Facilities Validation of Oral Solid Dose

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PRESENTATION OVERVIEW

- Knowledge of the industry is paramount.
- GMP and the design.
- Design issues to consider.
- What to consider to be successful.
- Cost, is it the key driver?
- Commissioning and Qualification

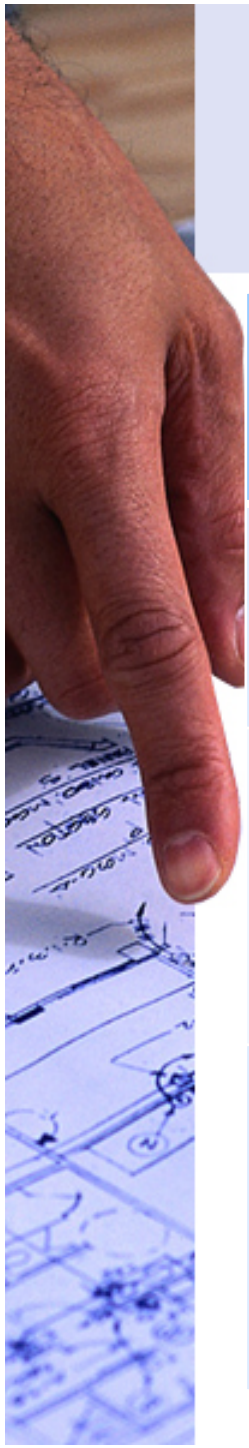
Can we be flexible?
Can we be cost and quality conscience?
Do regulations allow us to be competitive?

GMP Design

- Must know how the facility is to be operated.
- How will it be validated?
- GMP criteria must be included in facility conceptual design.
- The foundation to the facility design is the manufacturing process(es) and product(s) that will be produced, tested, and/or held in the facility to be designed.

Regulatory Requirements Designer needs to know

- Regulatory agencies that will have jurisdiction over Operation
- Preparing User Requirements Specifications, process and operational flow diagrams
- Developing system design criteria
- Developing the facility conceptual design
- Corporate philosophies
- Operating philosophies
- Knowledge of manufacturing process
- Material, personnel, and equipment flow patterns
- Commissioning, qualification and validation approach



Pharmaceutical Manufacturing Facility

Process understanding	Validation vs. continuous verification	Regulatory burden
Current levels of processing understanding	3 batch validation – open loop	No regulatory relief over current levels
Processing understanding allowing feedback incorporated	Continuous verification	Regulatory “relief” related to level of risk management achieved
Process understanding with feed forward predication and feed back verification	Continuous verification with maximum risk mitigation	Lowest level of regulatory involvement after proof of concept

Facilities Validation of Oral Solid Dose

- Are current and new facilities different from facilities 30 years ago?
- Testing & Controls different?
- What is different about current manufacturing equipment?
- Do we need to upgrade/update?
- WHY?

Facilities Validation of Oral Solid Dose

Today's Manufacturing Processes

- Large inefficient batch equipment
- Low utilization 30-40% on average
- Low product yield
- Excessive amounts of product non-conformance
- Long lead times due to stage and final testing
- High operating costs
- High inventories and excessive warehouse use

Global Business-Global Quality

- Quality depends on knowing the science of our product, if we have a quality issue we must be able to determine root cause of defect

- We must determine what attributes contribute to quality and focus on those, maximize the use of our resources

- Manufacturing science is knowing product, process, technology, risk, and quality systems that yield high quality each and every time

- Designing quality into the manufacturing process is Imperative

- Innovation, flexibility and continuous improvement techniques must be designed into the facility and product from the beginning

- Variability is the enemy of operations, the design must reduce variability where appropriate

- Real time feedback must be employed in the design

Facility Conceptual Design

- The conceptual design are developed during the creation of the process flow diagram (PFD).

- Support utilities are derived when the quantity of the utility is known and determination if segregation of process and utility buildings is necessary.

- When manufacturing process and support utility conceptual designs are completed, the facility layout is developed.

- Detailed report on facility requirements and presenting the above concepts that were investigated, (schematic design e.g.). This is used for the Design Development phase.

- Input is required from a multi-disciplined team consisting of facilities professionals that include manufacturing, quality, engineering, and validation.

Facilities Validation of Oral Solid Dose

Design Process Phases

- Programming is the problem seeking phase. Design criteria, not solutions, are defined. Space program are created during this phase.

- Design phase now determines the architectural design by organizing the facility into a two and three dimensional layout and tests the criteria based on the program.

- The architect designs facility around the process and the engineering systems required to support the process.

- Construction

- Commissioning/Qualification/Validation

- Operational/utilization

Facilities Validation of Oral Solid Dose

Planning Phases

- Facilities and equipment must be easily cleaned and maintained.

- Cross contamination is a significant issue. People flow as well as HVAC systems and dust control systems must be designed to minimize or eliminate the potential for cross contamination.

- A disciplined approach is required ensure that the intent of the regulations are met.

- Designer must be current with new technologies. i.e. PAT

Commissioning Plan

Documents to Support Equipment Qualification

- Construction Documentation
- Vendor Turnover Package
- Commissioning Documents
- Factory Acceptance Testing (FATs)
- Site Acceptance Testing (SATs)
- Piping & Instrumentation Drawings (P&IDs)
- Equipment/Instrument Lists
- Layout drawings
- Spare Parts List
- Operation & Maintenance Manuals
- Change Control Documents
- Calibration Reports
- Standard Operating Procedures (SOPs)
- Qualification Protocols

Good Engineering Practice (GEP)

- “Established Engineering methods and standards that are applied throughout the project lifecycle to deliver appropriate cost-effective solutions”

Commissioning

- A well planned, documented, and managed engineering approach to the start-up and turnover of Facilities, systems, and equipment to the End User that results in a safe and functional environment that meets established design requirements and stakeholders expectations.

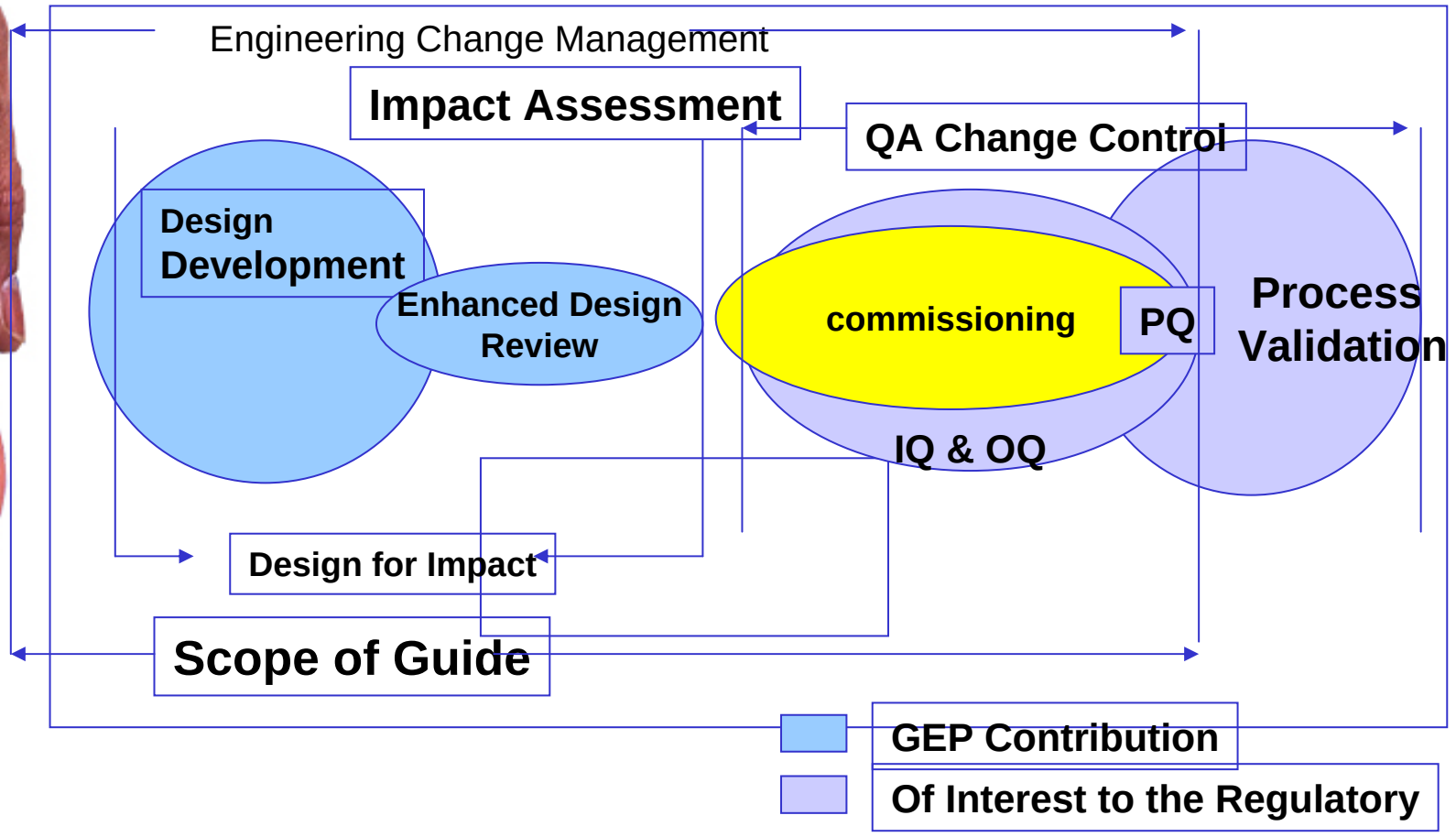
Commissioning Testing

Organizing and Planning
Factory Acceptance Test (FAT)
Site Acceptance Testing (SAT)
Static Testing (pre-commissioning)
Operator Training
Walk Down & Tagging
Full Functional Testing
As-Built Documentation
System & Equipment Manuals
Spare Parts Management

Commissioning Plan

- Commissioning Plan should contain the following deliverables: (Direct Impact Systems)
  - Commissioning Plan
  - Commissioning Schedule
  - Commissioning Budget
  - Overall Test Plan
  - Factory Acceptance Test/Report
  - Site Acceptance Test/Report
  - Inspection Plan/Report
  - Functional Test/Report
  - System Test Summary Reports
  - Commissioning Summary Reports

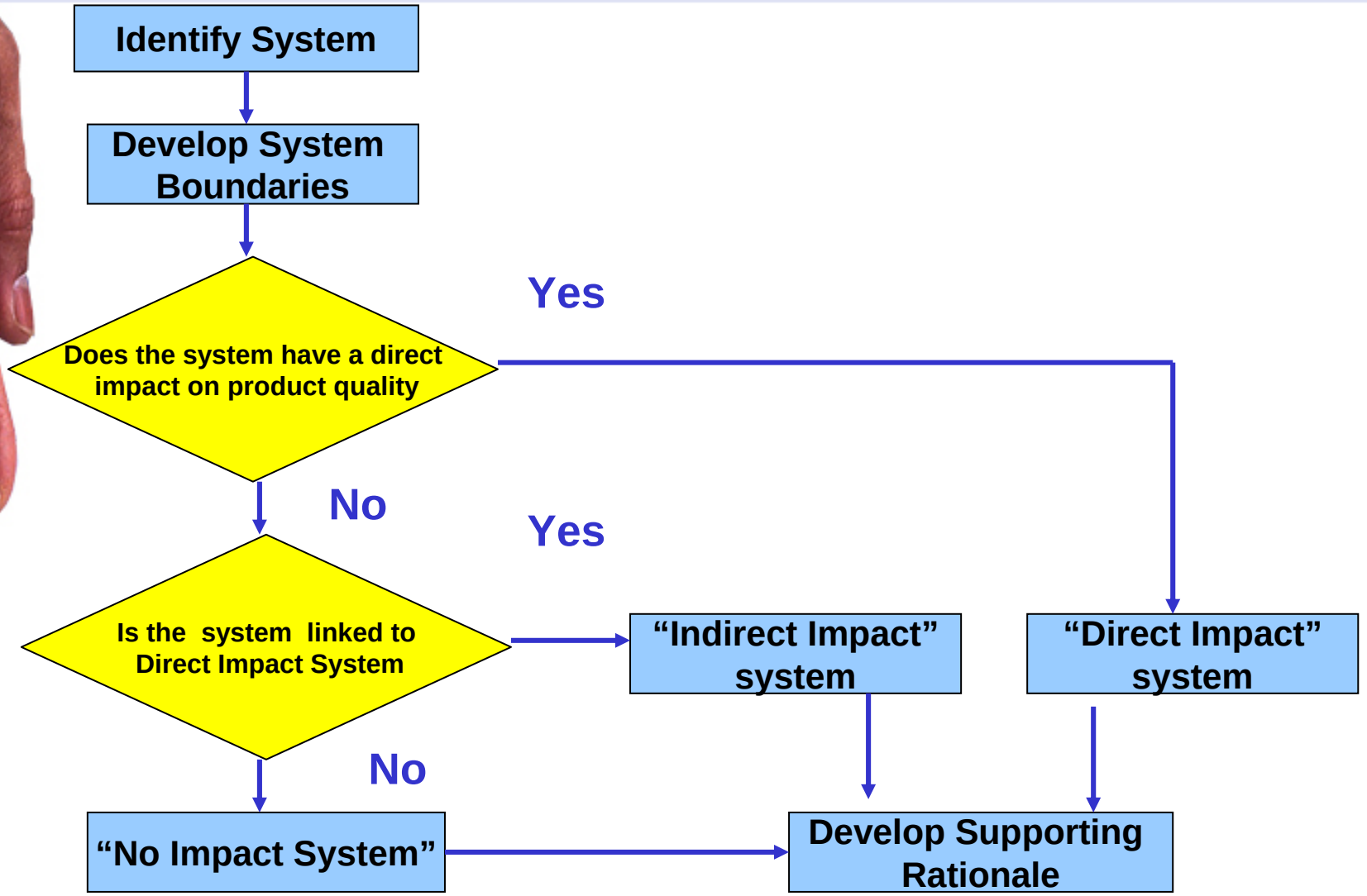
Scope of the Commissioning and Qualification Guide



SYSTEM QUALIFICATION

- System Boundary
  - A boundary is drawn on the appropriate engineering drawing – typically the P & ID (Process & Instrument Diagram).

System Impact Assessment Process Overview



Commission Strategy

Commissioning Plan

User Requirements

Performance Testing

Functional Specifications

SAT Plan

Setting –to-work

Regulation & Adjustment

Design Development

FAT Plan

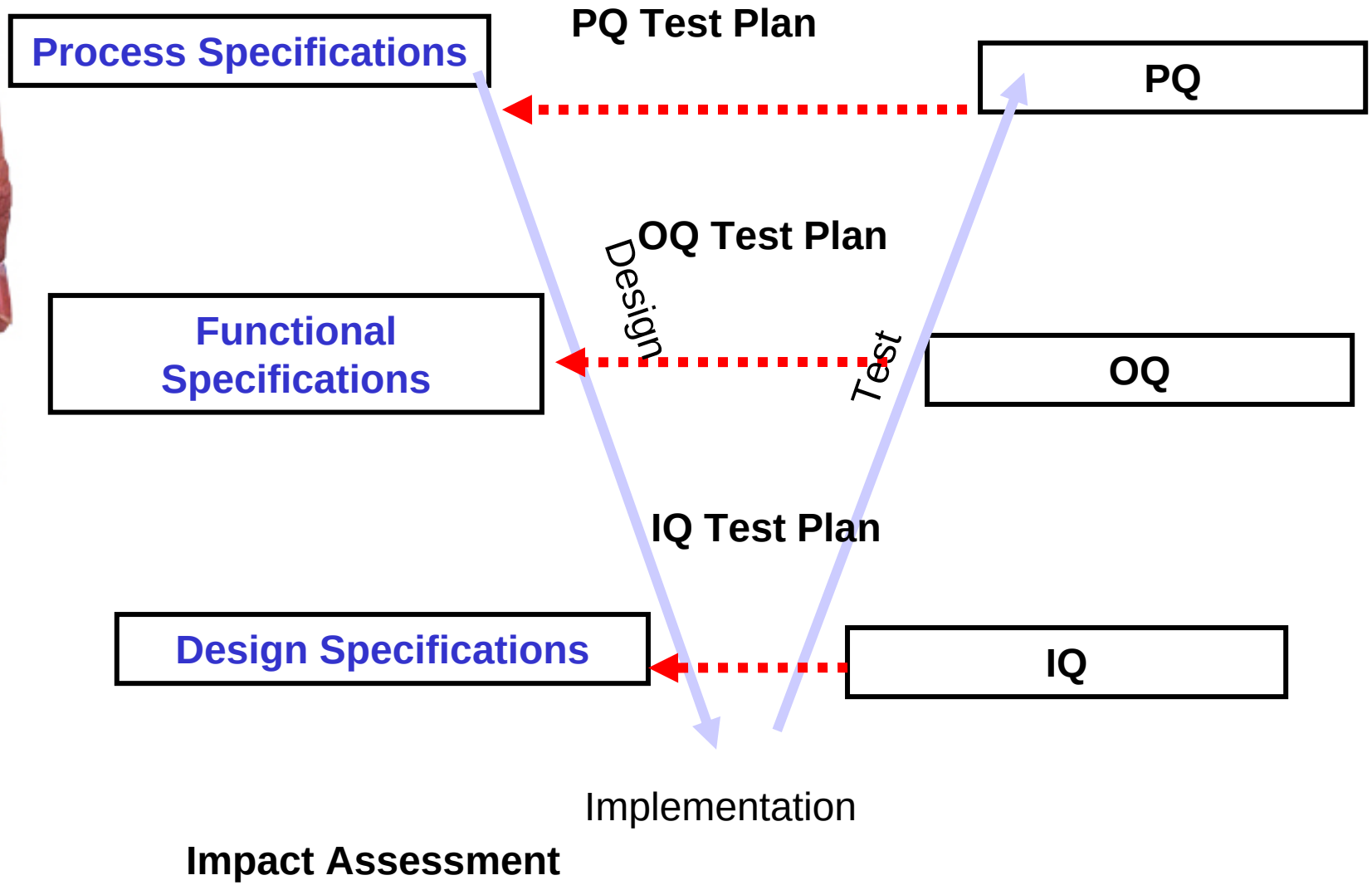
Design Specifications

Physical Completion & Inspection

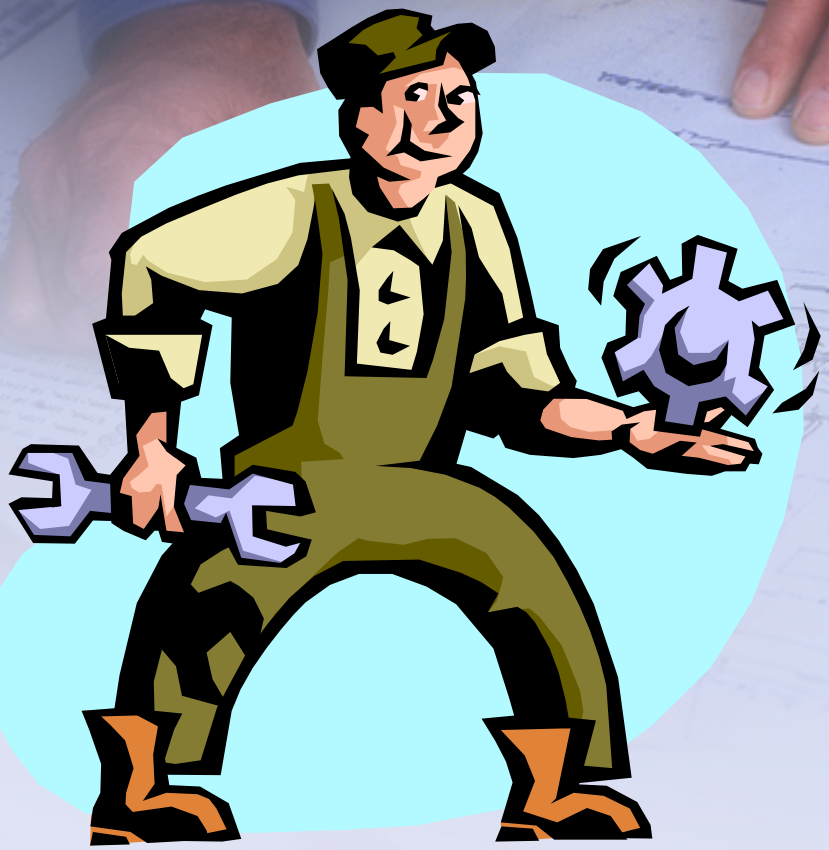
Impact Assessment

Implementation

Direct Impact Assessment



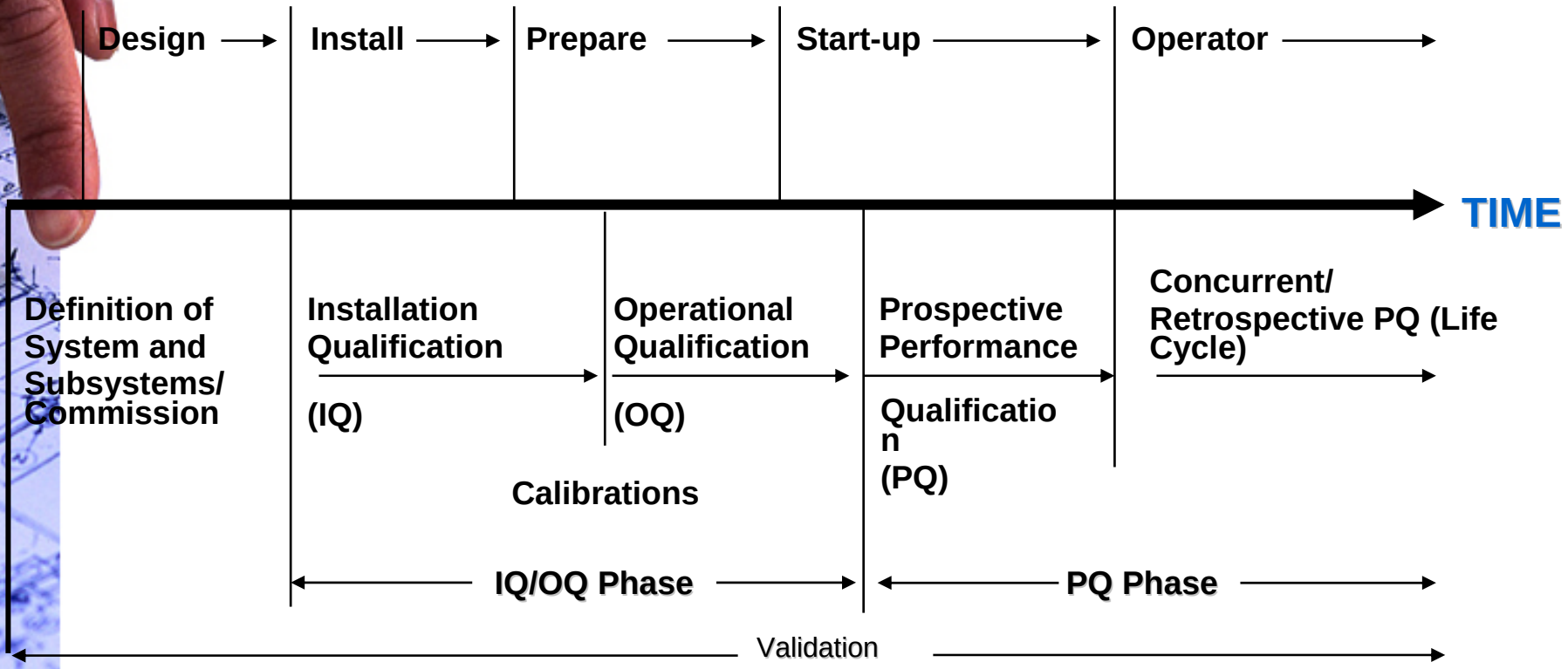
Facility And System Qualification



New Process Guidance
Three Phases of Process Validation

- **Stage 1: Process Design**
  - *Lab, pilot, small scale and commercial scale studies to establish process*
- **Stage 2:Process Qualification**
  - *Facility, utilities and equipment*
  - *Performance Qualification (Confirm commercial process design)*
- **Stage 3: Process Monitoring (Continued Process Verification)**
  - *Monitor, collect information, assess during commercialization*
  - *Maintenance, continuous verification, process improvement.*

The Validation Time Line (2009)



Master Plans

- Validation Master Plan
  - **A document which summarizes the firm's validation plans for establishing the reliability and consistency of the equipment, systems, and processes in the facility, as well as the ongoing program for maintaining a validated state of control.**
- Commissioning Plan
  - **A document which summarizes the firm's intentions, philosophies, and policies regarding the commissioning or facility equipment and systems.**

Facilities

- Typically focus on those elements of the facility that contribute to environmental control and, therefore, ultimately product quality

Qualification Protocol

- "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product, meeting its pre-determined specifications and quality attributes"[1]

- Each of these systems, including many others, must be "evaluated" in terms of installation and performance.

1. FDA definition (Guideline on Process Validation)

Facility Qualification

- Materials and Design are Compared to those specified.
- Remember you can only inspect plumbing and duct work at one time-- before the sheet rock goes up!
- Take photographs

System Qualifications (Startup)

- Troubleshoot and Startup by Equipment Vendor
- Finalize equipment protocols. Inventory instruments, calibrate and loop check instruments, organize vendor-provided documentation.
- Finalize procedures for equipment operation, cleaning, etc.
- Factory Acceptance Testing (FAT) and/or Site Acceptance Testing (SAT)

System Qualifications

- ***Prepare Design Documents*** -
  - Define reqt's for documentation required from vendor, including drawings, specs, manuals, etc.
- ***Generate Equipment and Process Specifications*** -
  - Define EQ and PV reqt's, including preparation of prelim protocols and SOPs for operation, maintenance, cleaning, etc.
- ***Procure and Install Equipment*** -
  - Secure and organize documentation provided with equipment, e.g., drawings, manuals, certification, etc.

System Qualifications

- Basic checklist is used for IQ -
- Defined Direct/In-Direct/Non-Impact System
- Manufacturer information: contact info., specs, P.O., manuals, etc.
- Equipment description (make, model, serial number, etc.)
- Instrumentation
- Spare Parts
- Control Panels
- Safety
- PM
- Calibration
- Support Utilities

Qualification Strategy

- *Validation Project Plan versus Validation Master Plan*
- *Qualification Protocols*
  - IQ Installation Qualification
  - OQ Operational Qualification
  - PQ Performance Qualification

Qualification Phase (Q1)

IQ — Installation Qualification

Documented verification that all key aspects of the installation adhere to approved design intentions according to system specifications and that manufacturers' recommendations are suitably considered.

Qualification Phase (Q2)

OQ — Operational Qualification

Documented verification that each unit or subsystem operates as intended throughout its anticipated range.

Qualification Phase (Q4)

Computer-Related System

1-Software

2-Hardware

3-Controlling system (Computer system)

4-Equipment

5-Operating procedures and documentation

6-Controlled process

7-Total System (Computerized System)

8-Operating Environment

Qualification Phase (Q3)

PQ — Performance Qualification

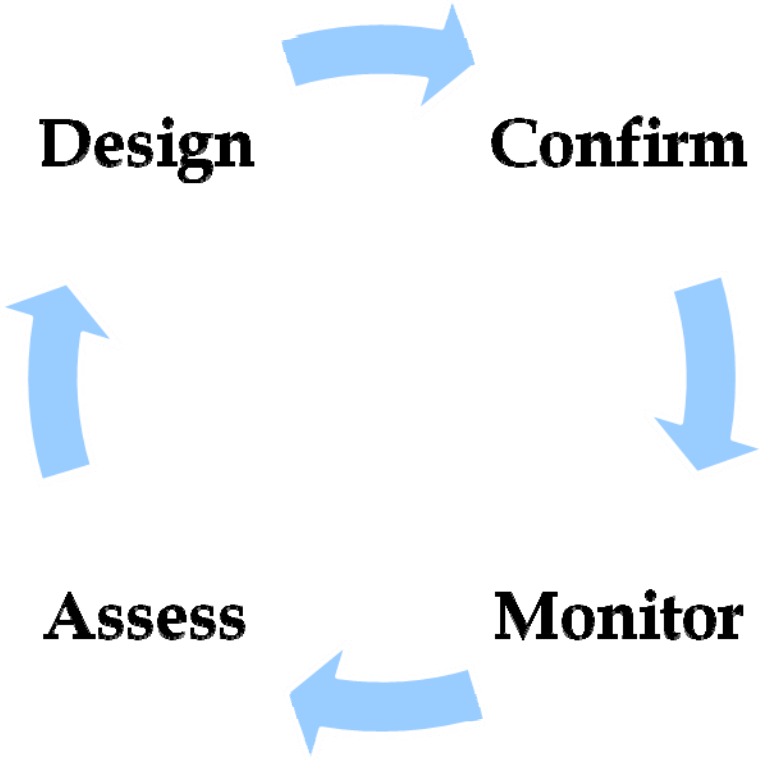
Documented verification that the integrated system performs as intended in its normal operating environment.

System Qualifications

- One of the outputs of OQ and PQ is the development of attributes for continuous monitoring and maintenance.
- Important aspects of Process Monitoring will be addressed later.

Life Cycle

- Lifecycle approach links product/process development to the commercial manufacturing process, and maintains the process in a state-of-control during routine production.



Summary

- Proper Planning
- Develop Matrix define upfront which activities will be performed during commission and qualification
- Insure that duplication of activities are not performed
- Engineer Change Management is in place.
- System for verification of document deliverables

How Much Validation is Enough? What's the Secret?

ENOUGH = *that which meets the test of*

COMMON

SENSE

and no more!!!

Thank You

- Question and Answers?