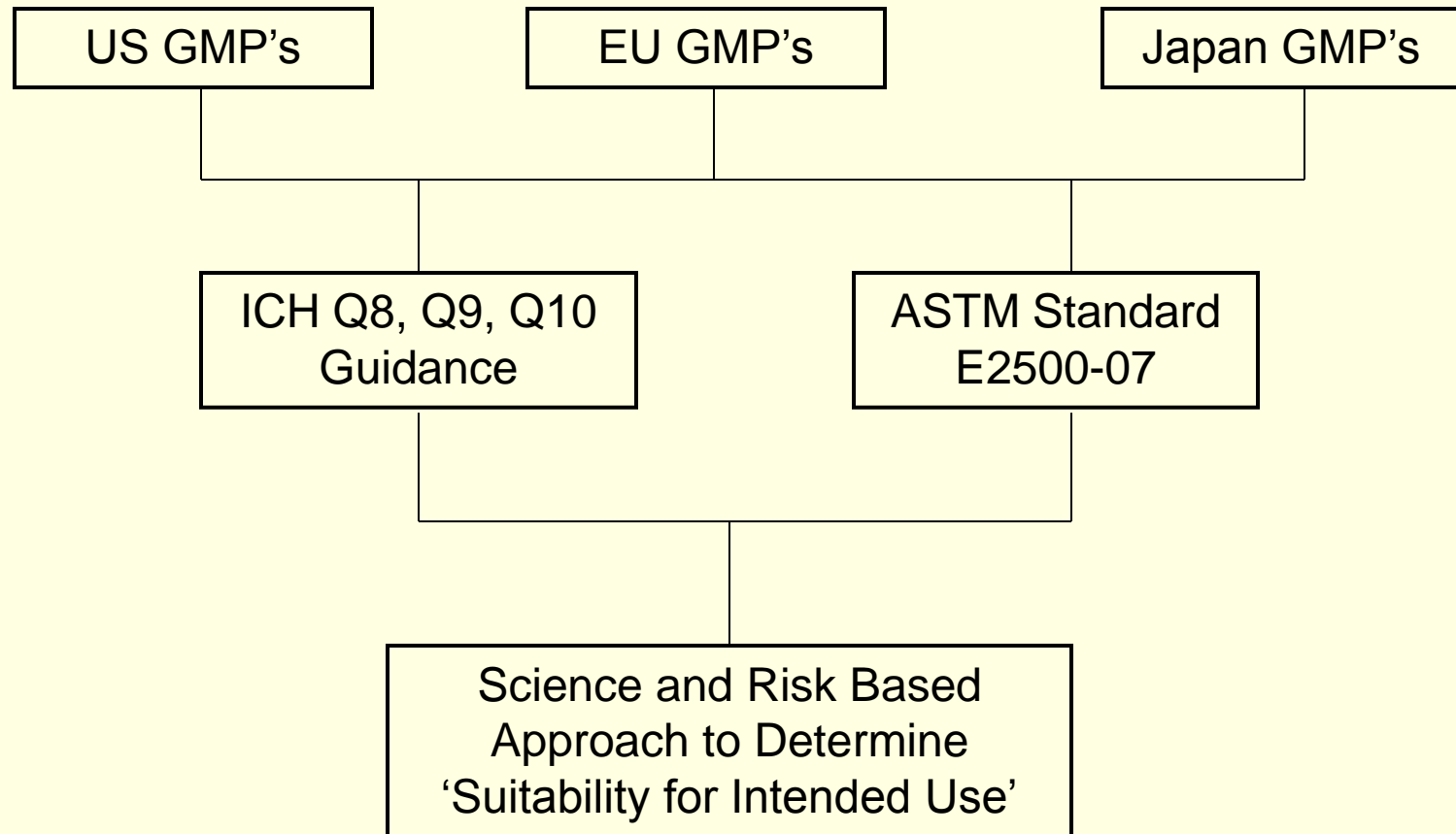

Impact Assessment in a Science & Risk Based Environment

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Background



Regulatory Drivers

- GMP's
 - US Code of Federal Regulations Title 21 Part 211
 - EU EudraLex (The Rules Governing Medicinal Products in the European Union), Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use

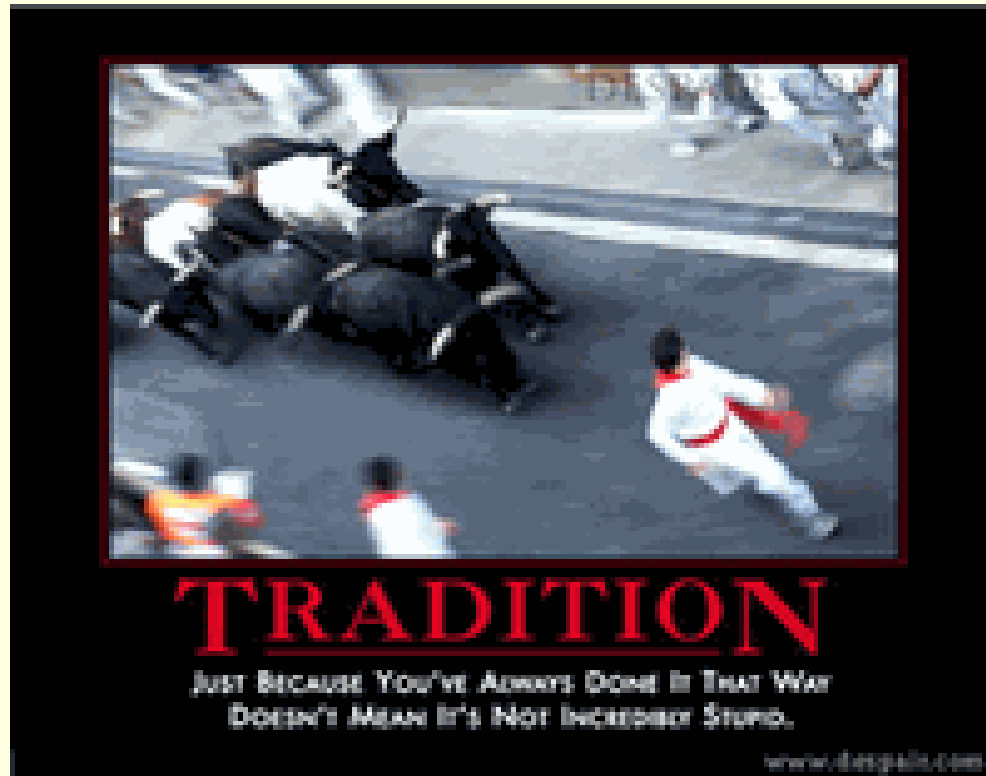
- ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
 - Q8 Pharmaceutical Development
 - Q9 Quality Risk Management
 - Q10 Pharmaceutical Quality System

- ASTM Standard E2500-2007: Guide for Specification, Design and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment

Concepts

- Suitability for Intended Use
 - Manufacture of safe and effective products
- Science Based Approach
 - Product and Process Understanding
 - Definition of Critical Quality Attributes (CQA's) and Critical Process Parameters (CPP's) usually compiled in a User Requirements document and serves as the basis of the process control strategy to assure suitability
 - Subject Matter Experts
 - Responsible for development of strategy, CQA's, CPP's
- Risk Based Approach
 - Quality Risk Management (QRM)
 - Focus on 'Risk to Patient' by managing and mitigating risks to product quality

Why a Science & Risk Based Approach?



Definitions

- System
 - An organization of components that have a defined operational function
- System Boundary
 - A limit drawn around a system to logically define what is and what is not included
- Impact Assessment
 - The process of evaluating impact of the operating, controlling, alarming and failure conditions of a system

Definitions (Continued)

- Direct Impact

- A system, change or failure that has, or can have a direct effect on product quality or patient safety

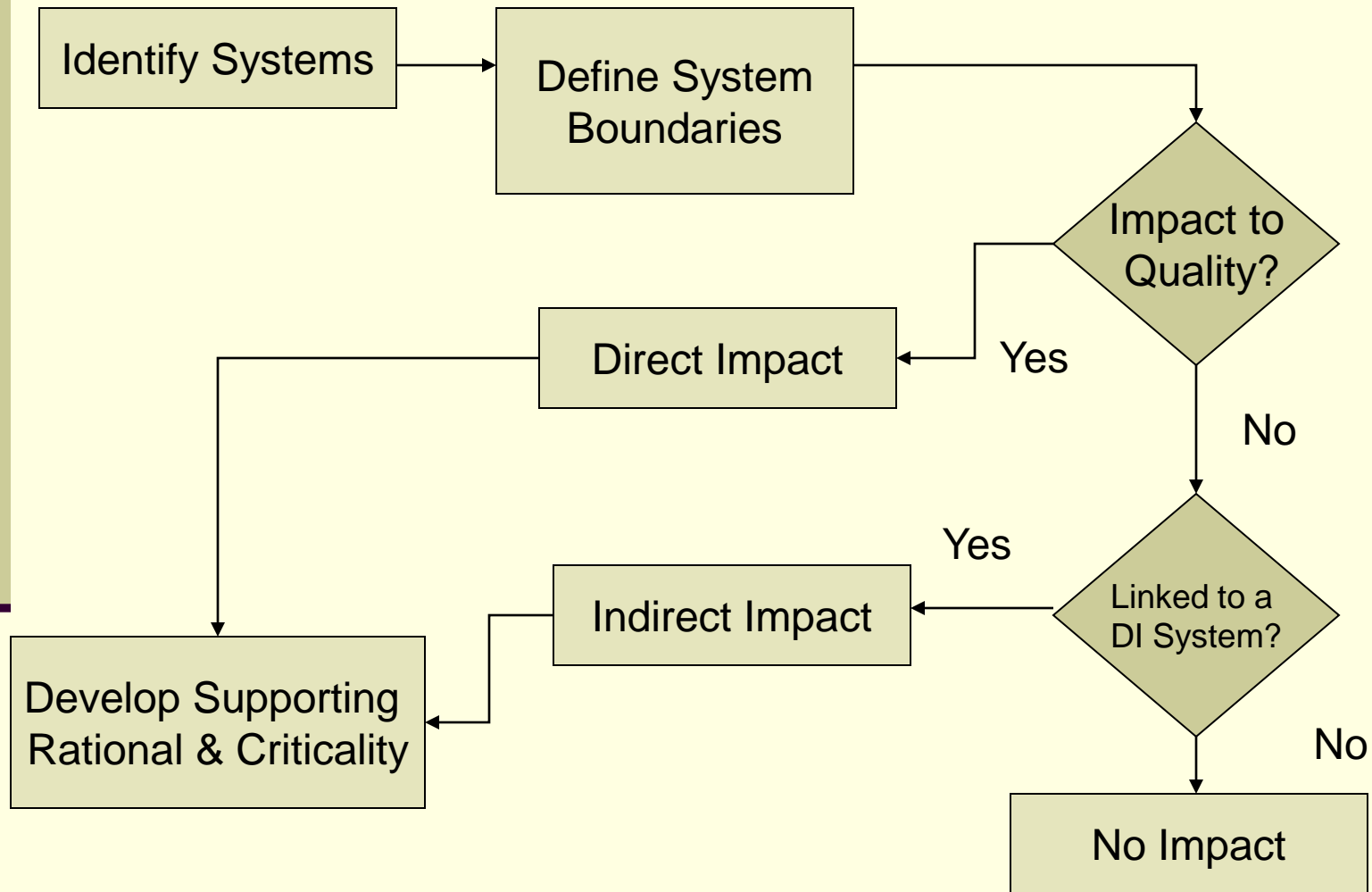
- Indirect Impact

- A system, change or failure that has or can have an indirect effect on product quality or patient safety

- No-Impact

- A system, change or failure that has no effect on product quality or patient safety

Impact Assessment Flowchart



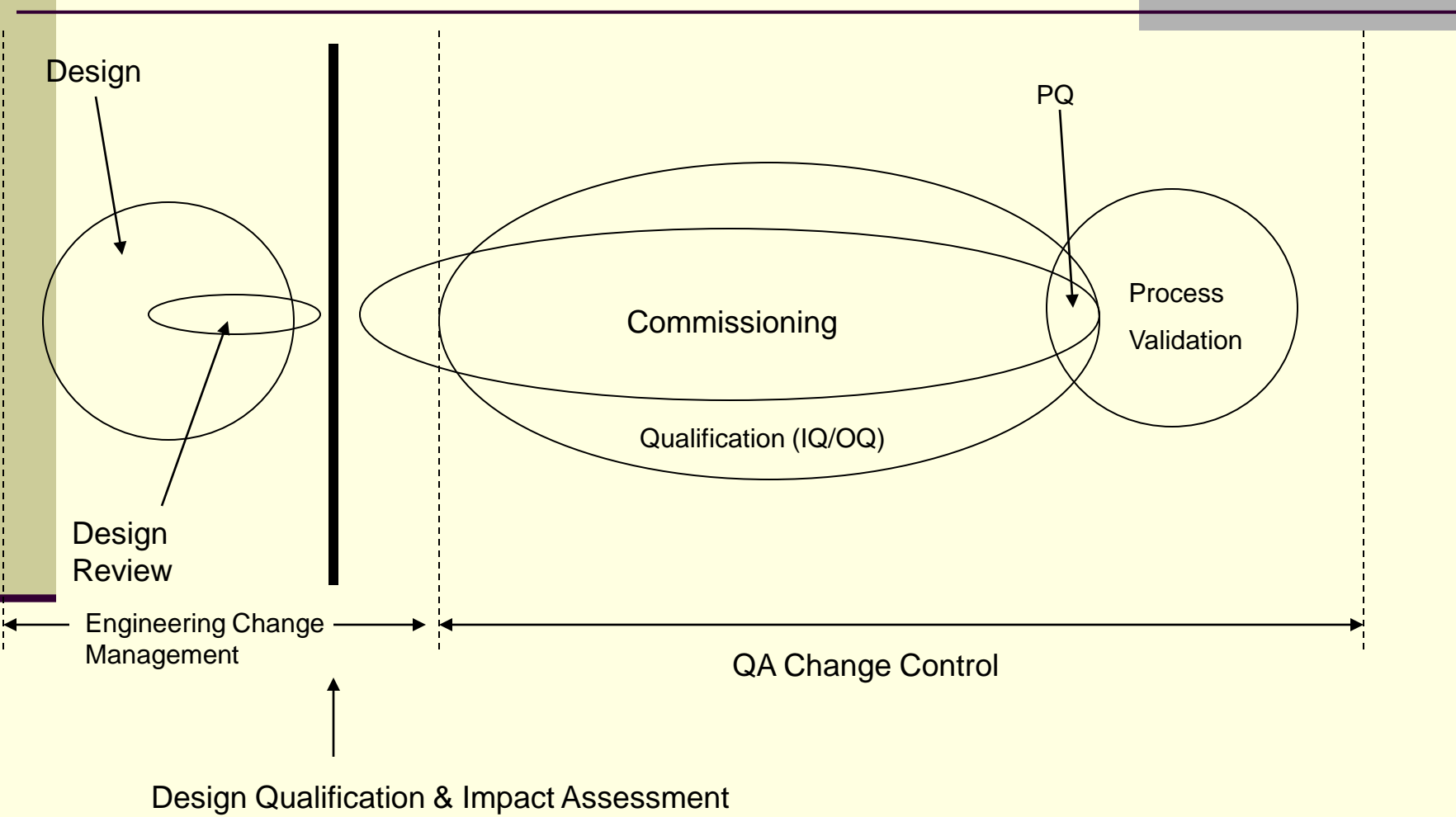
Tools for Criticality Assessment

- Failure Modes and Effects Analysis (FMEA)
- Fault Tree Analysis
- HACCP
- Cause and Effect
- Qualitative
- Quantitative

Where is Impact Assessment Used?

- Design Review
- Change Control
- Adverse Events
 - Deviations or discrepancies
 - Incidents involving system, component or process failure

Designing for Impact



Change Management

- Impact Assessment is a key part of the Change Management process
 - Assists with the defining the change
 - Identifies risk to quality and patient
 - Determines testing/verification of change to assure suitability

Adverse Events



Adverse Events

- Impact Assessment process should be integral in the deviation or discrepancy process to define what happened, determine the root cause and apply corrective and/or preventive action eliminate the go-forward risk

Example for Discussion # 1

- Compressed Air System in a Non-Sterile OSD facility which feeds product contact processes:
 - What are the CQA's?
 - What are the CPP's?
 - What is Direct Impact? Indirect? No Impact?
 - Where would you set the system boundaries?
 - What would the challenge strategy be?

Potential Answers for Example # 1

- Compressed Air System in a Non-Sterile OSD facility which feeds product contact processes:
 - What are the CQA's?
 - Cleanliness of the CA only at the product contact areas, usually Viable particle, oil mist and non-viable particulate IAW ISO standards
 - What are the CPP's?
 - Pressure dew point
 - What is Direct Impact? Indirect? No Impact?
 - Direct Impact: Final filters, dew point monitoring
 - Indirect: Primary filtration, dryers
 - No Impact: Anything upstream of primary filtration
 - Where would you set the system boundaries?
 - Around direct impact components
 - What would the challenge strategy be?
 - Verify monitoring equipment, dryers and filtration
 - Recurring CA testing

Example for Discussion # 2

- HVAC system supplying a Non-Sterile OSD processing room (manufacturing or packaging)
 - What are the CQA's?
 - What are the CPP's?
 - What's Direct Impact? Indirect? No Impact?
 - Where would I set the system boundaries?
 - What would the challenge strategy be?

Potential Answers for Example # 2

- HVAC system supplying a Non-Sterile OSD processing room (manufacturing or packaging)
 - What are the CQA's?
 - Room air cleanliness
 - Room T&RH conditions
 - Room pressurization control
 - What are the CPP's?
 - HVAC filter selection and DP
 - HVAC Leaving Air Temperature
 - Room pressurization control
 - What's Direct Impact?
 - HVAC AHU and distribution ducting
 - T&RH monitoring equipment
 - Where would I set the system boundaries?
 - Around AHU, excluding utilities like steam, HHW, electric, CHW, clean-steam for humidification, BAS, etc.
 - What would the challenge strategy be?
 - Verify direct impact equipment, commission utilities, recurring room air quality testing