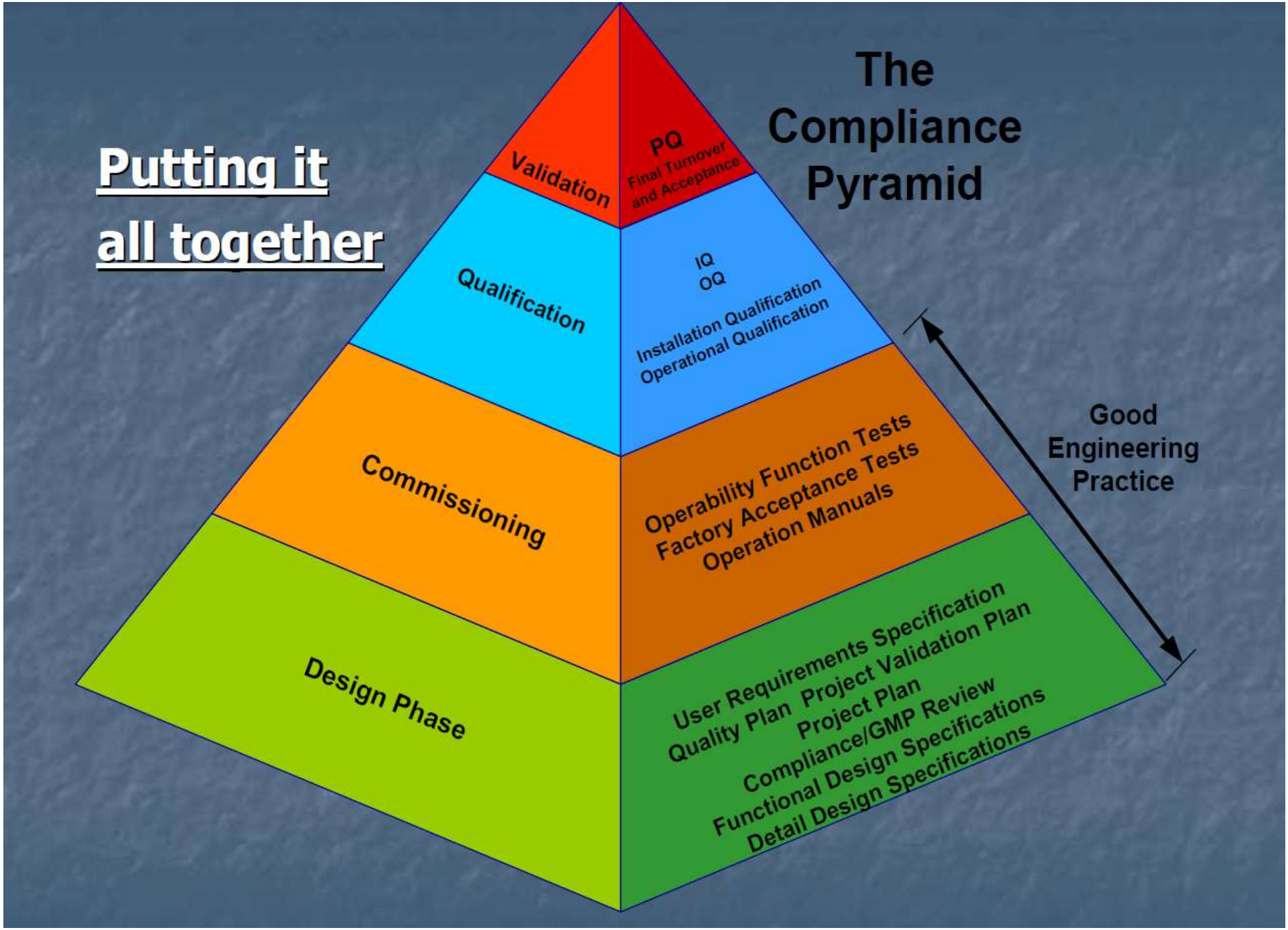
1. **Good design and control strategies**
2. **Good Risk Management strategies**
3. **Good Quality Systems**

Reduced intensity of Regulatory Oversight:
Reduction of submissions on changes/variations
Inspection of quality systems

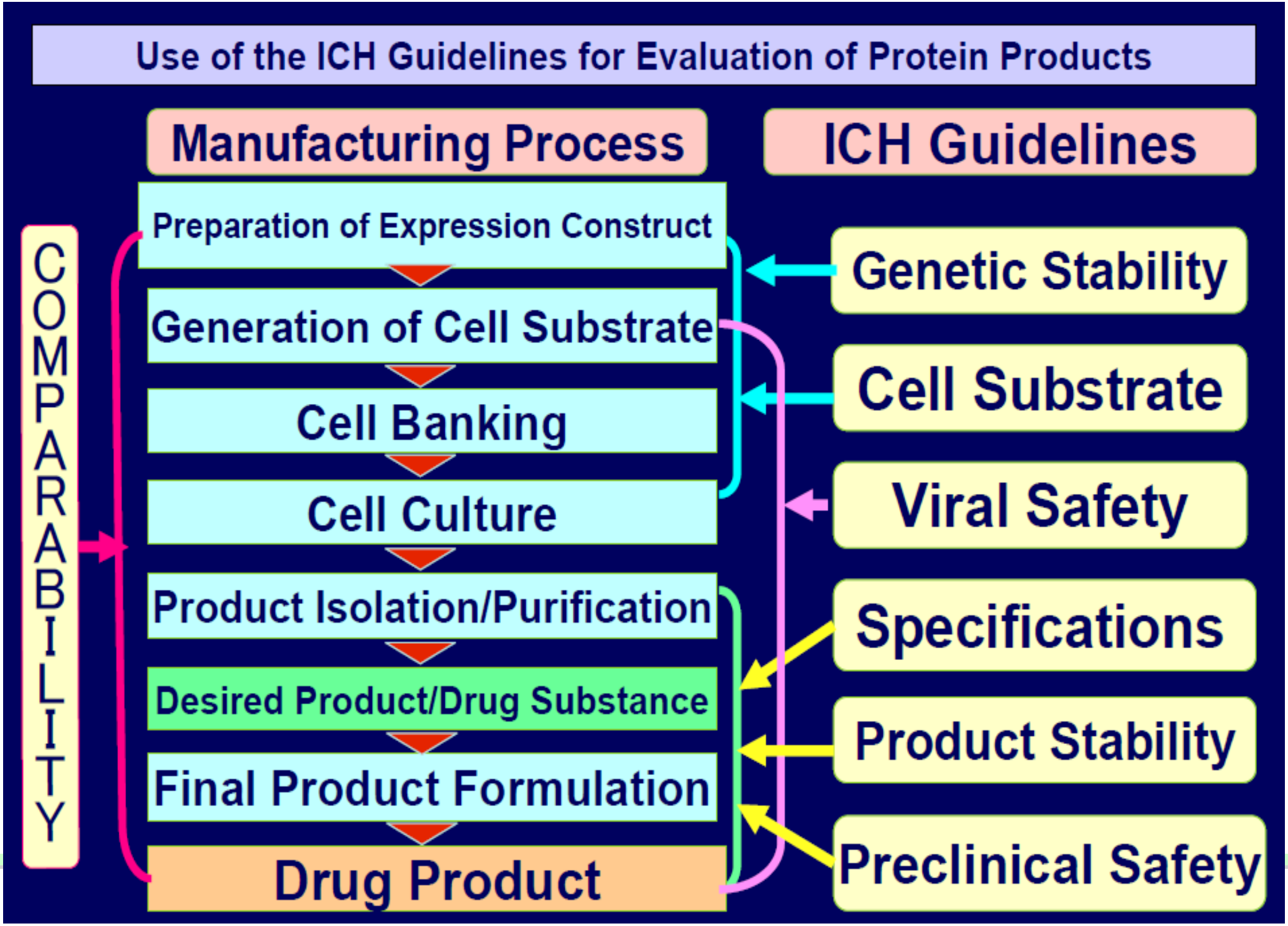
Critical Success Factors



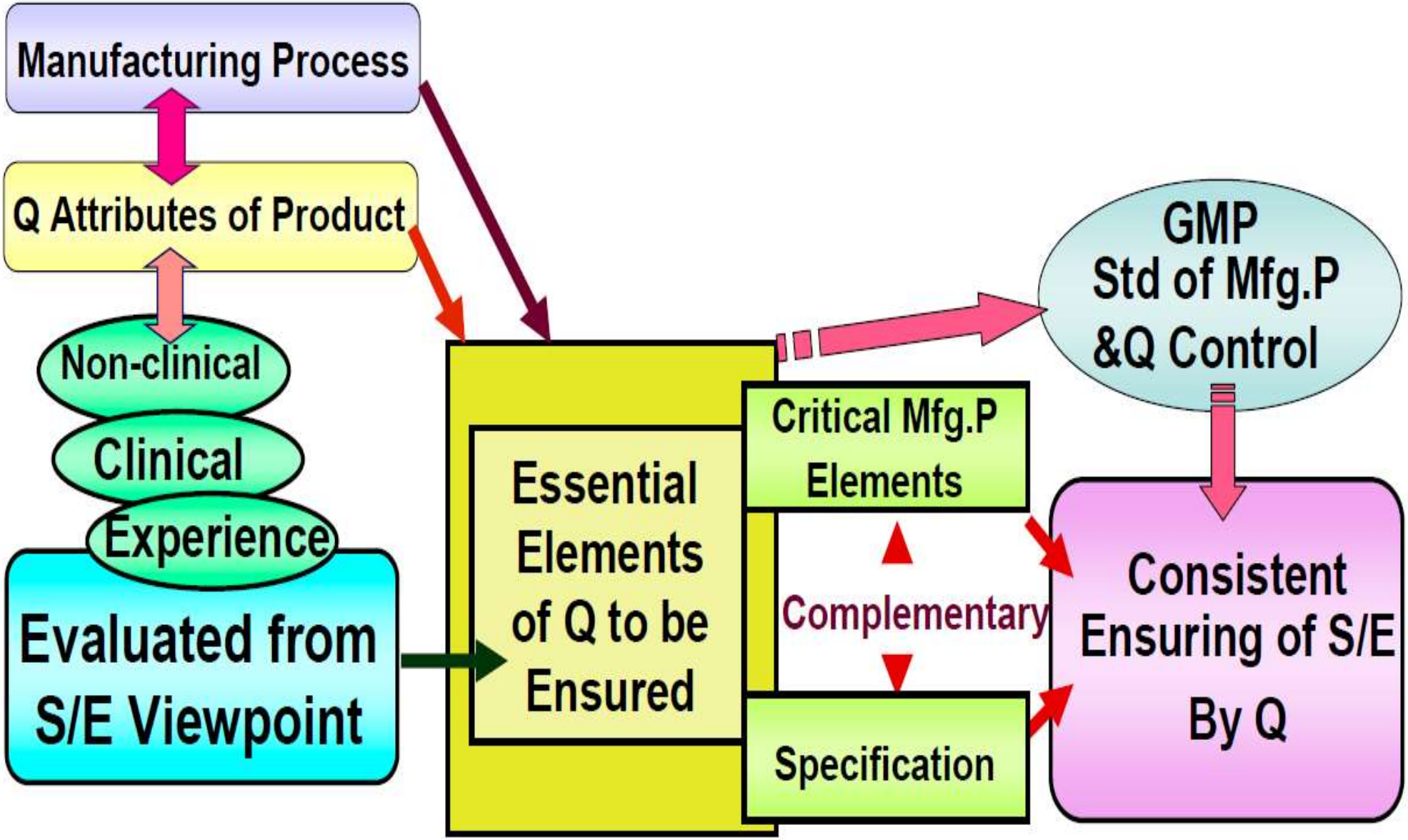
Putting it all together



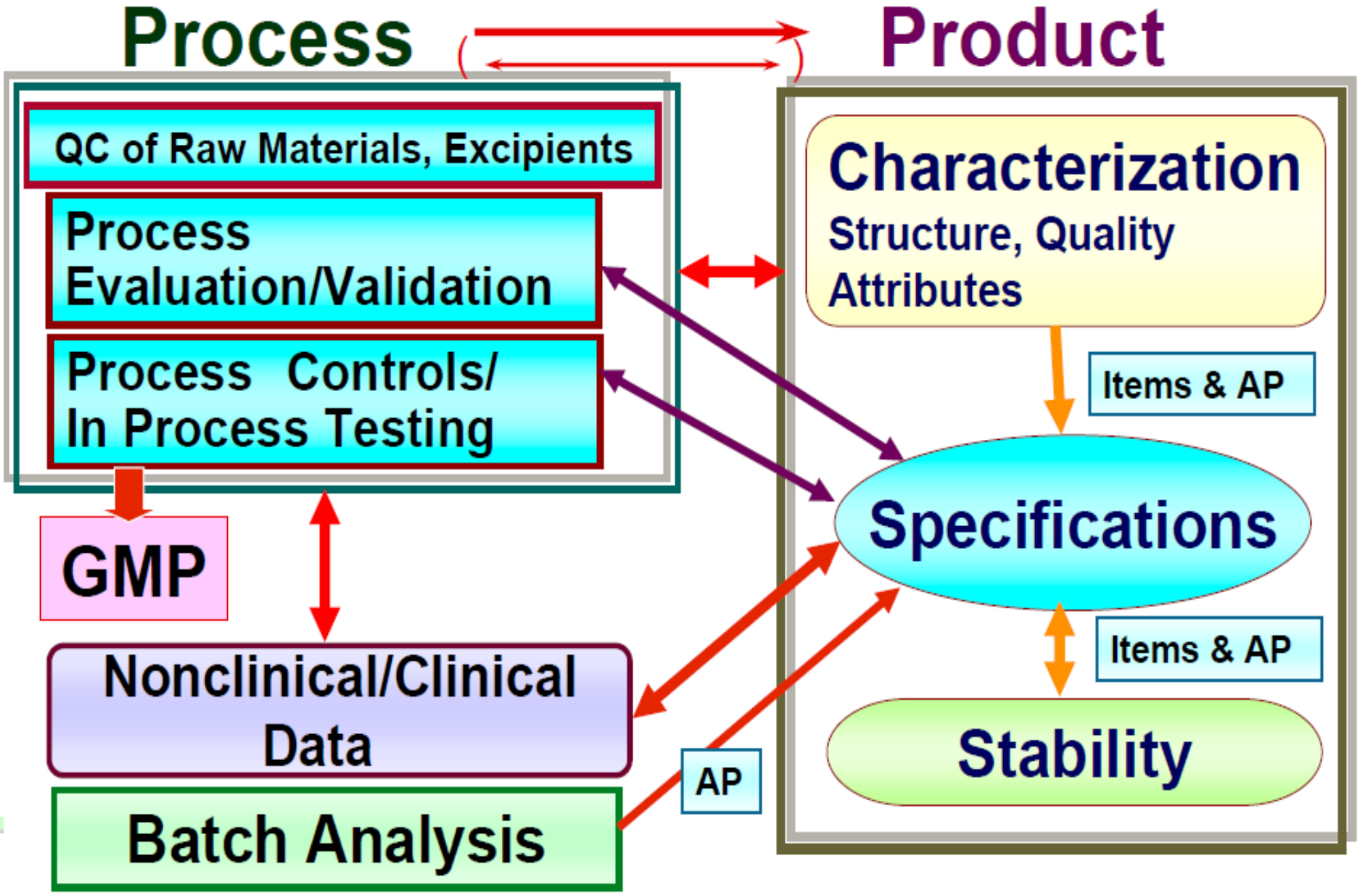
Build Company Competitive Advantage via Successful Product Lifecycle Management

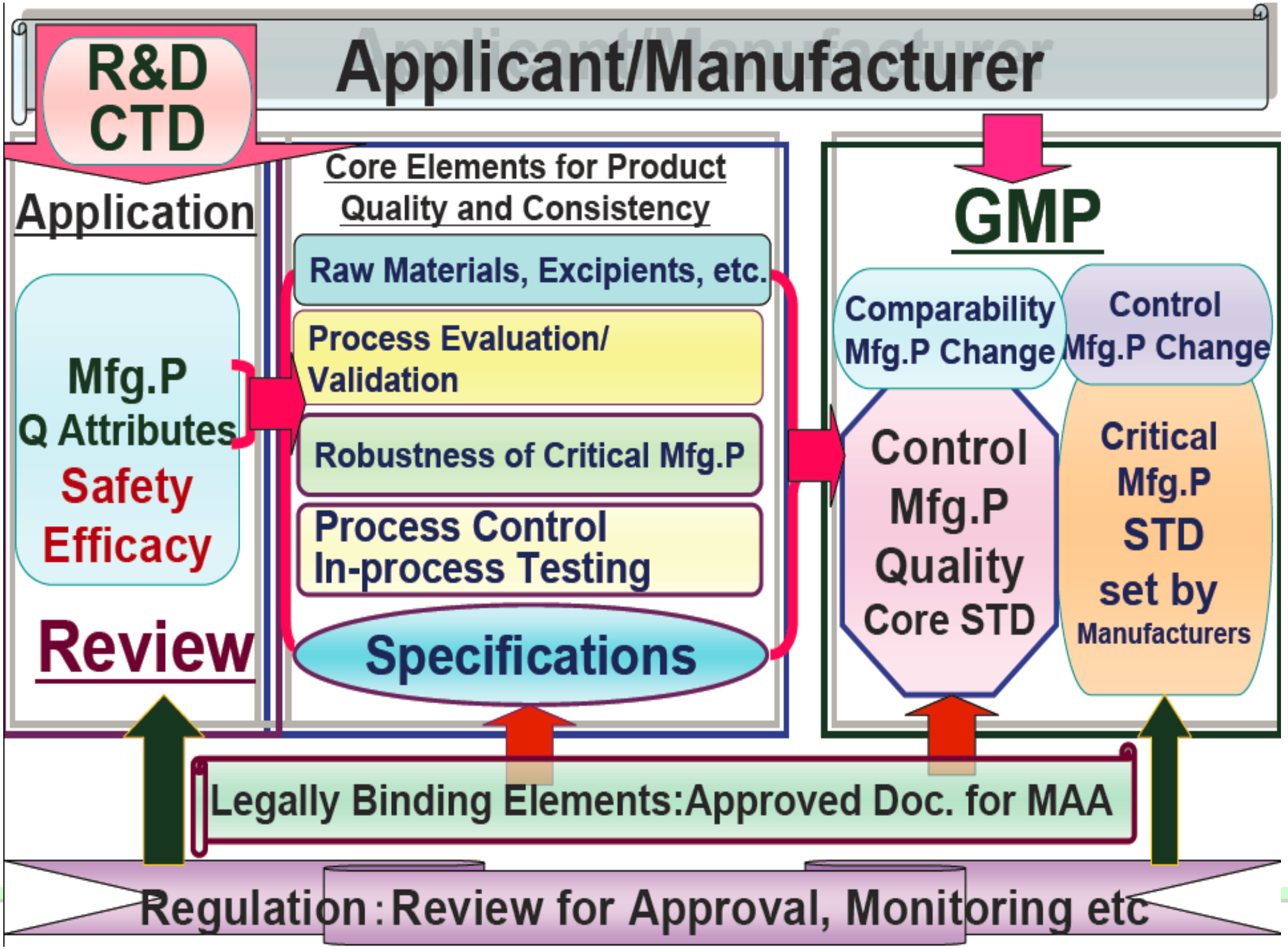

Use of the ICH Guidelines for Evaluation of Protein Products
Manufacturing Process
ICH Guidelines
Preparation of Expression Construct
Generation of Cell Substrate
Cell Banking
Cell Culture
Product Isolation/Purification
Desired Product/Drug Substance
Final Product Formulation
Drug Product
COMPARABILITY
Genetic Stability
Cell Substrate
Viral Safety
Specifications
Product Stability
Preclinical Safety

Effective/Efficient/Flexible Quality Regulation



Elements for Ensuring Product Quality and Consistency



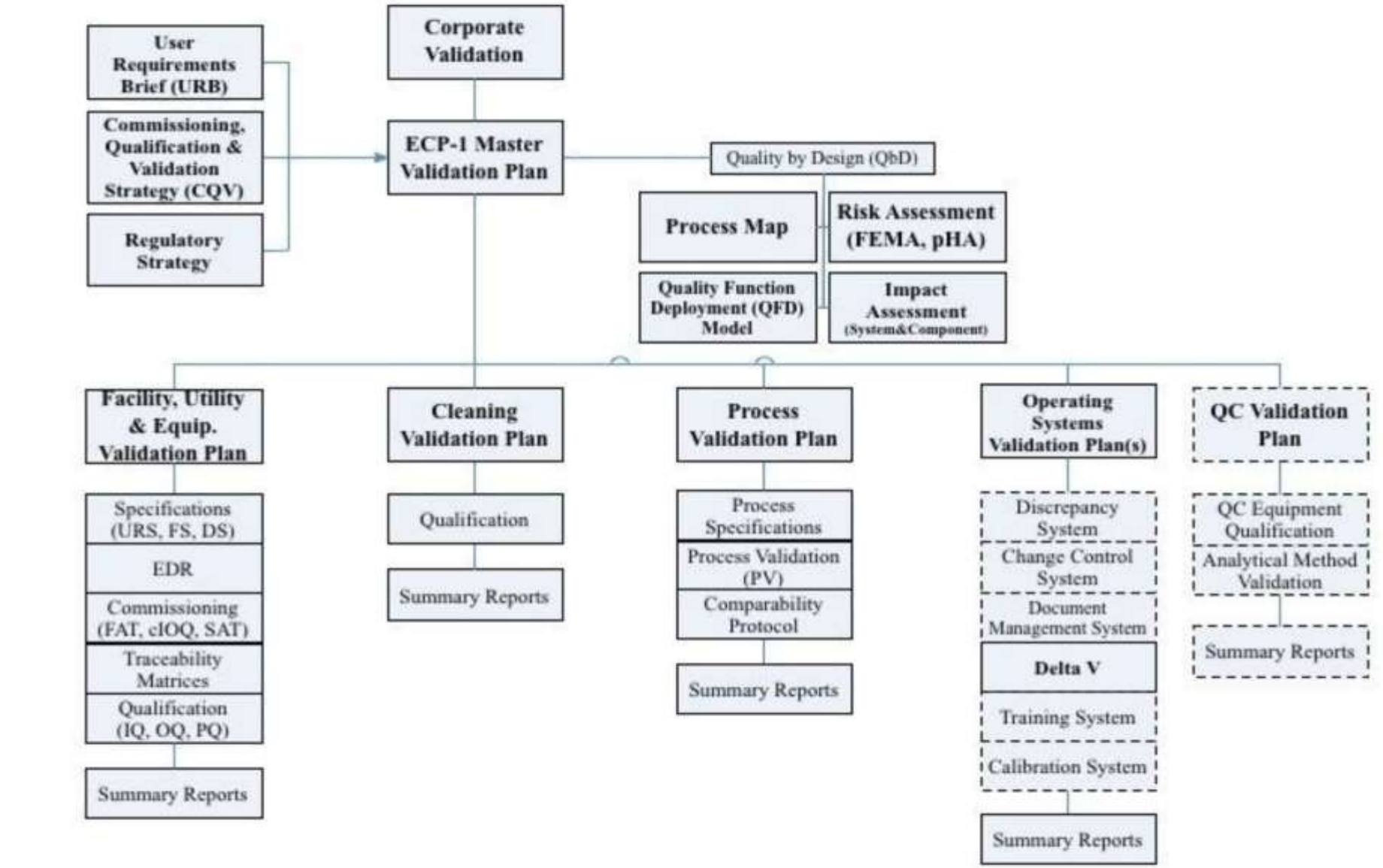

R&D
CTD
Applicant/Manufacturer
Application
Mfg.P
Q Attributes
Safety
Efficacy
Review
Core Elements for Product
Quality and Consistency
Raw Materials, Excipients, etc.
Process Evaluation/
Validation
Robustness of Critical Mfg.P
Process Control
In-process Testing
Specifications
GMP
Comparability
Mfg.P Change
Control
Mfg.P Change
Control
Mfg.P
Quality
Core STD
Critical
Mfg.P
STD
set by
Manufacturers
Legally Binding Elements:Approved Doc. for MAA
Regulation : Review for Approval, Monitoring etc

1. 质量协议文件-Quality Agreements

2. 新厂房设计-New Facility Designs

3. 生命周期起始［开发］：
FDA 之预期及送审文件-Beginning of Lifecycle［Development］: FDA's Expectations for a Submission

VALIDATION FLOW/ DELIVERABLES



Elements of Site Validation Master Plan

- Title page
- Table of Contents
- Introduction
- Responsibilities and Approvals
- Definitions
- Manufacturing Process Overview
- Facility Overview
- Utilities
- Equipment
- Qualification and Validation Approaches
- Key Validation Acceptance Criteria
- Automated Systems Validation
- Cleaning Validation
- Process Validation
- Validation Support Systems
- References
- Qualification Matrix
- Attachments
- Project Diagrams
- Revision History
- Validation Project Plans

Commissioning Documentation

- A typical commissioning document will include, but will not be limited to:
  - Instrument Calibration
  - Certificates and Report Verification
  - Change Part Verification
  - Construction Completion Verification
  - Design Requirement Verification
  - Documentation Verification
  - Environmental Conditions
  - Equipment Installation Verification
  - Filter Verification
  - Major Components
  - Preventive Maintenance Verification
  - Product Contact Verification
  - Spare Part List Verification
  - Lubricant Verification
  - Utilities Verification
  - I/O Verification
  - Wiring Verification
  - Drawing Verification
  - Electro-Magnetic Interference Verification
  - Radio Frequency Interference Verification
  - Specific Functional Tests
  - Controls Verification
  - Power Failure Verification
  - Operational Testing
  - Alarms/Interlocks Verification
  - Operational Run Verification

1. 供应链管理-Supply Chain Management
2. 药典-Pharmacopeia
3. 稽查趋势-Inspection Trends
4. 无菌过濾-Filtration
5. 制程确效-Process Validation
6. 预充针制剂-Pre-filled Syringe
7. 质量系统-Quality System

1. 了解测量标准 Understand Metrics
2. 微生物实验室及化学实验室缺失-Microbiology and Chemistry Lab Findings
3. 询问药监机关：审计-Ask the Regulator: Inspection
4. 美国药典之更新-USP Updates

1. 优良运销规范

-Good Distribution Practices

2. 外包之革新

-Outsourcing Innovation

3. 缺药危机管理

-Managing Supply Crisis / Drug Shortages

1. 审计与国际合作之趋势-International Trends: Inspection and Collaboration

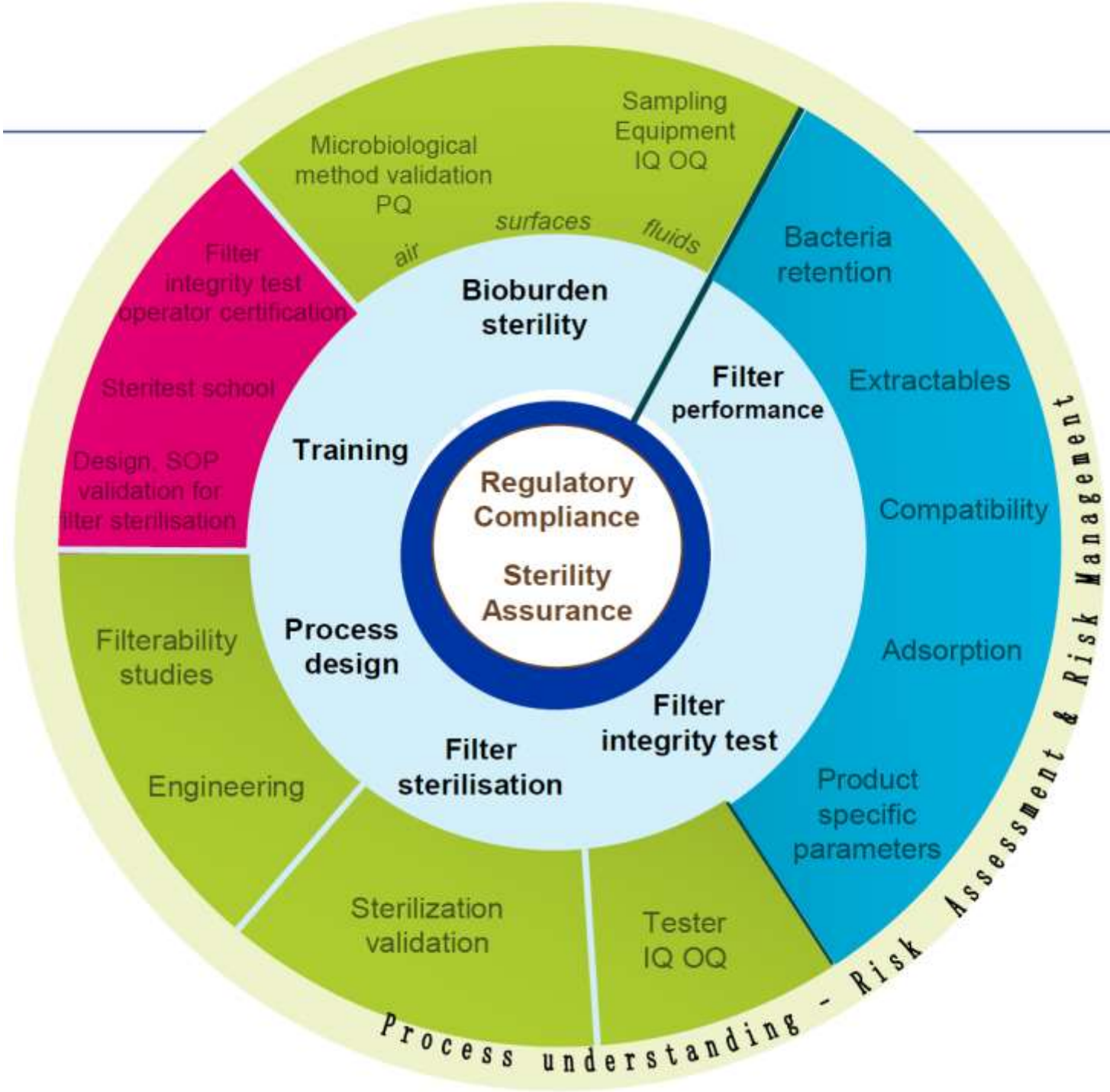
2. 组合药物及诊断 Combination Products and Companion Diagnostics

3. 产品生命周期至量产-Lifecycle Towards Commercial Manufacturing

1. 审计后之跟进-Post Inspectional Follow-up

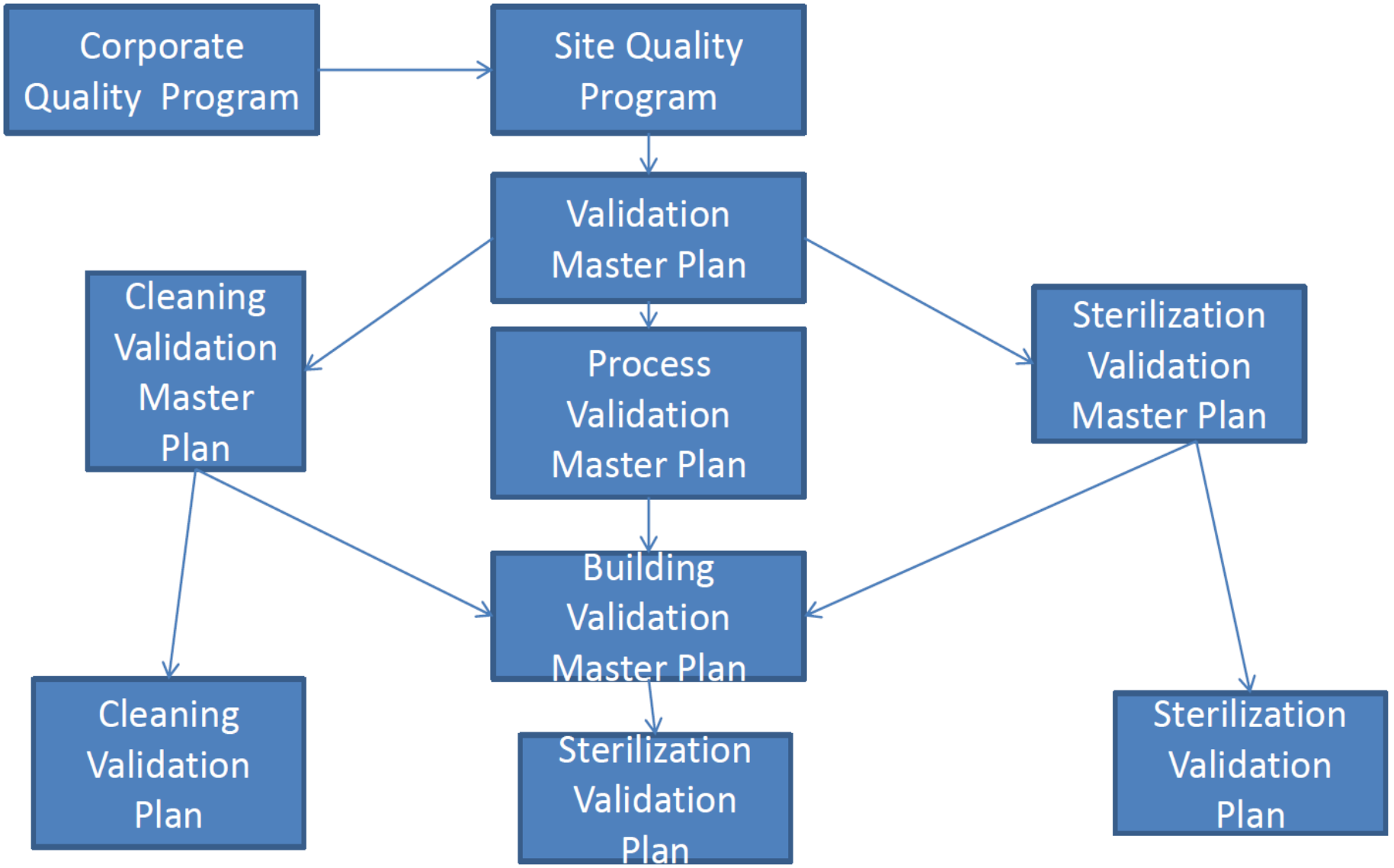
2. 审阅送审文件-Submission Review

3. 持续改进-Continuous Improvement


Sampling
Equipment
IQ OQ
Microbiological
method validation
PQ
surfaces
fluids
air
Bacteria
retention
Filter
integrity test
operator certification
Bioburden
sterility
Filter
performance
Extractables
Steritest school
Training
Design, SOP
validation for
filter sterilisation
Regulatory
Compliance
Sterility
Assurance
Compatibility
Process
design
Adsorption
Filterability
studies
Filter
integrity test
Filter
sterilisation
Engineering
Product
specific
parameters
Sterilization
validation
Tester
IQ OQ
Process understanding - Risk Assessment & Risk Management

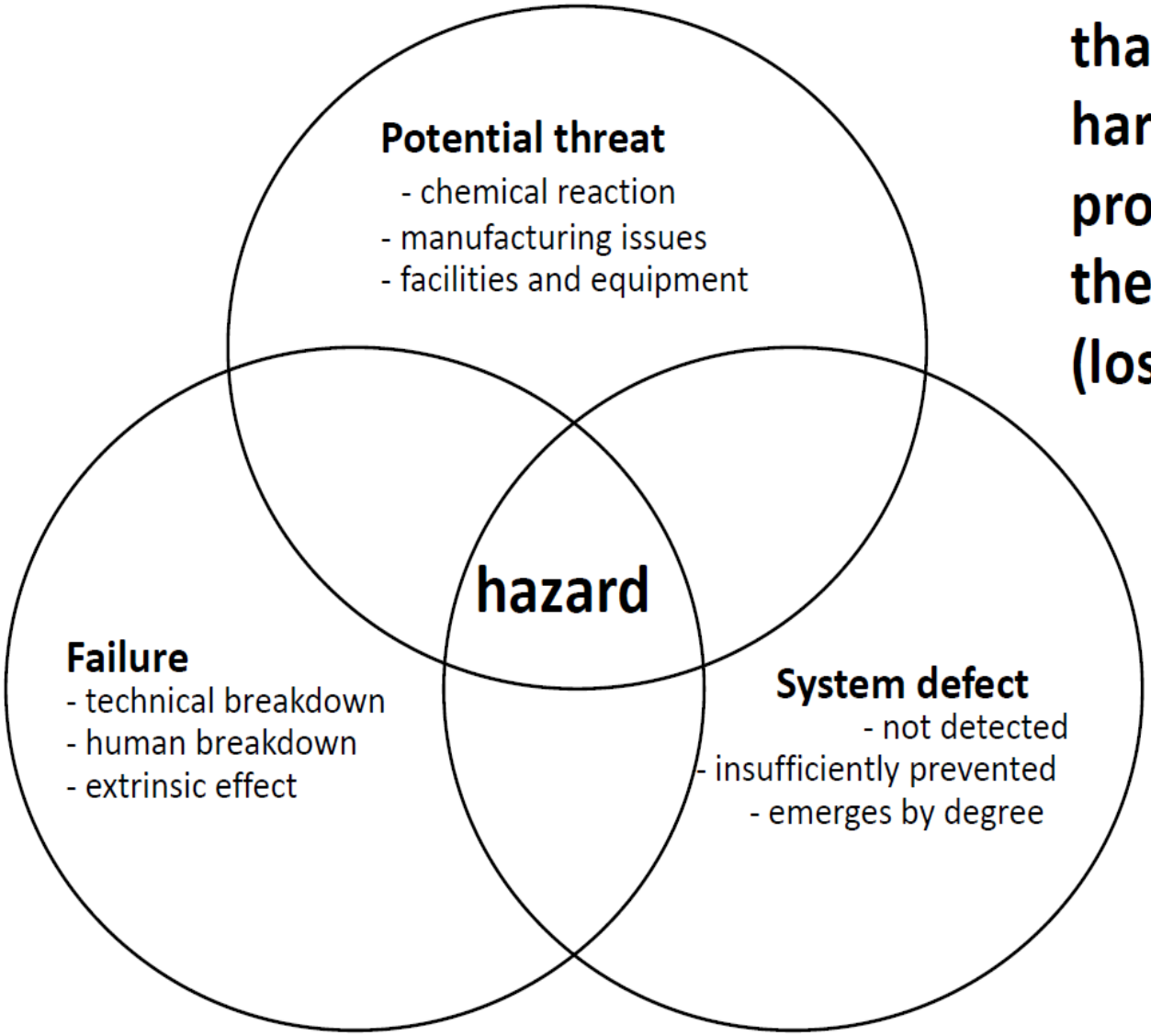
System

- Documentation Hierarchy



- Systems
  - Quality and training
  - Materials
  - Laboratory Controls
  - Production
  - Packaging and Labeling
  - Facilities and Equipment

Hazard

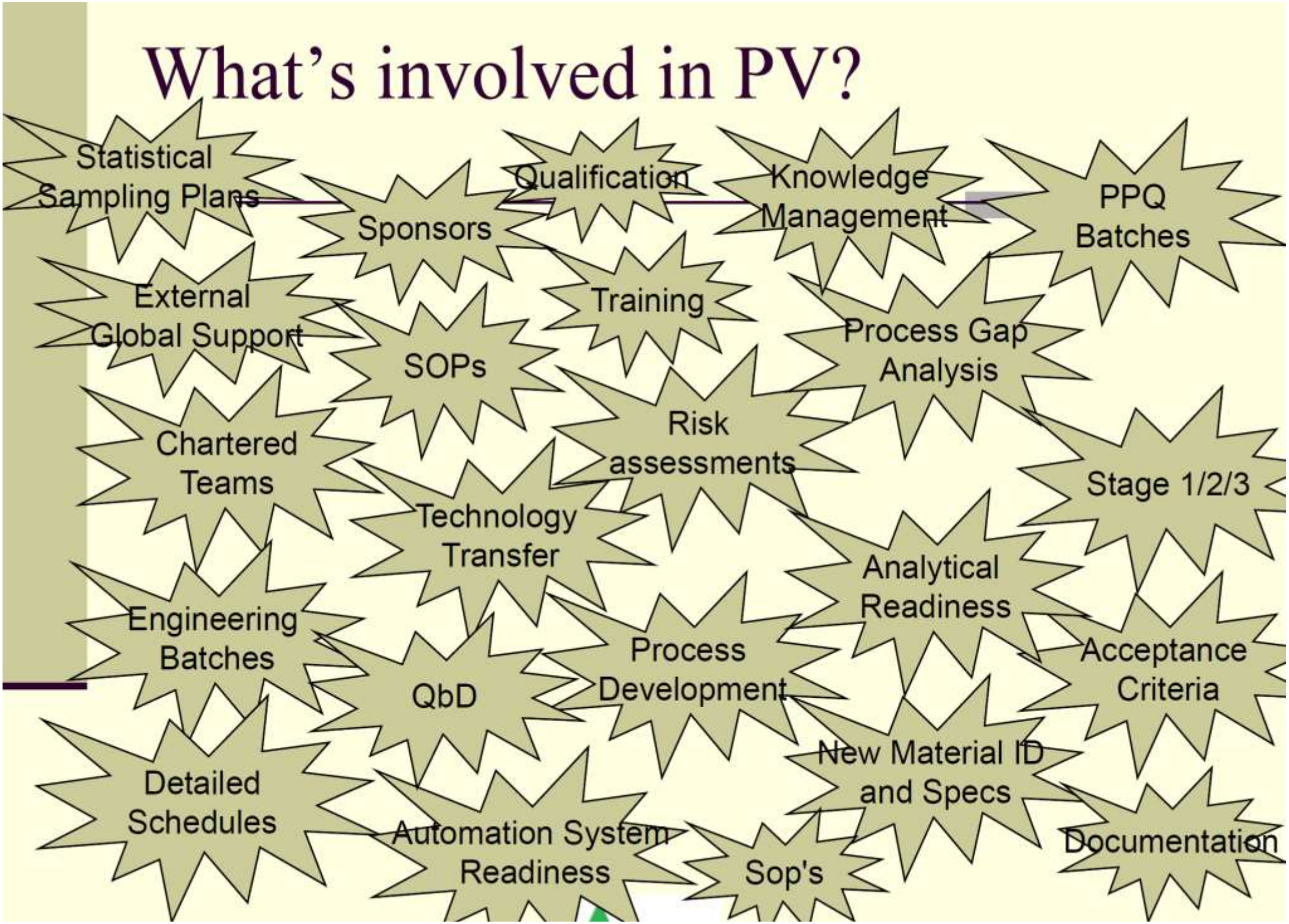


Anything
that has the potential to
harm patients,
product quality or
the business
(loss, interruption, image)

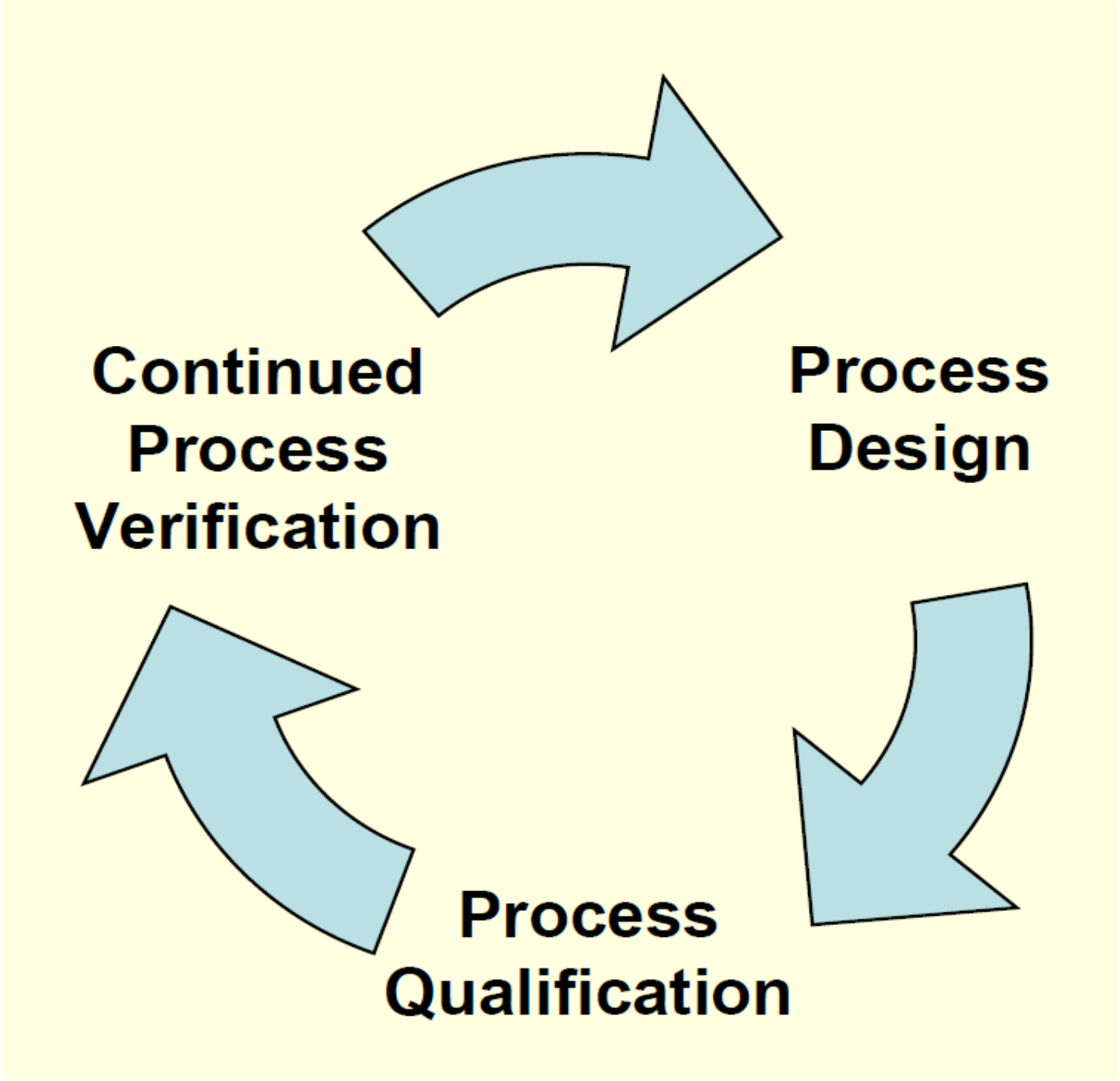
The Q10 Journey: ICH Documentation

- ICH Q1 – Stability Testing of New Drug Substances and Products (A-F)
- ICH Q2 -Validation of Analytical Procedures
- ICH Q3 Impurities in New Drug Substances (A-D)
- ICH Q4 Pharmacopeias (A-B) Harmonizes many of the CQA's for solid Dose
- ICH Q5 Quality of Biotechnological Products (A-E)
- ICH Q6 Specifications : Test Procedures and Acceptance Criteria for New Drug Substance s and Product (A-B Biologics)
- ICH 7 – Good Manufacturing Practice
- ICH 8 – Pharmaceutical Development
- ICH 9 - Quality Risk Management
- ICH10 –Pharmaceutical Quality Systems
- ICH 11 – Development and Manufacture of Drug Substance (Chemical Entities and Biotechnological/ Biological Entities

What's involved in PV?

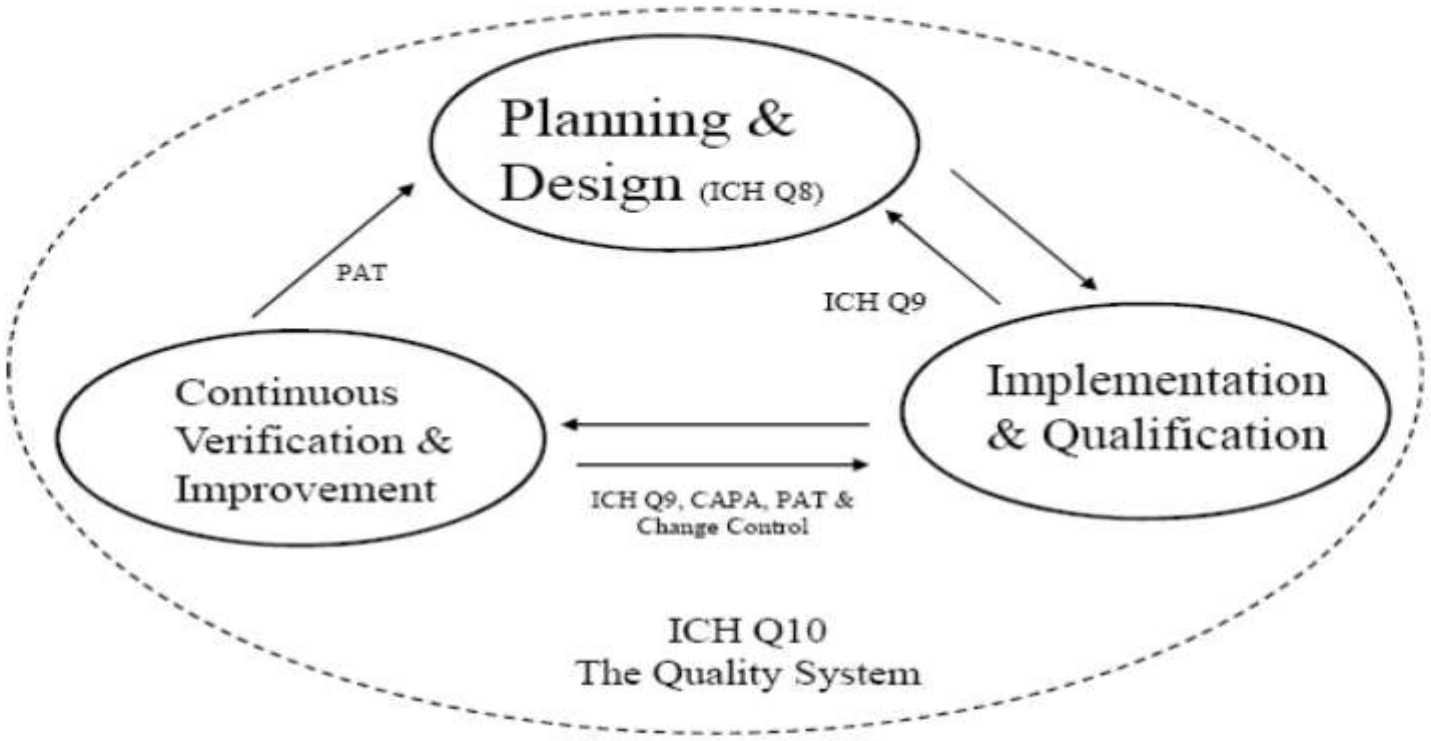


- PDA Technical report no 36 - Current practices in the Validation of Aseptic Processing.
- PIC guideline - PI 007 - Validation of Aseptic processes
- Various ISPE guides.


Process Design
Process Qualification
Continued Process Verification

Life-cycle approach as per FDA and ICH guidance documents

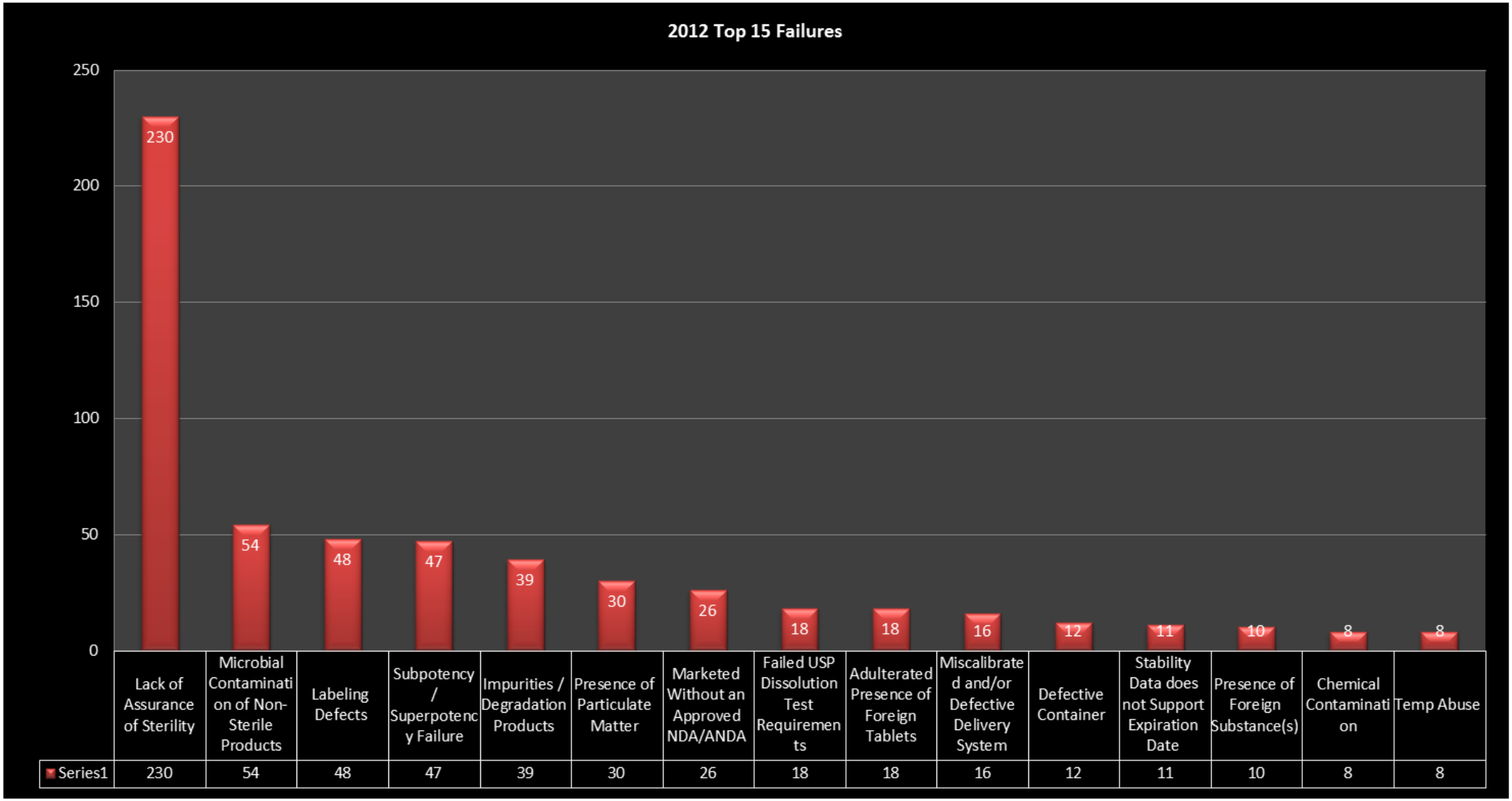
The Life Cycle Approach to Process Validation



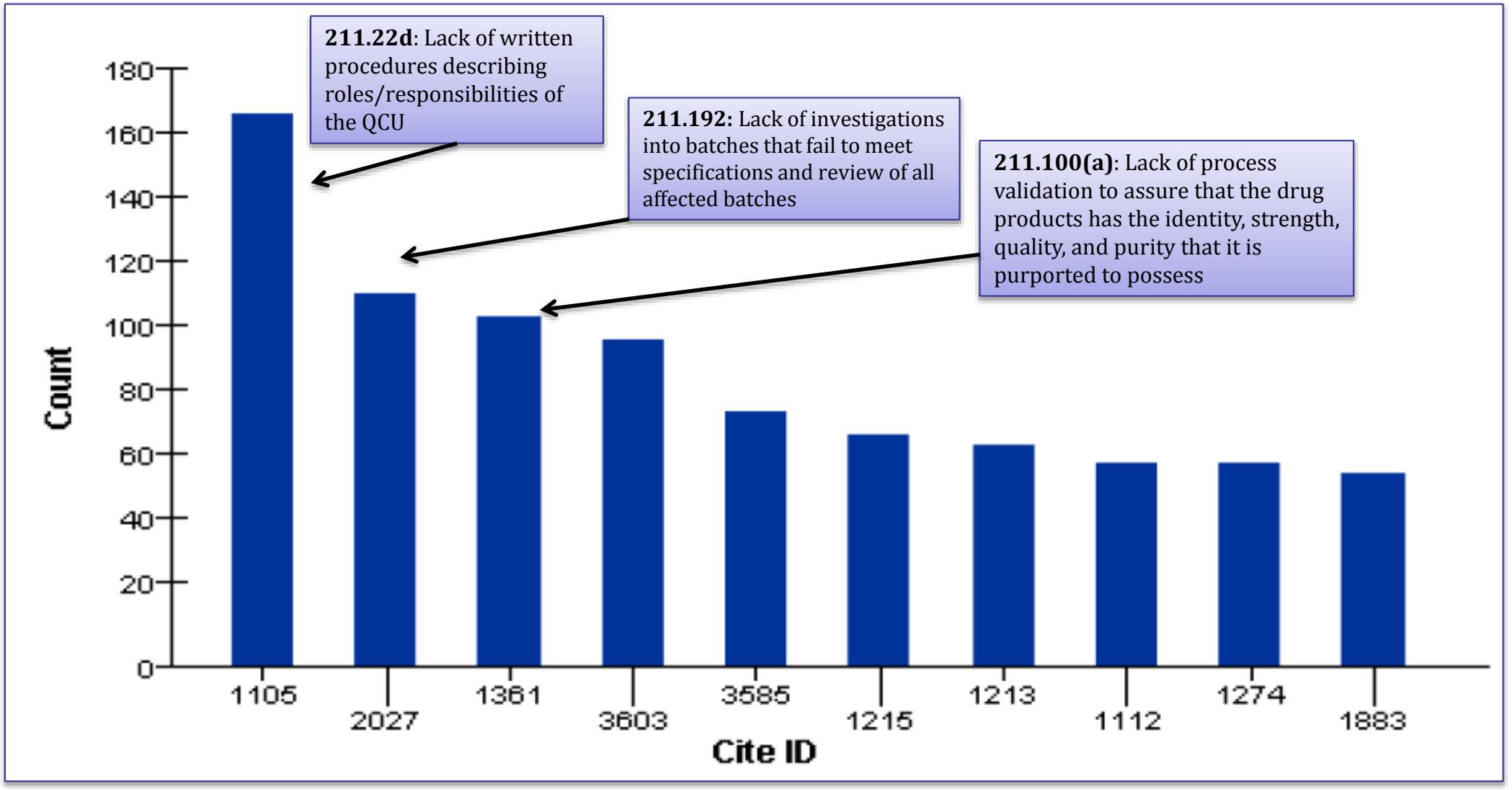
Documentation in support of the new FDA guidance document

Stage 1	Stage 2	Stage 3
Development Report	Project Validation Master Plan	Risk assessments
Risk assessment	IQ/OQ/PQ protocols and reports	Continued Process Verification Plan
Control Strategy Document	PPQ Validation Master Plan	Continued Process Verification Report
Process Description	PPQ protocol	
	PPQ report	

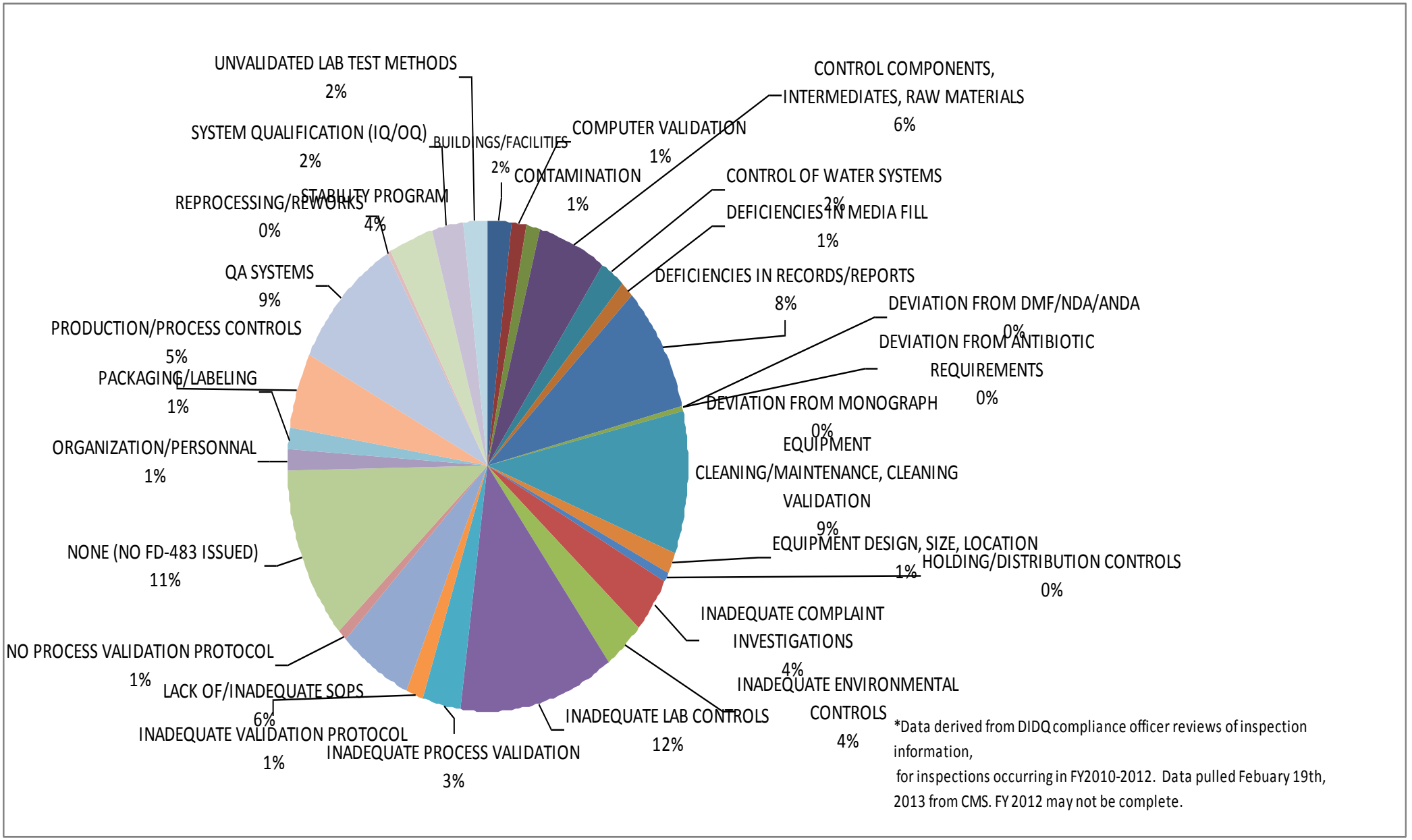
2012 Top Recall Failures



Top 10 Drug Observations Used in Turbo EIR between 01 Jan 2012 and 31 Dec 2012 *(as of 24 Jan 2013)*

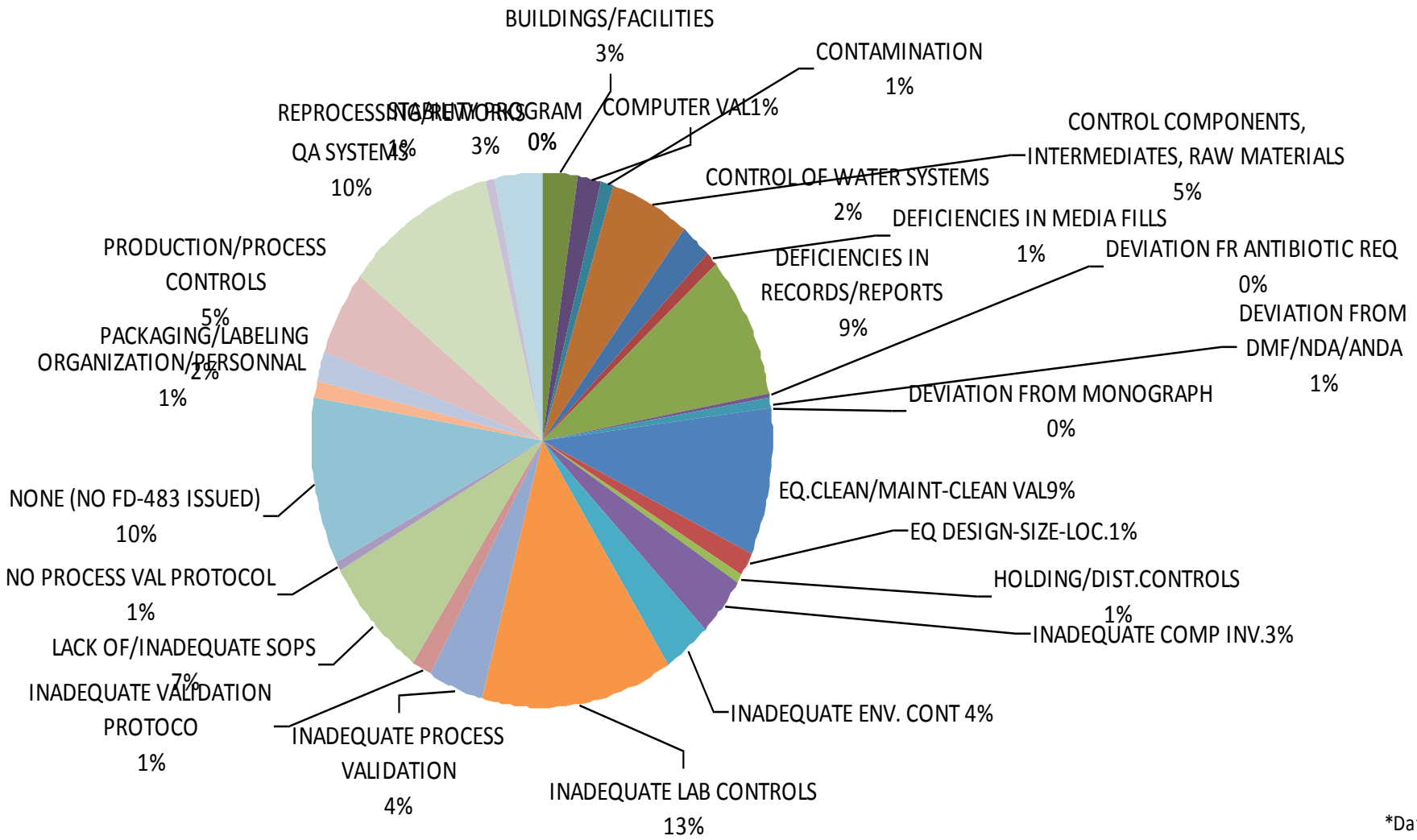


GMP Issues Found on International Inspections FY 2012



*Data derived from DIDQ compliance officer reviews of inspection information,
for inspections occurring in FY2010-2012. Data pulled Febuary 19th, 2013 from CMS. FY 2012 may not be complete.

GMP Issues Found on International Inspections FY 2011



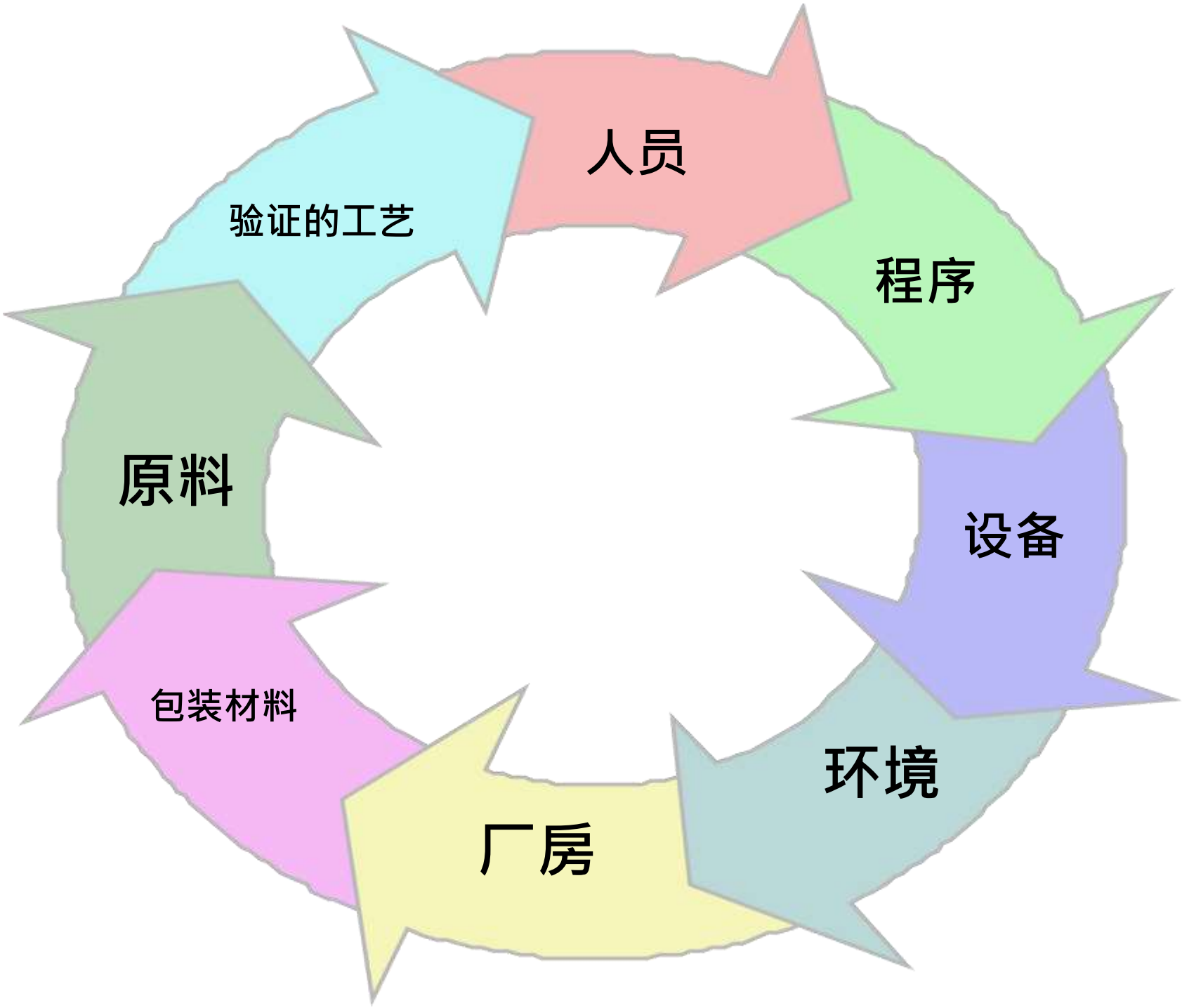
*Data derived from DIDQ compl
FY2010-2012. Data pulled Febu

The Quality System:
Foundation for Assuring an Ongoing State of Control

FDA Inspection Program Includes:

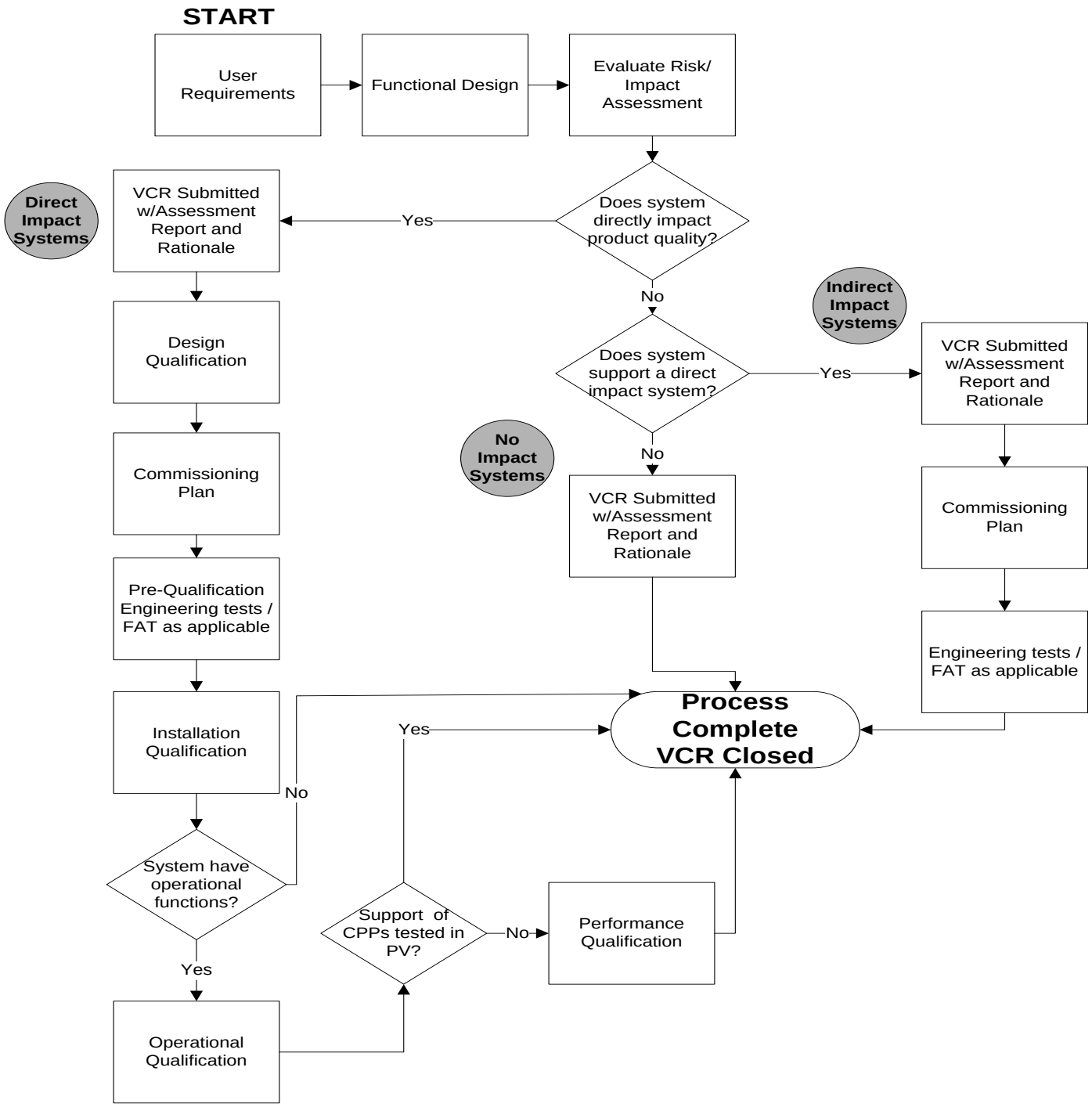
- Materials System
- Equipment & Facilities
- Production
- Laboratory
- Packaging & Labeling
- Quality System

Investigations Operations Manual (IOM):
http://www.fda.gov/ICECI/Inspections/IOM/default.htm


人员
程序
设备
环境
厂房
包装材料
原料
验证的工艺

Science & Quality Risk Management Qualification Process Flow

VCR: Validation Change Request



- **Products and Processes are Fit for the Intended Use**
  - Ensured by implementing harmonised GMPs / GDPs

- **No Surprises**
  - Ensured by implement a '*Quality by Design*' mind set

- **Preventing Emerging Regulations**
  - Ensured by implementing the sprit of existing requirements

mikeleeok@126.com