GENESIS ENGINEERS

Project Management Process for Aseptic Processing Facilities (APF) Training Module 4

NIH National Institutes of Health

Introduction

- This is the final module of a four-module training course, each module consists of
  - A half-day training sessions
  - A 10 question assessment to be given at the end of each module

- This course provides introductory training on Project Management Process for Aseptic Processing Facilities (APF)

- This course is intended for facility management and personnel, laboratory personnel, Quality Assurance (QA), and contractors

Introduction

- Module content
  - ➢ APF Overview
    - What and Why of cGMP
  - ➢ Definitions
  - ➢ Structured Design Process for Aseptic Processing Facilities
  - ➢ Structured Qualification Process for Aseptic Processing Facilities
  - ➢ Validation
  - ➢ Key Issues and Lessons Learned

Introduction

Department

Position

Years of Service

Interesting Fact

What is cGMP?

- **cGMP** — "current" Good Manufacturing Practice
  - Regulations
  - Assure proper design, monitoring, and control of manufacturing processes and facilities
  - Assure the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations.
- The "c" in **cGMP** is added to remind manufacturers that they must employ up-to-date technologies and systems in order to comply with the regulation.
- It may be necessary to comply with multiple regulations depending on the location of the manufacture vs. the location of distribution and sale.

Definitions

- **GEP –** Good Engineering Practice
  - Established engineering methods and standards that are applied throughout the product life cycle to deliver appropriate and cost-effective solutions.
  - Engineering Processes & Systems to meet institutional needs

- **GEP vs GMP**
  - GEP Serves the institution by assuring good design and decision making to support institutional goals.
  - GMP Serves the patient by assuring good design and decision making to support Safety, Identity, Strength, Purity and Quality (from 21CFR210).

Definitions

- **GDP –** Good Documentation Practices
  - Established documentation methods and standards that are applied to all cGMP documents that assure clarity and accuracy. These include:
    - Revision History
    - Consistent Dating Practices
    - Formal Approvals
    - Consistent naming, signatures and initials
    - Document Numbering
    - Document Control

Definitions

- **Critical Parameter**
  - A room variable (such as temperature, humidity, air changes, room pressure, particulates, viable organisms, etc.) than, by law or by determination from pharmaceutical product development data, affects product strength, identity, safety, purity, or quality (SISPQ)
- **Acceptance Criterion**
  - The predetermined result of a specified test. In HVAC, the upper and lower limits of the room environment (critical parameters). If these limits are exceeded, the exposed pharmaceutical product may be considered adulterated.

Who Regulates & Enforces cGMPs?

THE FDA CODE OF FEDERAL REGULATIONS

- FDA Code of Federal Regulations (CFR) is a huge sea of regulations that the FDA has created for regulating all products that come under its purview of regulation. The FDA codes of federal regulations are numbered and cover all products, processes and the activities that go into their creation.

GMP Regulatory Basics

- ✓ You must have accurate, written, and approved procedures.
- ✓ You must check calculations and critical steps.
- ✓ You must check conclusions & document them.
- ✓ You must Investigate aberrant results.
- ✓ You must document all actions and decisions.
- ✓ You must prevent cross-contamination and mix-ups by segregation, labeling, and control procedures.

History of cGMPs

cGMPs and their predecessors have generally been established as a result of crises or disasters in the industry.

In the U.S.A.:

- Food & Drug Act of 1906
  - In response to the conditions in the meat industry (“The Jungle”)
- Food, Drug & Cosmetic Act (1938)
  - Makes it illegal to sell unsafe drugs
  - In response to the large number of deaths from elixir of sulfanilamide ("elixir of death")
- 1st GMP regulations published in the Federal Register (1963)
  - Now codified as 21 CFR Parts 210-226
- Proposed cGMPs in LVPs (Large Volume Parenterals) (1976)
  - Never approved but were used for guidance by industry 1978

History of cGMPs

In the U.S.A.: continued

- cGMPs for Finished Pharmaceuticals (1978)
  - Parts 210 and 211 of the Federal Register
  - Other GMPs for Devices (QSR, 820) & Blood Products (600)
- FDA Modernization Act of 1997 (FDAMA)
  - Amended the FD&C Act
  - Enacts many FDA initiatives undertaken under REGO (Reorganizing Government)
- FDA was the first national agency to make GMP a legal requirement.
- Cephalosporin 10% cross-reactivity rate in 1960's and 70's proved to be penicillin cross-contamination – 1987 FDA Requires Penicillin Separation
- Guidance for Cephalosporins and Monobactams follows – 26 years later (2013)

What constitutes the cGMPs?

- GMPs and Quality System Regulations identified in the *Code of Federal Regulations Title 21*
  - *https://ecfr.io/*
- FDA issued Compliance Policy Guidance Manuals and Compliance Policy Guides
  - https://www.fda.gov/ICECI/ComplianceManuals/default.htm
- FDA issued “Guidance for Industry Documents”
  - They represent the FDA’s current interpretation of 21 CFR Title 21 Regulations and how they should be applied. Guidance documents, while not legally binding, are best to be implemented if possible.
  - Regulations can be found on the FDA website: www.fda.gov, by Center and product (CDER (drugs), CBER (biologics), CDRH (devices and radiologic products), CFSAN (food and cosmetics), CVM (veterinary products), and CTP (tobacco)
- FDA issued Letters to Industry
  - Represent FDA’s opinion on a particular activity and requires immediate action by industry – typically enforceable.
- Current Accepted Industry Practices “Standard”
  - Standards typically issued by recognized professional societies.

What constitutes the cGMPs?

Current Good Manufacturing Practices address all aspects of the production of pharmaceuticals (or devices or biologics).

The primary areas of focus are:

- Personnel
- Facility
- Process
- Products
- Documentation

The cGMPs (US, EU, et al) are generally considered to be ambiguous – they would say “flexible”.

They define what must be achieved, very generally, but not how.

What constitutes the cGMPs?

Formal documentation includes:

- 21 CFR Part 11 - Electronic Records and Signatures
- 21 CFR Part 58, Good laboratory practices for nonclinical laboratory studies
- 21 CFR Parts 210 and 211 - Manufacture, processing, packing and holding of drugs
- 21 CFR Part 212 Current Good Manufacturing for Positron Emission Tomography Drugs"
- 21 CFR Part 600, Biological products: general
- 21 CFR Part 606 - Current good manufacturing practice for blood and blood components
- 21 CFR Part 820 - Quality System Regulation (medical devices)
- 21 CFR Part 803 - Medical Device Reporting
- 21 CFR Part 1270, Human tissue intended for transplantation
- 21 CFR Part 1271, Human Cells, Tissues, And Cellular And Tissue-Based Product
- Directive 91/356/EEC - Medicinal products for human use
- Directive 91/412/EEC - Medicinal products for veterinary use

These are regulation and **MUST** be followed

In addition to the actual regulation, the cGMPs are written down in the form of *guidance* documents from a variety of sources.

What constitutes the cGMPs?

Related documentation includes:

- Industry Guidelines
  - ISPE Baseline Guides (e.g. Bulk Pharmaceutical Chemicals, Sterile Manufacturing Facilities, High Purity Water, C&Q, Process Gases)

- Regulatory Agency Guidelines
  - FDA Guidelines (Sterile Drug Products Produced by Aseptic Processing)
  - ICH (Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients)

These are guidelines which, although not law, help organizations comply with the regulations when followed.

The Role of Standards in our GMPs

Standards

- Set by industry experts and interested parties
- Detailed and specific
- Regularly reviewed and updated
- Slow but responsive to changes in technology

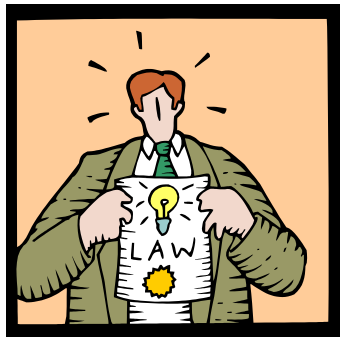
Regulations

- Set by agency employees and/or hired experts
- Generally, vague and open to interpretation
- Glacially slow to change

The Role of Standards in our GMPs

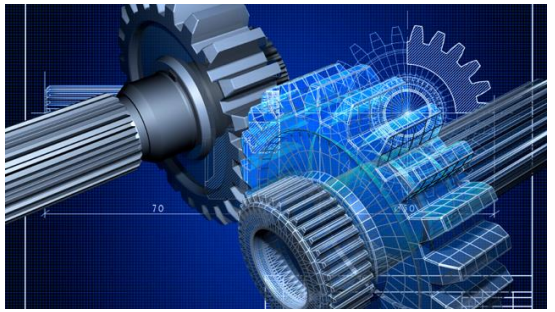
Regulations

- Carry the force of law, but are usually to vague to be directly enforced
- Cite Standards, making them enforceable



Standards

- Provide the technical detail needed for regulations to be meaningful and enforceable



The Role of Standards in our GMPs

Guidelines

- Opinions from regulators and others
- Not regulations but absent specific regulation, like industry practice, they impact enforcement

Industry Practice – “c” of cGMP

- Might be called “What the inspector has seen before”, Standards and “Good Engineering Practice” impact enforcement.

The Role of Standards in our GMPs

GMPs and ISO 14644

The GMPs invoke ISO 14644-1 to define the following:

- Classification of air cleanliness by particles
- The test method for classification
  - Defines the number of sample locations
  - Defines air sample size at each location
  - Specifies how to evaluate the data

The Role of Standards in our GMPs

Table 1 — Classification of air cleanliness by particle concentration

ISO Class number (*N*)	Maximum allowable concentrations (particles/m³) for particles equal to and greater than the considered sizes, shown below[a]					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
1	*10*[b]	d	d	d	d	e
2	100	*24*[b]	*10*[b]	d	d	e
3	1 000	237	102	*35*[b]	d	e
4	10 000	2 370	1 020	352	*83*[b]	e
5	100 000	23 700	10 200	3 520	832	d, e, f
6	1 000 000	237 000	102 000	35 200	8 320	293
7	c	c	c	352 000	83 200	2 930
8	c	c	c	3 520 000	832 000	29 300
9[g]	c	c	c	35 200 000	8 320 000	293 000

[a] All concentrations in the table are cumulative, e.g. for ISO Class 5, the 10 200 particles shown at 0,3 µm include all particles equal to and greater than this size.

[b] These concentrations will lead to large air sample volumes for classification. Sequential sampling procedure may be applied; see Annex D.

[c] Concentration limits are not applicable in this region of the table due to very high particle concentration.

[d] Sampling and statistical limitations for particles in low concentrations make classification inappropriate.

[e] Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

[f] In order to specify this particle size in association with ISO Class 5, the macroparticle descriptor M may be adapted and used in conjunction with at least one other particle size. (See C.7.)

[g] This class is only applicable for the in-operation state.

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Why does NIH need cGMP?

NIH is constantly undergoing changes in order to keep up with advances in technology and regulatory environments

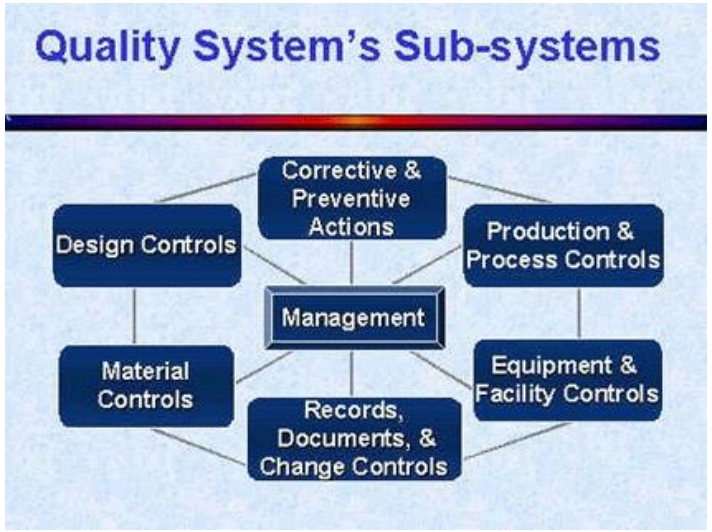
- Modernization
- Renovation
- Innovating spaces for new medicinal discoveries

National Institutes of Health

GENESIS ENGINEERS

Why does NIH need cGMP?

NIH is concerned with regulated Pharmaceuticals (issued by prescription), medical devices, tissues, and biologics (Cell products, blood products, vaccines, viruses, and plasmids).



National Institutes of Health

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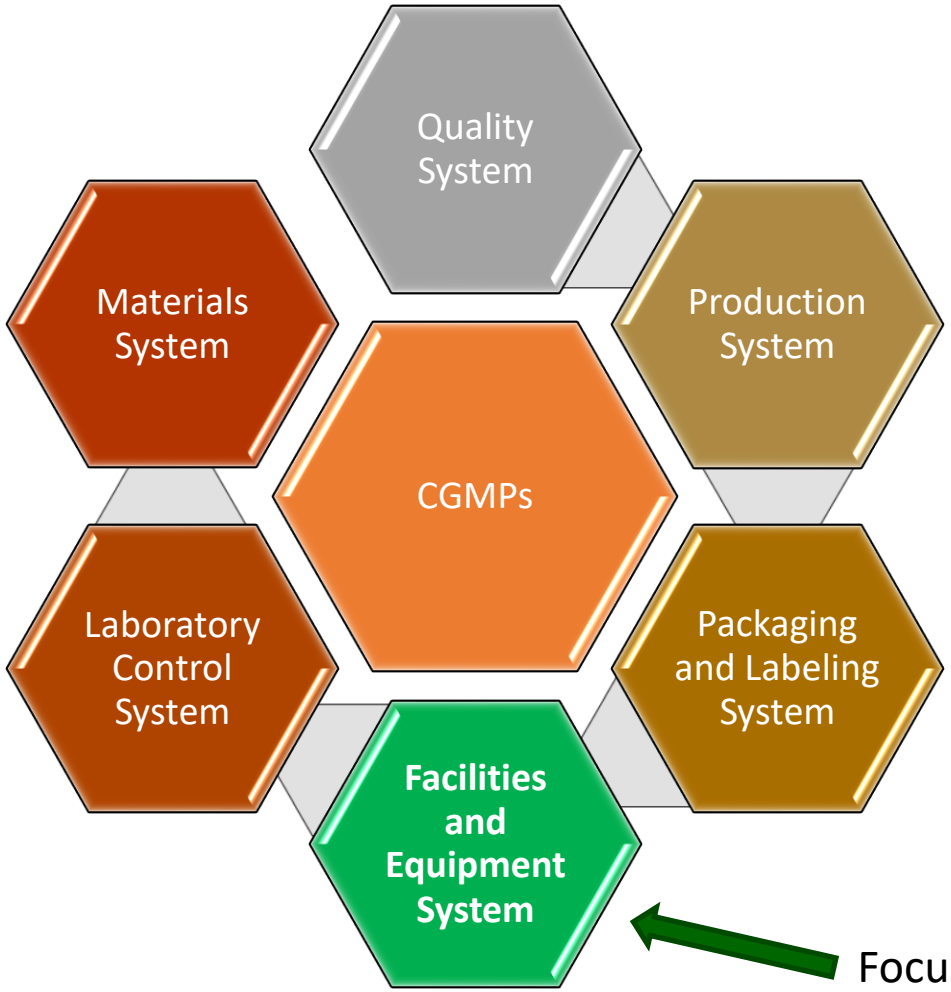
Components of GMP



Focus of this training module

Why do we need to follow cGMP?

- FD&C Act 21 USC 331(a) prohibits, among other things, "The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded“
- FD&C Act Section 501(a)(2)(B): “Failure to follow GMP requirements causes a drug to be adulterated”

What is the applicability of cGMPs ?

The FD&C Act requires that all drugs be manufactured, processed, packed, and held in accordance with current good manufacturing practice.

Standards for the manufacture of any regulated product:

- Drug Substances and Finished Drug Products
- Human and Animal Drugs
- Medical Devices
- Diagnostic Instrumentation & Equipment
- Biotechnology Products
- Natural Products for ‘medical’ use

The first five bullets are within the scope of patient treatment plans performed by NIH at the Clinical Center.

How Does FDA Interpret & Enforce cGMPS

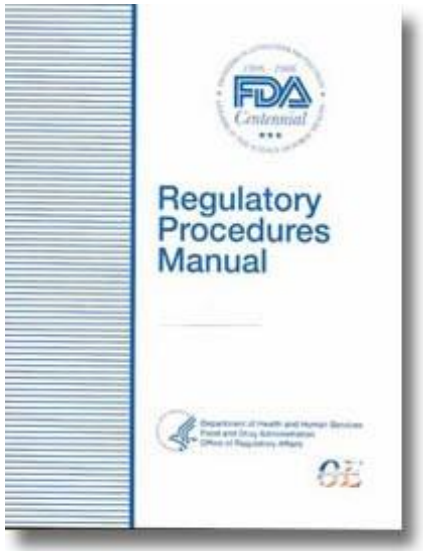
FDA issued Compliance Policy Guidance Manuals and Compliance Policy Guides

- https://www.fda.gov/ICECI/ComplianceManuals/default.htm
- Compliance Program Guidance Manual (CPGM)
  - The Compliance Program Guidance Manual (CPGM) provide instructions to FDA personnel for conducting activities to evaluate industry compliance with the Federal Food, Drug, and Cosmetic Act and other laws administered by FDA. Compliance Programs are made available to the public under the Freedom of Information Act. (See FDA Freedom of Information Act Handbook for Requesting Information and Records from FDA).
  - Compliance Programs do not create or confer any rights for or on any person and do not bind FDA or the public. An alternative approach may be used as long as the approach satisfies the requirements of the applicable statutes and regulations.
- Compliance Policy Guides (CPG)
  - Compliance Policy Guides (CPG) contains FDA compliance policy and regulatory action guidance for FDA staff.

How Does FDA Interpret & Enforce cGMPS

FDA issued Compliance Policy Guidance Manuals and Compliance Policy Guides

- Regulatory Procedures Manual (RPM)
  - The Regulatory Procedures Manual is a reference manual for FDA personnel. It provides FDA personnel with information on internal procedures to be used in processing domestic and import regulatory and enforcement matters. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.



GMPs are Everyone's Responsibility!

Failures to comply with cGMP can lead to FDA enforcement actions

- "483" – An FDA form (FORM 483) listing cGMP-related observations from on-site inspections. These observations refer back to the GMP regulations FDA feels are violated
- Establishment Inspection Report (EIR) – 483 follow-up
- Warning Letter – an opportunity to take "prompt corrective action" for serious deviations
- Consent Decree – an enforcement action, typically with fines and binding plans for compliance decreed in court where corrective action is court ordered

For malicious acts, "persons" can be fined and/or incarcerated!

- A "person" may be the company, its CEO. President, Director, Manager, Supervisor, or even the Operator / Technician who failed to follow GMPs
- "Persons" can be barred from working in the industry

Ensure cGMPs Are Followed

When do we test?

- Quality Control - Monitoring & Testing at the End
- No, this is not enough

Assurance of Quality during ALL phases of manufacturing.

Quality Assurance (or Quality Control) must be designed into the process, not just the product.

QA/QC Defines systems, standards, procedures and methodology employed to ensure compliance with cGMPs

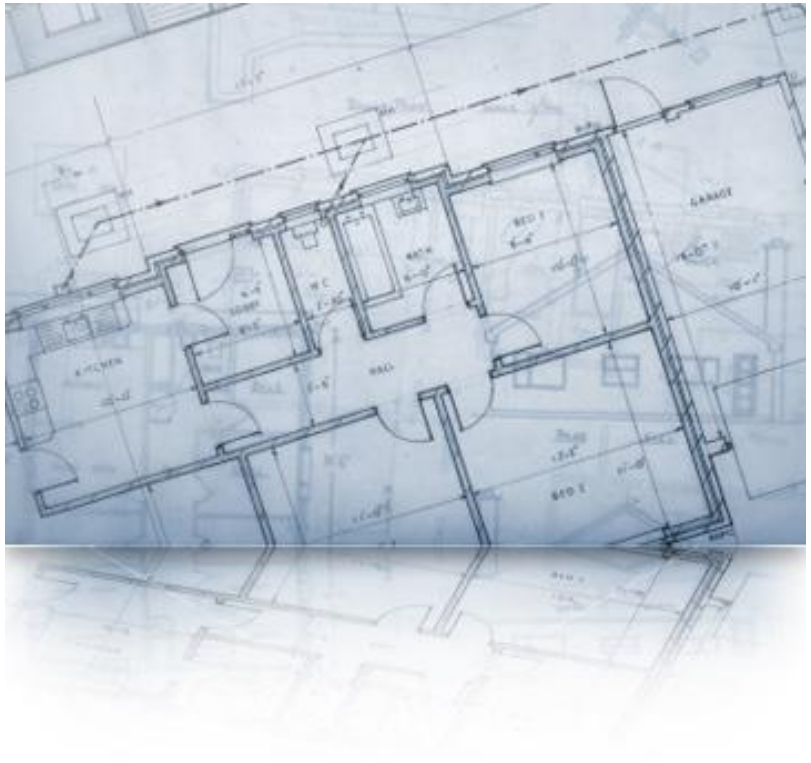
The Quality Control unit is essential to all aspects of manufacture, including CQV related activities.

cGMP Aspects - Facilities

“Fit for Intended Use”

Areas to Consider

- Appropriate Size
- Layout
- Personnel & Material Flow
- Interior Finishes and Architectural Details
- Ventilation Requirements
- Room Classification
- Temperature / Humidity
- Room Differential Pressure
- HVAC Control
- T/RH/DP Monitoring & Electronic Records
- Cleaning & Disinfecting
- Maintenance & Calibration



cGMP Aspects - Equipment

“Fit for Intended Use”

Areas to Consider

- Material of Construction (product contact?)
- Lubricants or any substances required for operation (product contact?)
- Appropriate Size (capacity, loads)
- Location
- Identification
- Performance
- Monitoring / Electronic Records
- Cleaning & Disinfecting
- Maintenance & Calibration

Number One Rule of GMP

UNDERSTAND THE PRODUCTS!

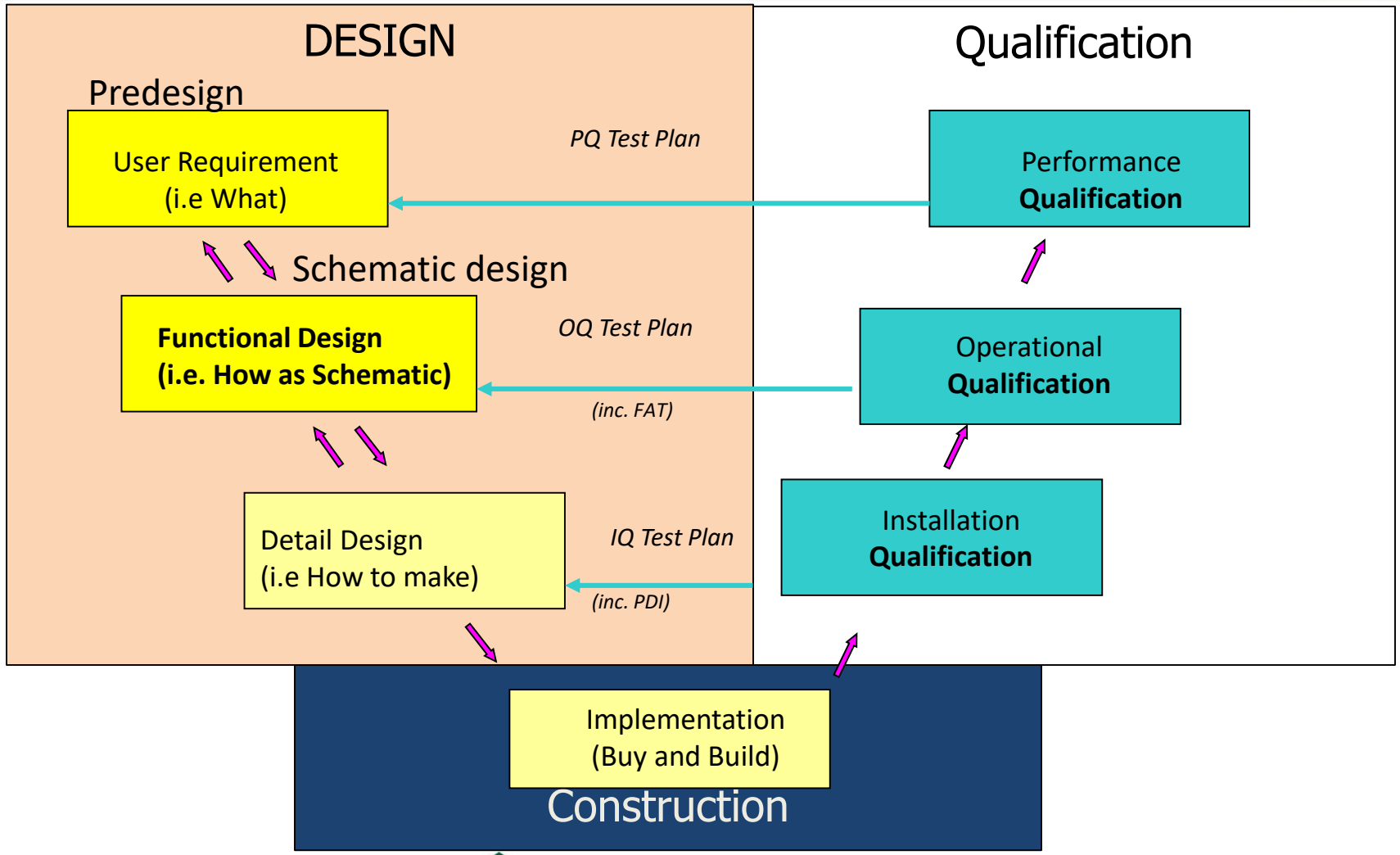
- You don't need to know everything, just a few key things…
  - Route of Delivery
    - Oral
    - Sterile
  - Process and its risks
    - Open processing
    - Not sterile filtered before use
    - No sterility test before use
  - Critical process variables

Structured Design Process

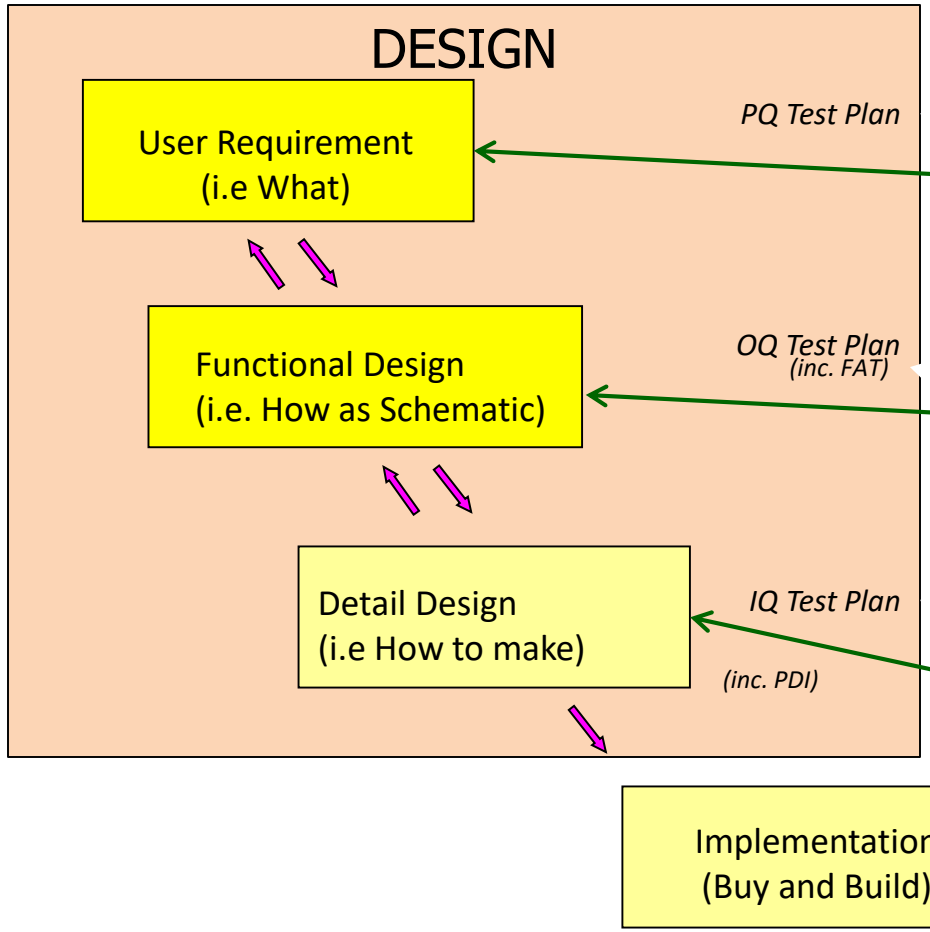
Roles and Responsibilities (what's different in APF?)

- **Pre-Design/ Design SME** – Provides cGMP review and guidance to the development of the early stages of concept development (think pre-POR) and/or during later design.
- **Commissioning Agent (CxA)** – Provides facility operational review and guidance to the Design team and is responsible to startup the facility.
- **Commissioning, Qualification , Validation Authority (CQV)** – Provides qualification and validation review and guidance to the Design team and is responsible to qualify/validate the facility.
- **cGMP Project Execution Manager (PEM)**– End-to-end support for PO/COR.

Structured Design Process



Risk Assessment at Every Stage

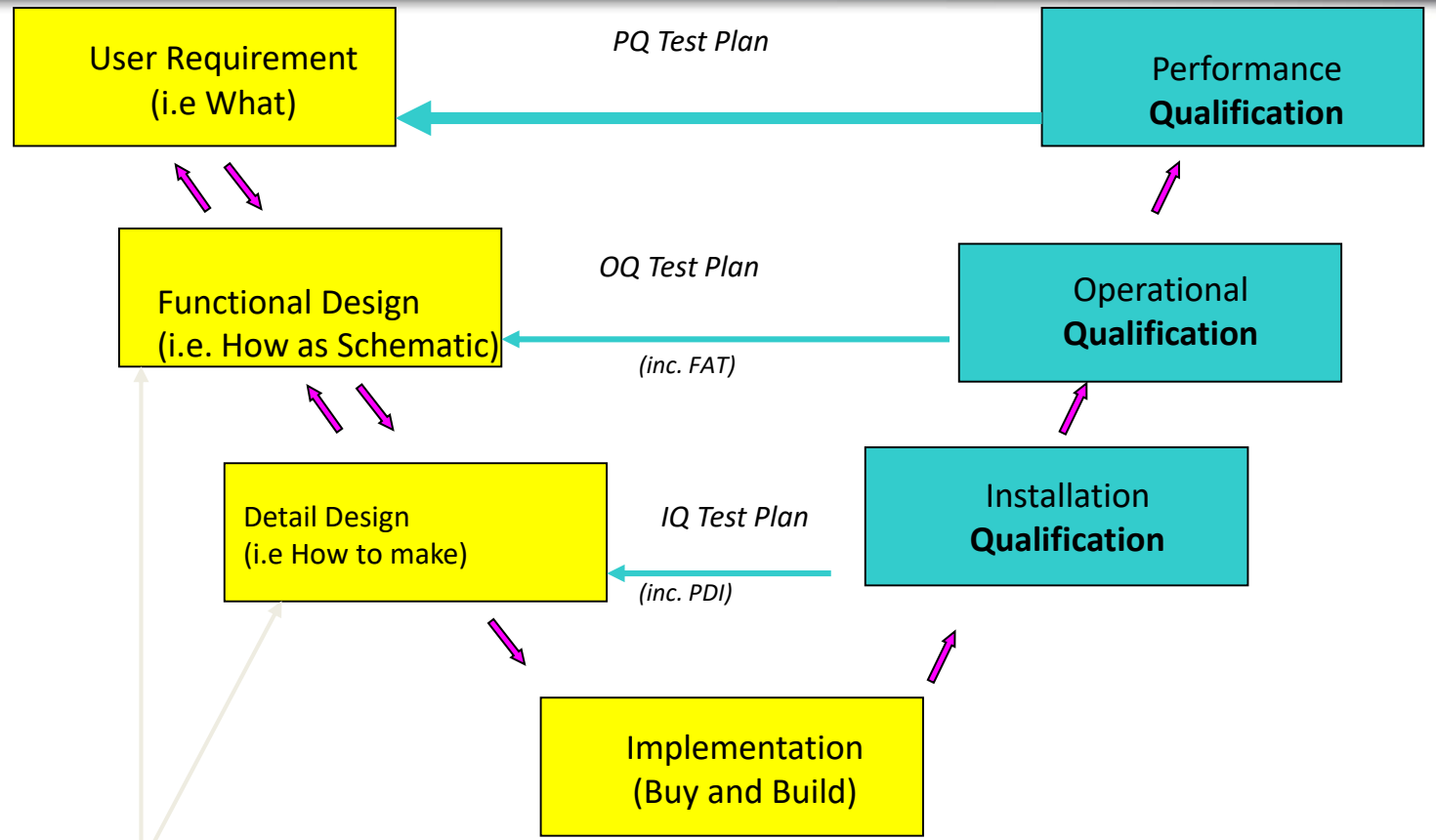


Use risk tools to set:
- Critical Parameters
- Acceptance Criteria
- GMP and Non-GMP

Use risk tools to Evaluate:
- Design Configuration
- Critical Components
- Qualification Needs

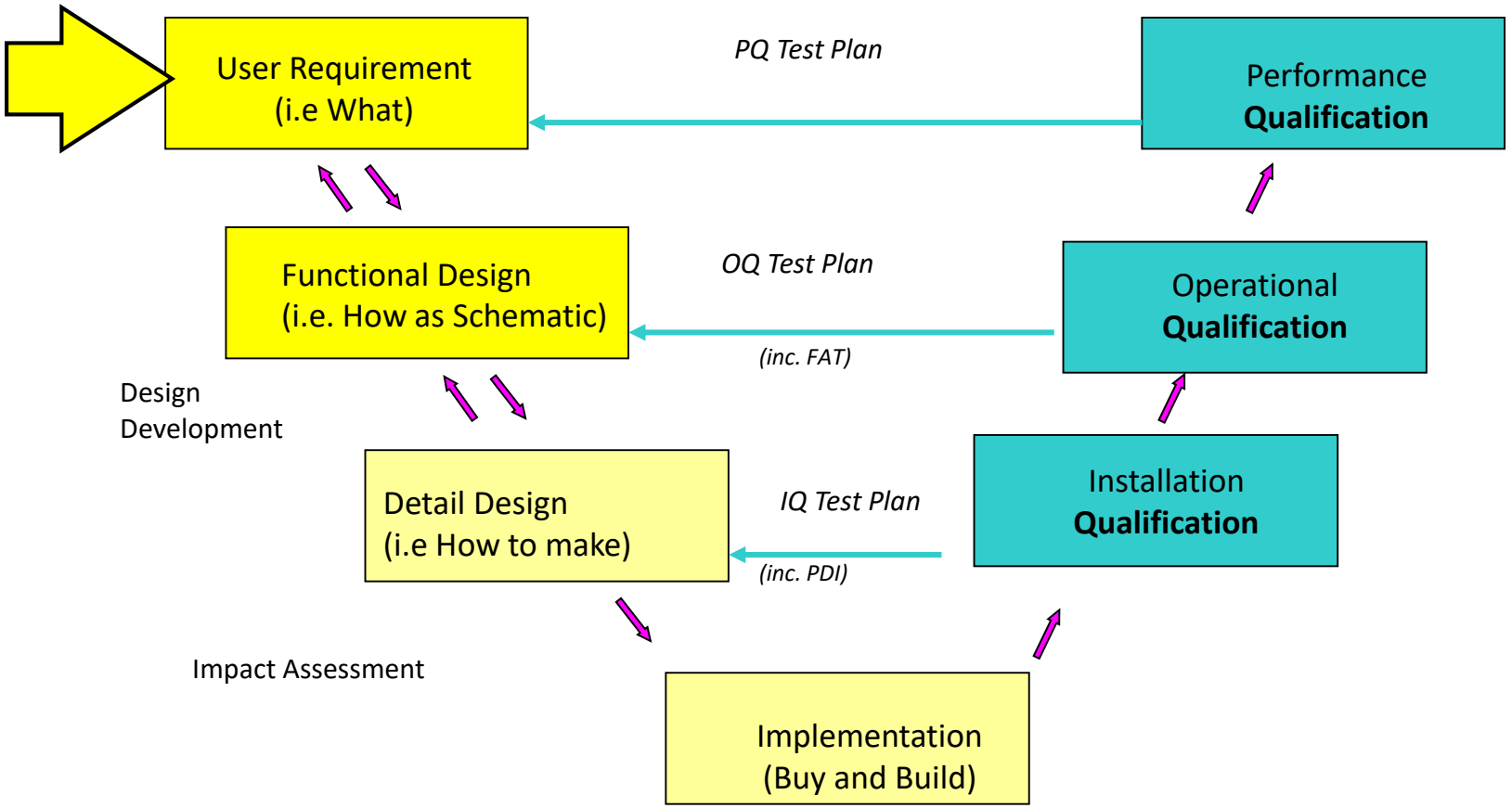
Use risk tools to Finalize:
- Critical Instruments
- Qualification Plan
- Startup and Testing Plan

Where Does Qualification Start?



During these phases, start to develop the Qualification Plan and documents

Setting User Requirements



Define User Requirements EARLY & Make Them Sacred

User Requirements:

- Applicable GMPs and other Regulation
- Critical Parameters that affect product or operations, usually…
  - Temperature
  - RH
  - Classification (particle count, viable counts)
  - Room Pressure
  - Flows (Raw Materials, Product, Personnel, Waste, Equipment)
  - Cross-contamination risk
  - Contamination risk
    - Facility Construction (materials, cleanability, sealing, etc.)
    - Gowning
    - Cleaning

Define User Requirements EARLY & Make Them Sacred

User Requirements cont…

- Requirements (General and by Room/System) with
  - Acceptance Criteria (the values of the CPs)
  - The driver or classification
    - Quality
    - Safety
    - Institution / Operations
    - Optional
- Block facility layout with cleanliness levels
  - Requirements for each room/area
  - Pressurization and HVAC Zoning Plans
  - System Diagrams (as appropriate)
- Reliability

Non-GMP User Requirements

- DRM Requirements
- Environmental Health and Safety
  - Operator Exposure Limits (OEL)
  - Environmental restrictions or Targets
  - Productivity
  - Maintenance Targets
- Construction Code Requirements
- User Preferences

Example User Requirements

NIH Clinical Center – Department of Pharmacy

Building 10 Interim Intravenous Admixture Unit (I-IVAU) Expansion

FACILITY AND FACILITY SYSTEMS URS

TABLE OF CONTENTS

APPENDIX

Example User Requirements

REVISION HISTORY

Revision	Prepared By	Date	Description of Change
0a	John Sakowski	17-Jul-2018	New Document
0b	Norman Goldschmidt	31-Jul-2018	References to Project and Dept. Corrected
0c	John Sakowski	14-Aug-2018	Final Draft Review
0d	John Sakowski	30-Aug-2018	Final Draft Review #2
0e	John Sakowski	18-Dec-2018	Final Draft Review #3
0f	JD Marsh	10-Jun-2019	Incorporating April 2019 comments, check vs. 100 Percent BOD
0g	JD Marsh	28-Jun-19	Updating approvers and check vs. 65% Construction Review Drawings
0h	JD Marsh	19-Aug-2019	Incorporated new comments and 13-Aug-19 meeting. Issued for approval.
0i	JD Marsh	01-Oct-2019	Updated per reviewer comments.

Example User Requirements

3. BACKGROUND

The objective of this document is to provide facility and utilities compliance requirements which are the basis of the design. Details on the design and configuration of the facility mechanical systems, architectural elements and other utilities systems will be developed in the Basis of Design Document for the I-IVAU - Interim Intravenous Admixture Unit Expansion Interim Pharmacy, Building 10 C-Wing, NIH WR #C106585, specifically:

- Indoor Design Conditions
- Ventilation Criteria
- Pressurization
- Air Handling System
- Exhaust System
- BAS / Control Systems
- Chilled Water
- Architectural Features, Systems and Finishes
  - Walls
  - Floors
  - Ceilings
- Mechanical
- Electrical
- Plumbing
- Fire Protection

This URS document should be used to help guide critical quality and safety aspects as the project Basis of Design and Detailed Design are developed. The design will continue to be developed consistent with NIH DRM, except where more stringent requirements are stated here-in or within the respective design document.

3.1 General Facility Description

The facility being constructed is located on the north side of the existing CNC Corridor that forms the north boundary of the existing I-IVAU facility on the NIH Bethesda Campus. The renovations will include the selective demolition of existing pharmacy laboratory space and the construction of the I-IVAU expansion, which includes construction of USP <797> and USP <800> compliant facilities.

Example User Requirements

6. RESPONSIBILITIES –VERIFY RESPONSIBLE GROUPS

Responsibilities for preparation, review and approval of this document are defined in the Document Approval Section of this URS. Additional responsibilities for implementing those requirements are listed below:

6.1 NIH OD/ORSC

- Review and approve URS to assure that QCA, SCA and OEA user requirements are met.
- Participate in decision on which optional requirements will be included.
- Ensure that the equipment is qualified against the Quality QCA user requirements.
- Ensure that that all pertinent regulatory requirements and organizational standards are met.

6.2 NIH Clinical Center Pharmacy

- Participate in the establishment of the URS.
- Review and approve URS to assure that QCA, SCA and OEA user requirements are met.
- Participate in decision on which optional requirements will be included.
- Ensure that the equipment is qualified against the Quality QCA user requirements.
- Ensure that that all pertinent regulatory requirements and organizational standards are met.

Example User Requirements

7. REQUIREMENTS

The following table specifies user requirements for the above systems.
There are four categories of requirements as defined below.

Attributes

URS TABLE	
Designation	Description
7.1.1. QCA	Quality Critical Attributes - Quality Critical Attributes (QCA) could have a direct impact on the quality of the product being produced or processed in the equipment. Quality attributes may affect the safety and / or efficacy of the product or processes. A quality attribute is a regulatory or compliance related attribute that can be measured / tested and will form the basis for qualification testing. Quality Critical Attributes must be included in the project.
7.1.2. SCA	Safety Critical Attributes - Safety Critical Attributes (SCA) could have a direct impact on the safety of the employees or the community at large. These attributes may also relate to cross-contamination protection of the product. A safety attribute is a regulatory or compliance related attribute that can be measured / tested and will form the basis for qualification or commissioning testing. Safety Critical Attributes must be included in the project.
7.1.3. OEA	Operations Essential Attributes - Operations Essential Attributes (OEA) are attributes that have been identified by site operations, the business unit or the company as being essential strictly from a business perspective. They define capacity parameters necessary to meet the plan and will include personnel health and safety or environmental protection. OEA attributes will be tested during equipment commissioning, but will not be tested again during equipment qualification. Operations essential attributes must be included in the project.
7.1.4. OA	Optional Attributes - Optional Attributes (OA) are attributes that have been identified by the team as being desirable, but not essential. Optional attributes may increase the capability or life expectancy of capital equipment, or reduce the manpower required to operate a system. Those optional attributes that remain in the project will be qualified if they could be QCAs in the future, or commissioned only if they will not. Whether or not an OA requirement remains in the project will be determined based on a cost / benefit analysis.

Example User Requirements

Facility Systems

URS TABLE		
Designation	Description	Type
General User Requirements		
7.1.5.	Critical instruments shall have NIST (National Institute of Standards and Testing) traceable calibration certificates except where approved otherwise and be maintained under a calibration program. EMS and BAS critical sensors shall be 3 point calibrated.	QCA
7.1.6.	Equipment, valves and instrumentation shall be accessible for routine maintenance outside of the classified areas when possible.	OEA
7.1.7.	Equipment/Systems will be maintained under a preventive maintenance program.	OEA
7.1.8.	Material Pass-Throughs shall be provided between USP <797> and <800> rooms and the CNC corridor. Material Pass-Throughs shall be HEPA filtered Active Pass-Throughs and shall meet the ISO requirements of the more stringent side the pass-through is serving. All Pass-Through doors are interlocked.	OEA QCA SCA

Don't Ask for it Because...

- We did it on the last job
- The Instructor said it was OK
- We've always done it this way
- The other guys do it this way
- **Do it because of its impact**

C.Y.A. (Cover Your Associates)

Whatever you decide,

WRITE IT DOWN !!!

- Include the rationale for decision

Avoids second guessing

- Everybody (including inspectors) understands the objectives

Control changes to User Req's

Use TABLES and Charts

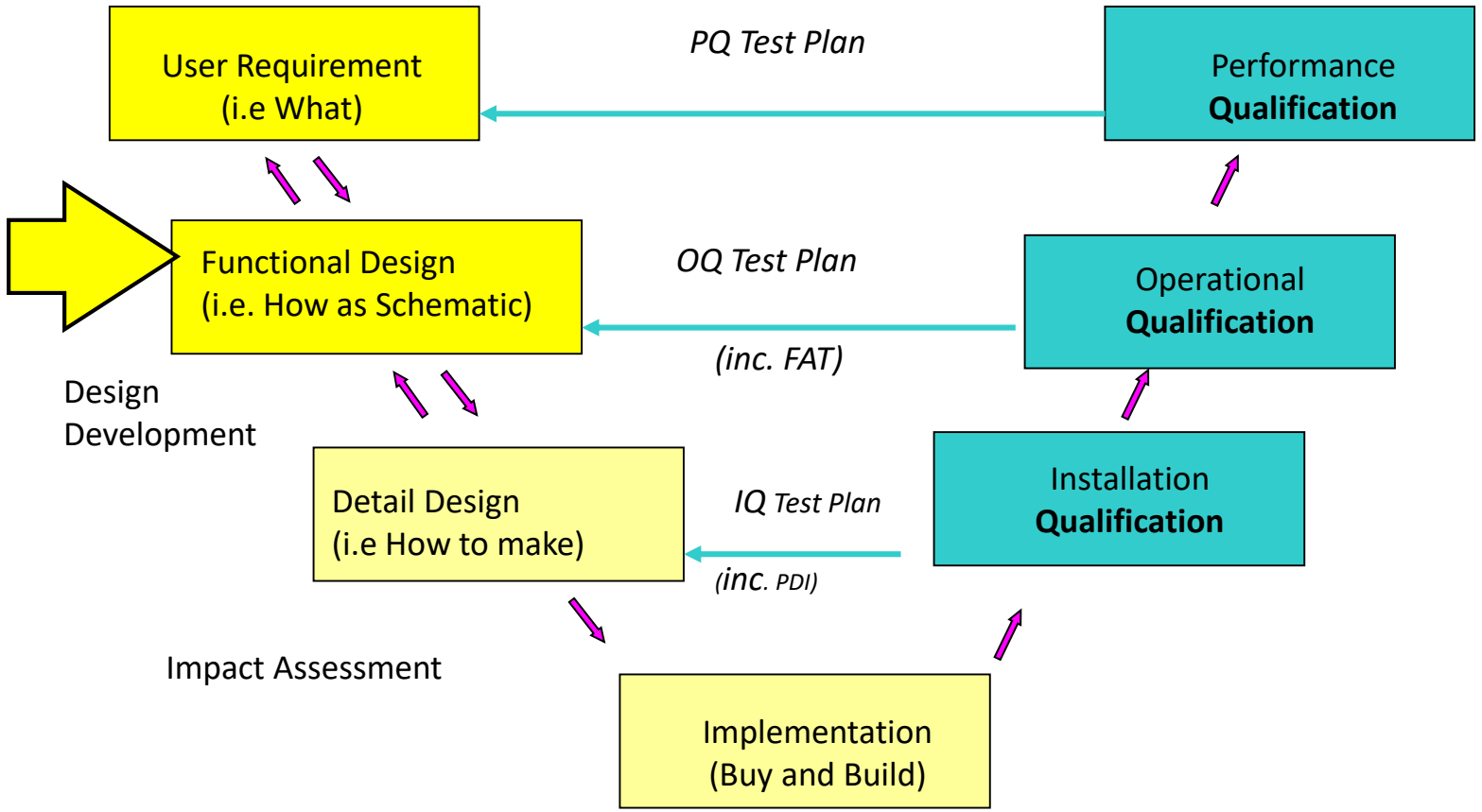
		USER REQUIREMENTS		FUNCTIONAL DESIGN	
AHU ZONE	**Room**	**Critical Parameter & Acceptance Criterion**	**Why**	**Critical Devices**	**Maintenance**
AHU-A1	Room 100	Room temp 15-25C	Product exposed	T loop* A1A	Calibrate q 6 mo
Sterile Zone	Sterile	Room RH 30 - 60%	Product exposed	RH loop A1A	Calibrate q 6 mo
	Filling	Airborne class 10,000	Class 100 zone in this room	Particle monitor	Calibrate q 6 mo
		HEPA scan 99.99%	Class 10,000 room	Terminal HEPA filters A100a,b,c	Scan q 6 mo
		Room pressure >15 Pa above room 103	Class 10,000 room	Pressure loop A1A	Calibrate q 6 mo
		Recovery in 15-20 minutes = minimum air changes 20	EU GMP requirement	Airflow monitor on AHU (AF loop A1)	measure room supply q6mo

* Loop = sensor, transmitter, indicator, alarm, recorder

- **You can expand this as you develop**
- **the design. Add tag numbers, SOPs,**
- **dates qualified, etc.**
- **Keep it all in one set of data.**

(You have this in a handout)

Functional Design



Functional Design: HOW the Facility will Work

Agree on control of critical GMP parameters
- EMS Vs BMS
- Number of HVAC systems and areas served
- Level of automation
- How to deal with spills, deviation & alarms

Expected maintenance

Energy concerns

Safety & insurance concerns

Also called a Basis Of Design (BOD)

Isn't this a POR?

Elements Of Functional Design

- What is the critical item? **What** does it do? **What** data are needed to assure it works?
- **How** does it protect the product? **Why** is it critical or non-critical? **What** are its critical attributes (spec)?
- **When** is it maintained?
- **Where** is it located?
- **Who** owns it? **Who** performs the work? **Who** reads the data ?
- **What** is the operating range? Vs. acceptance criteria?
- **Effect** of item's failure?

At the End of Functional Design

Engage the CQV or Cx and Vx

- Develop the VMP
  - Protocol List
  - Start Protocols as early as practical
- Develop Prelim Commissioning Plans
  - Systems List
  - Start Checklists as early as practical

KIS (Keep it Schematic) the Functional Design (FD)

A BOD is a combination of drawings, Narrative and supporting documents:

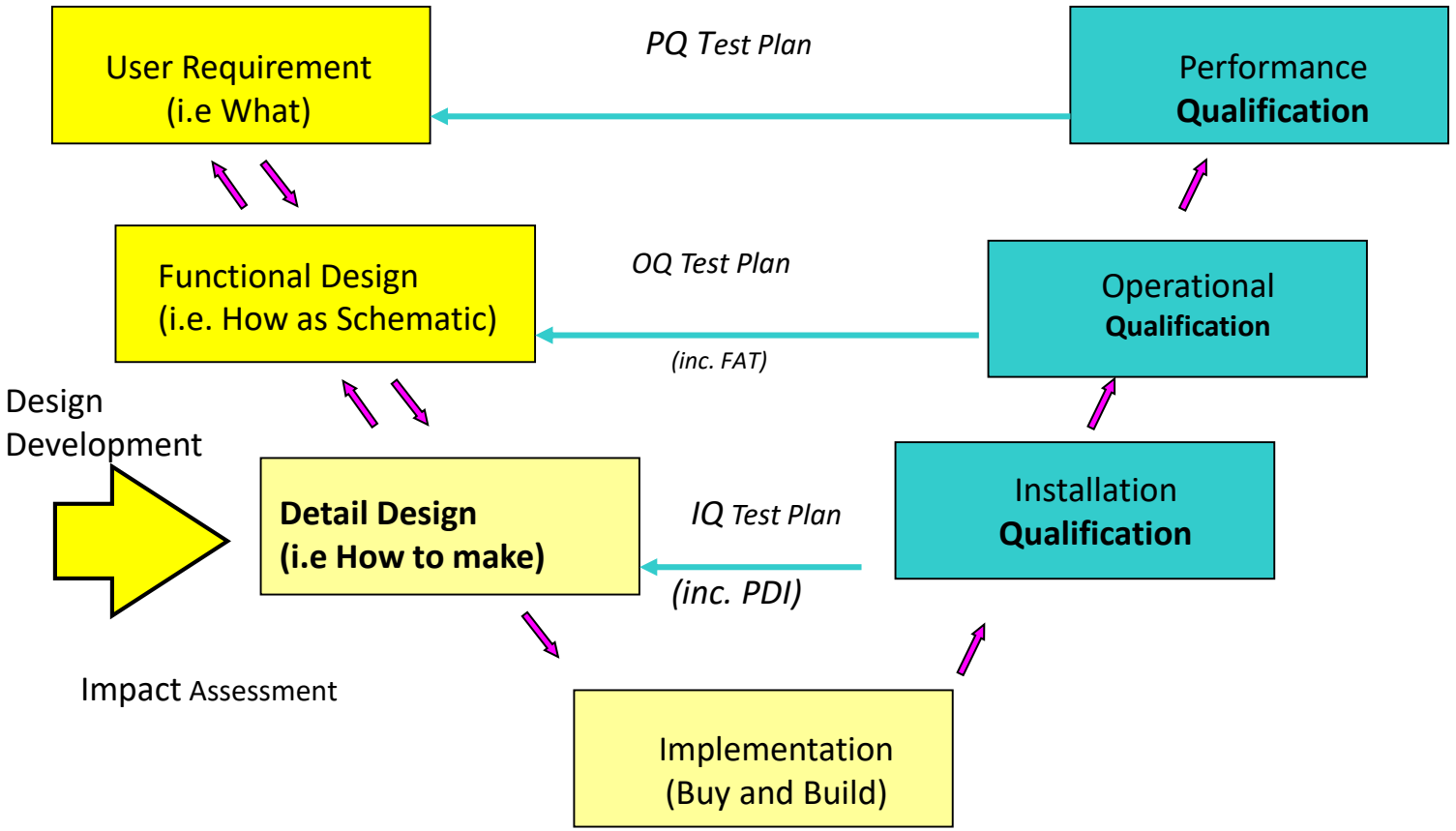
- Layout
- General Arrangements
- FDA style flow diagrams
- Risk Assessment
- VMP
- Updated URS
- P&IDs
- HVAC airflow diagram (AFD)
- DRM Chapter 13 review points
- Short narrative to describe each room, finish and system with its sequence:
  - Areas served
  - Critical parameters, How HVAC works and why
    - Table of critical components and direct impact systems
  - Expected maintenance activities and frequencies
  - Interaction with SOPs
  - Interlocks with other systems
  - Action & alert points?
- Put F.D. under change control!!!

Summarize!

List of critical Components

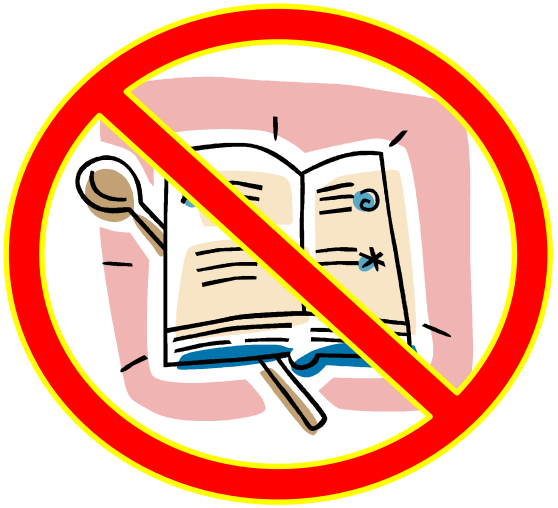
System	System Impact	Critical Parameter	Critical Component	Why	Tag Prefixes	Future	Future
HVAC for Sterile Fill	Direct	Filling Room Temp	Temperature loop with alarm, record	Room temperature affects product temperature under hood; not measuring product temperature directly	TE, TT, TI, TR, TA	List actual tag numbers, SOPs, etc.	
		Room air particle counts	Terminal HEPA filter	HEPA filter determines quality of room dilution air, not measuring room air particles continuously	FIL	FIL-211A thru FIL-211H	SOP 11
Compressed air	Indirect	Air pressure in stopper seating	Air pressure gauge and alarm	Low air pressure = poor stoper seating, no way to test each vial	PI, PA	PI-21, PA-21	SOP134445
Chilled glycol	Indirect	Product tank jacket temperature	Glycol lowtemperture alarm	If glycol too cold, can freeze product at vessel wall; no other way to measure at vessel wall	TAL, TR	TAL-17A, TR-17A	SOP 1288

Detailed Design



Addressing Risk – Why Risk Management?

- **We need tools that are Strong enough to assure quality… yet Flexible to evolve with technology evolving risks.**
  - **Evaluate alternatives**
  - **Look for weaknesses**
  - **Look for opportunities**
  - **Balance conflicting needs**



NO Cookbooks!

"There's never enough resources to do it right…
but always enough to do it over"

Balancing the Needs

1. Bio-Containment
    a. Employee Safety
    b. Separation of products
    c. Environmental Safety
2. Cleanliness
    a. Bioburden reduction
    b. Sterility

"Sterility and bio-containment often oppose one another; GMP is based on the concept of keeping contaminants out, whereas bio-containment is based on the concept of keeping organisms and byproducts in."

GenEng 2006

What is Risk?

Formal Definition:

- **ISO 31000 defines Risk as:**

  "the effect of uncertainty on objectives…"

Our Definition:

- **Risk is:**

  A measure of the importance of an event that includes both the factors of Impact and Probability

What Can I Do About Risk?

Avoid – Don't do it

Reduce (Mitigate) – Make it better

Transfer – Make Someone else do it

Accept – Live with it

Acceptable Risk?

- We accept risks of injury, even death, every day…
  - Driving to the conference >30,000 deaths/yr
  - Flying 500-1000 deaths/yr
  - Taking a shower >5,000 deaths/yr
  - Shaking the hand of a stranger

    "Hi my name is patient zero…"

- Some people even thought that the following risks were acceptable…


TOYOTA
KOMATSU
FB15-10
FB15-10

NIH
National Institutes of Health

GENESIS ENGINEERS

NIH
National Institutes of Health

ENGINEERS

What is Risk Management?

Formal Definition:

- **Risk management is:**

(Risk) … followed by coordinated and economical application of resources to minimize, monitor, and control the probability and/or impact of unfortunate events…"

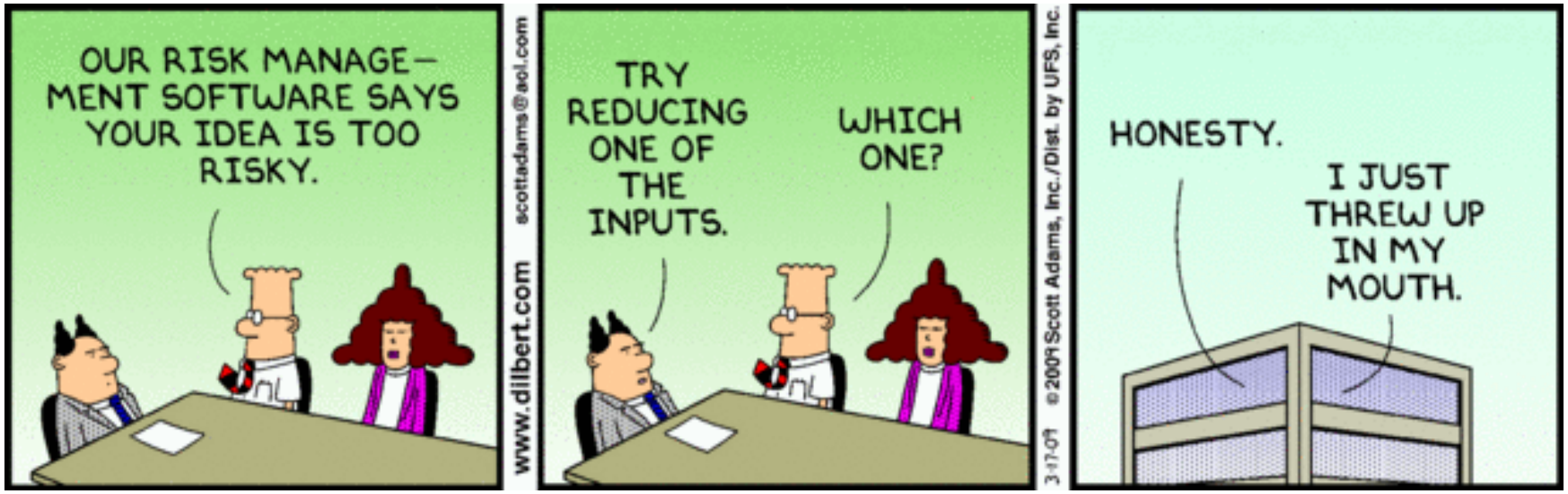
Our Definition:

- **Risk management is:**

A method for identifying potential problems and prioritizing responses – across a lifecycle

What ISN'T Risk Management?

What risk management is not for…

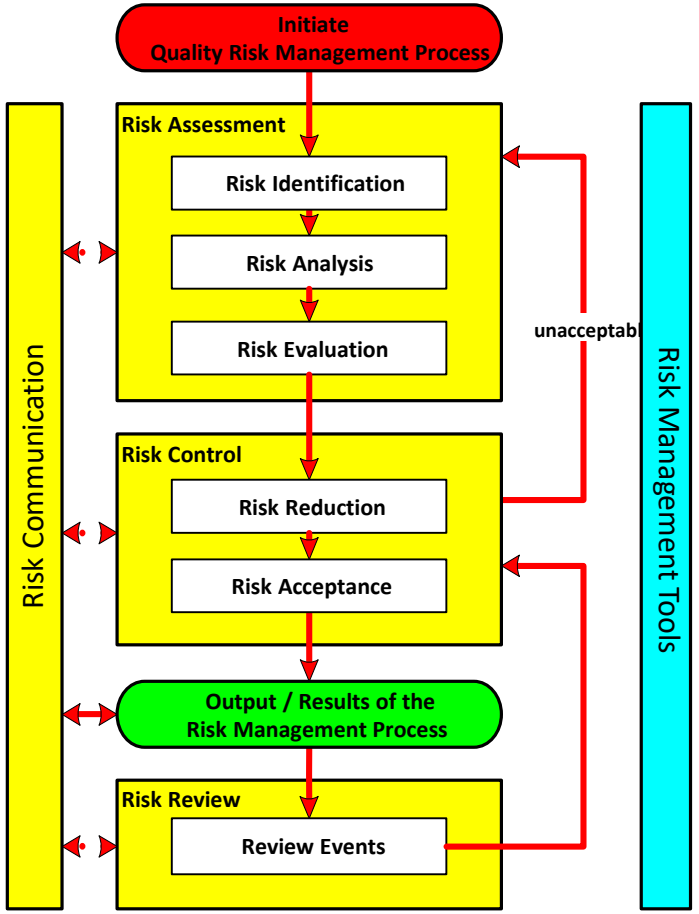


Courtesy Dilbert.com

What is Risk Management? *(Continued)*

Risk Management is a multi-step process

- Identifying risks
- Analyzing risks
- Evaluating risks
- Controlling and reducing risks
- Reviewing to assure control
- Accepting residual risk



Courtesy ICH Q9

Failure Mode and Effects Analysis (FMEA)

- Roots in engineering but can easily be applied across the industries
- Involves calculation of a:

RISK PRIORITY NUMBER

derived from a combination of:

  - The **SEVERITY** of the consequence of failure **S**
  - The probability of **OCCURRENCE** of failure **O**
  - The probability of **NON-DETECTION** of the failure **D**

$$RPN = S \times O \times D$$

DETAILED DESIGN: HOW do we build it

Agree on means and methods

- Materials of Construction
- Product Standards
- Testing Standards
- System testing obligations (Field, FAT, SAT, etc)
- Oversight of construction

Expected maintenance

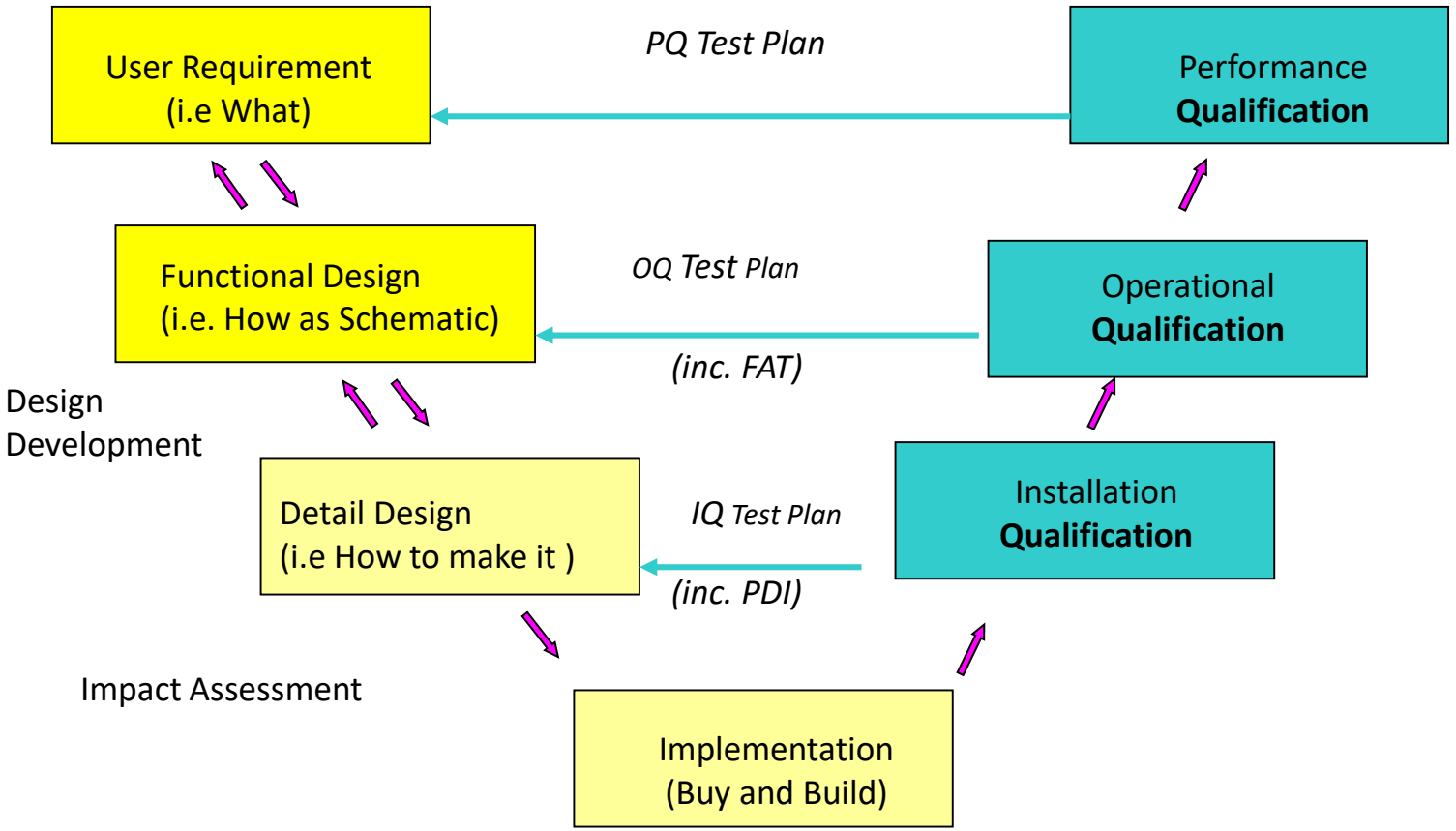
- Access and clearances

Safety & insurance concerns

Detailed Designs need Details!

- Updated BOD
- Updated URS
- Plan view drawings
- Details of all unique construction, especially cleanrooms
- Sections and Elevations
- Schedules of equipment and devices
- Commissioning Specifications
- Interstitial space zoning and routing
- Valve and damper access
- Equipment hookup details
- Equipment and construction specifications

Notes and Lessons Learned - Design



Smart Design

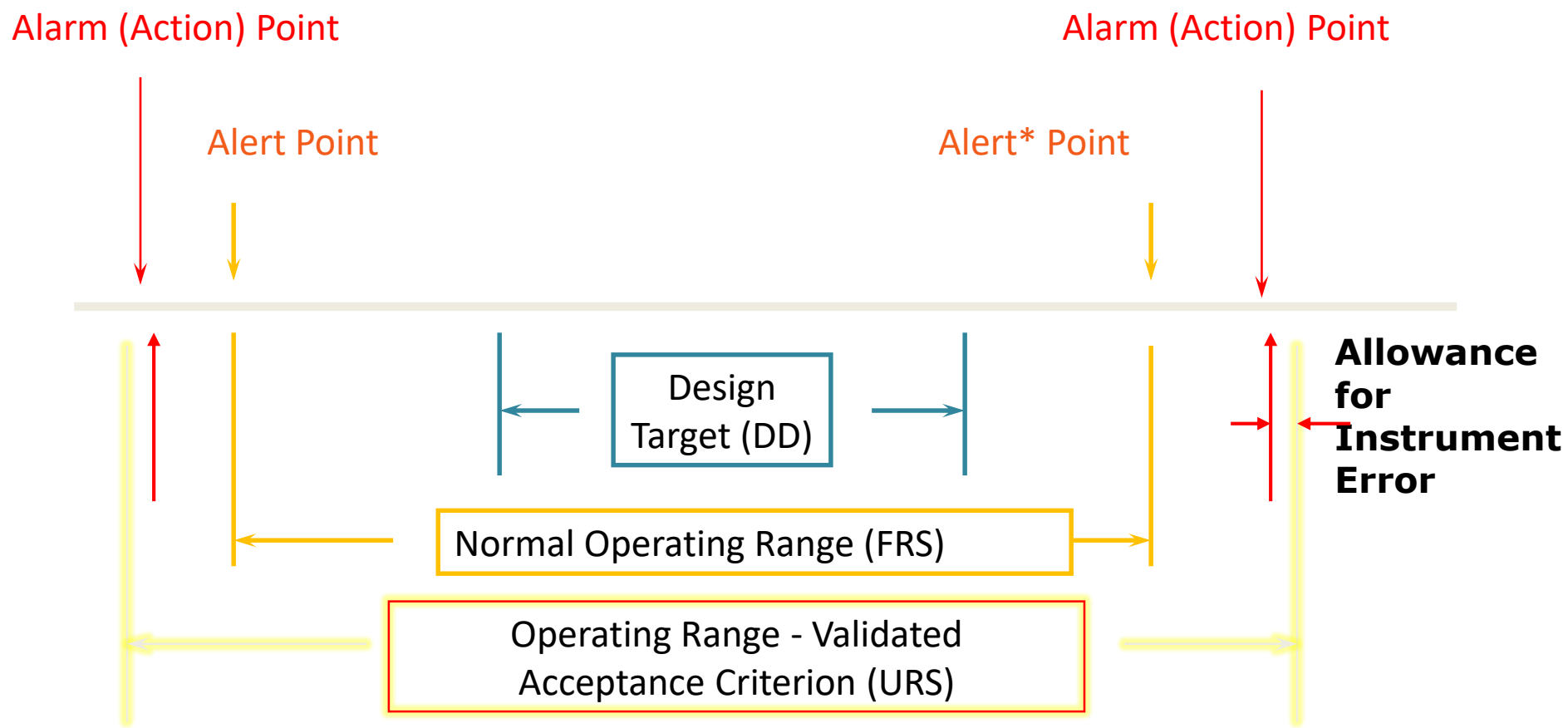
Set Acceptance Criteria - the action alarm points; based on product and possible future product limits

Set Operating Limits - the values of parameters that you would like to maintain most of the time. Make them reasonable.

Set Design Targets - for purchase and construction specifications

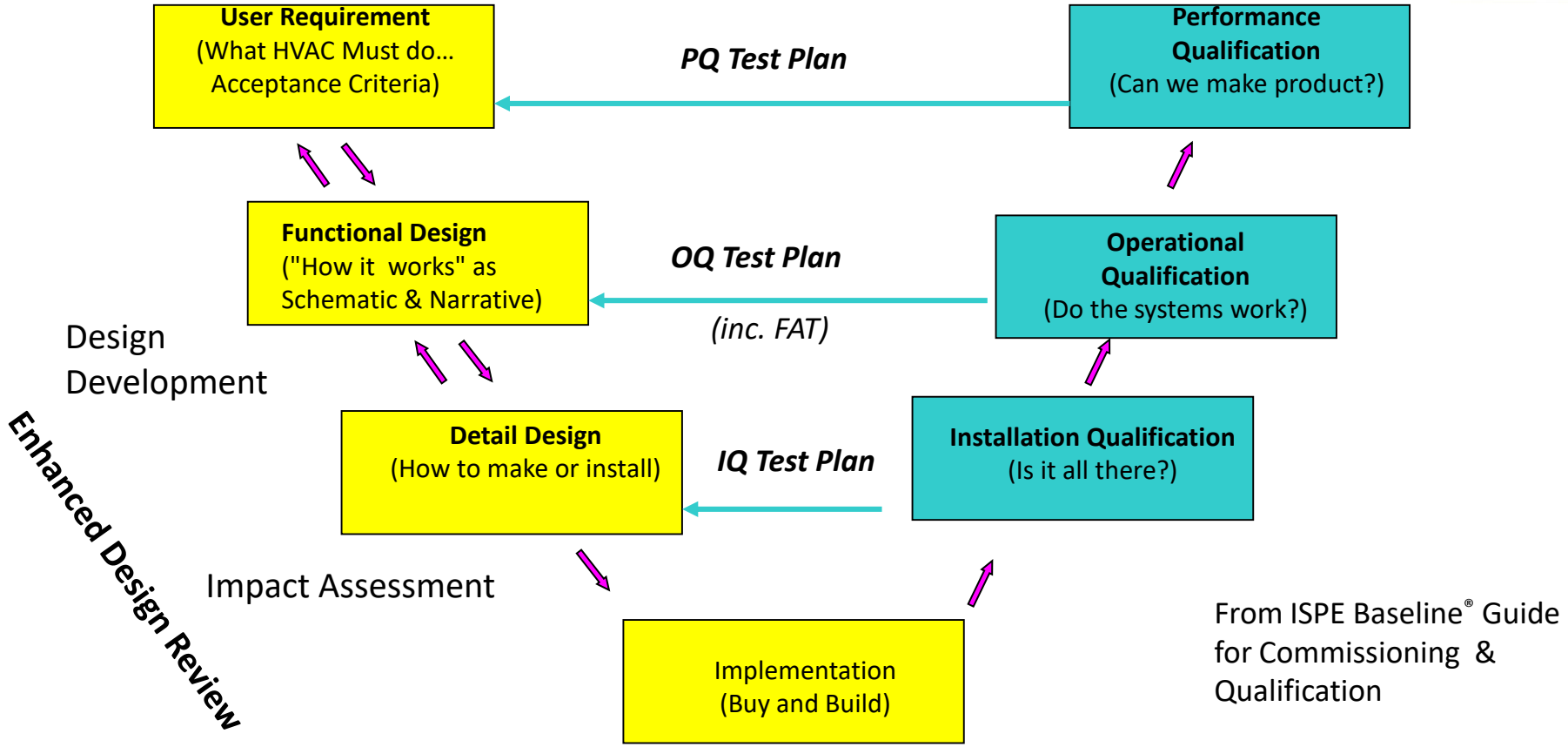
Don't Tighten Design Too Much!

Source: ISPE Baseline® Guide for OSD Facilities



*** Alert = MAINTENANCE alarm**

BEFORE DESIGN ENDS…



From ISPE Baseline® Guide for Commissioning & Qualification

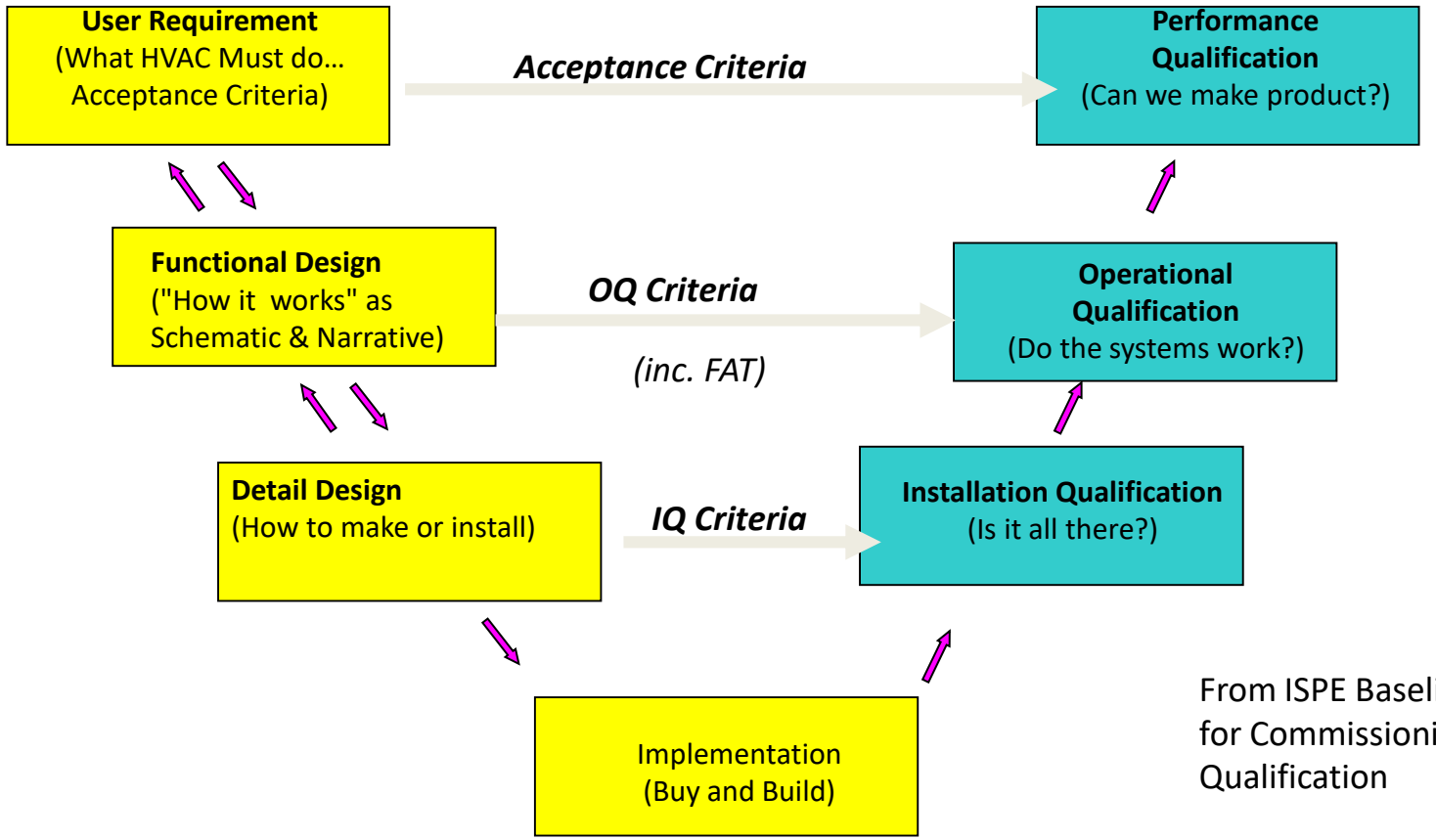
Enhanced Design Review occurs all through design.
For Q7A facilities, this is "Design Qualification"

Enhanced Design Review

- For API or for Europe, it's called Design Qualification (DQ)
- Enhanced Documentation that the design meets certain requirements:
  - System will satisfy User Requirements
  - System will perform according to Functional Design
  - Detail design elements
  - COVER DOCUMENT with signatures

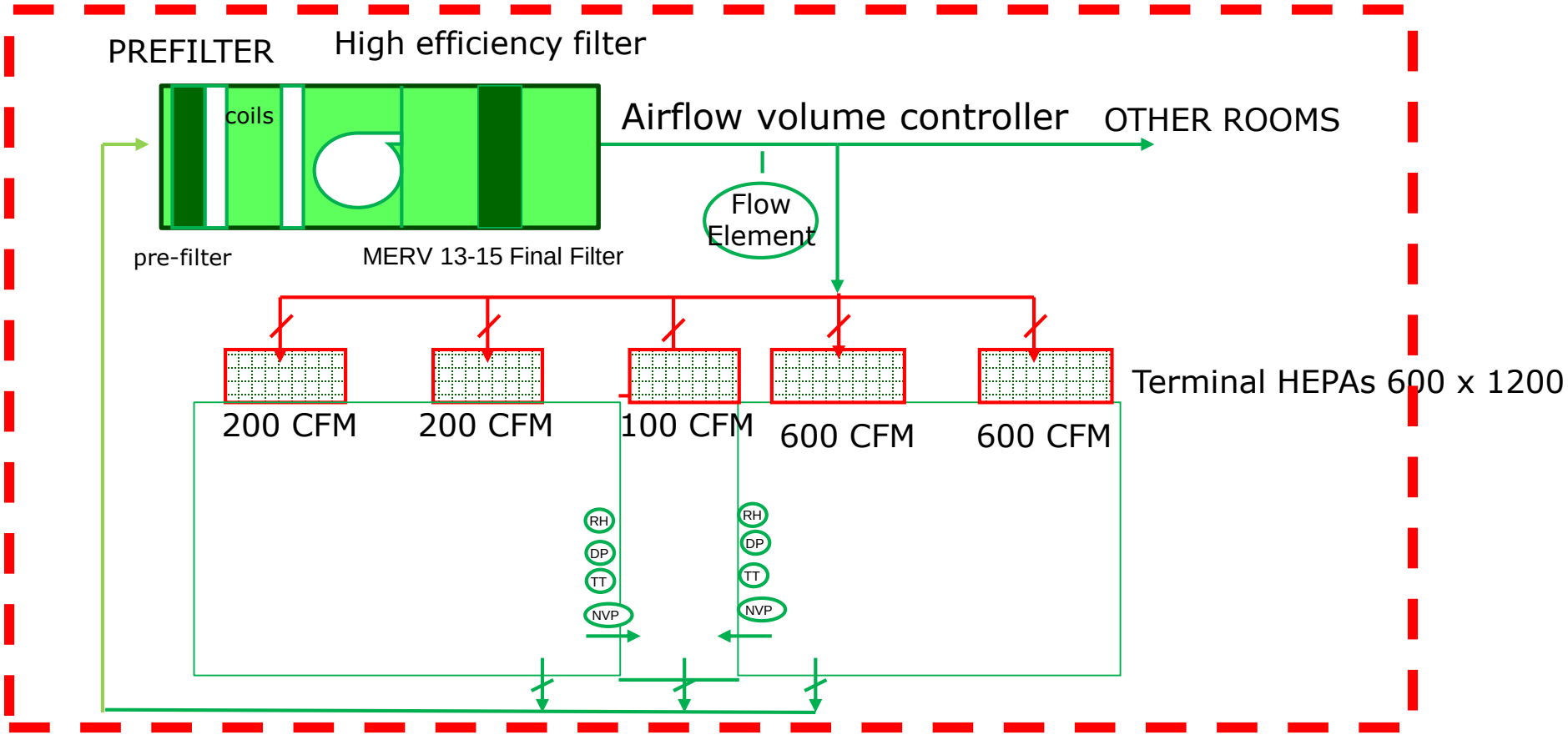
Design Issues

Understanding Relationships
Design to Qualification



From ISPE Baseline® Guide for Commissioning & Qualification

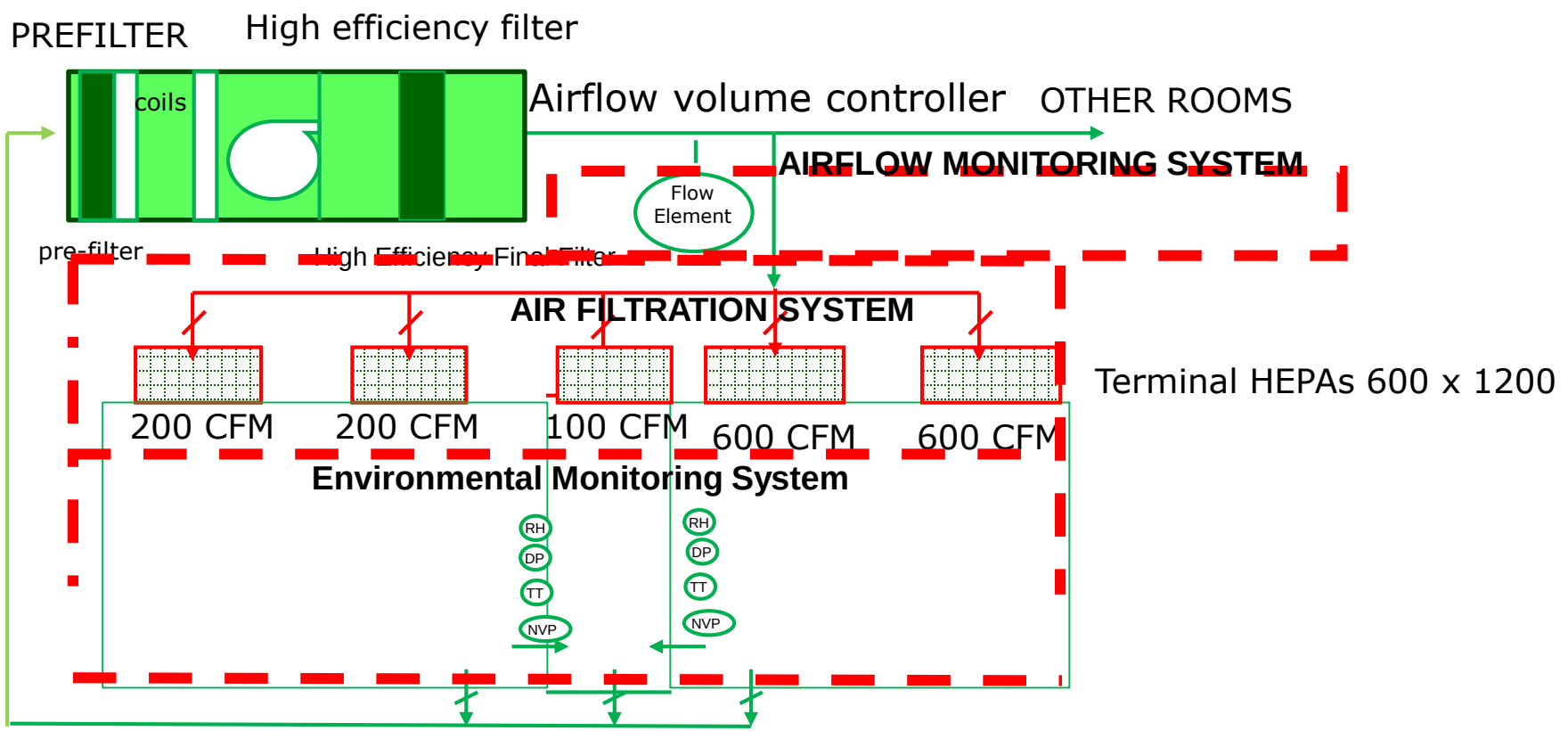
Define System Boundaries



All the components could be in one "system"

Define System Boundaries

IS AHU INDIRECT IMPACT?



Or Multiple "systems"

Typical Critical Devices in Direct Impact Systems

- EMS System and Transmitters, alarms, indicators, and recorders for CRITICAL PARAMETERS
  - Room Temperature, RH, Pressure,
  - Real-time particle counters
- HEPA filters for classified areas
- Compendial Water/Steam Systems
- Process Control Systems
- Process Equipment (incubators, BSCs, TFF, Centrifuge, etc)

Designing For Impact

- Conscious design decisions with respect to the impact of the system in operation, made at the beginning of design development
- Or "DESIGN TO QUALIFY“
- System Boundaries can have a profound effect

Qualification

Risk Processes and Qualification

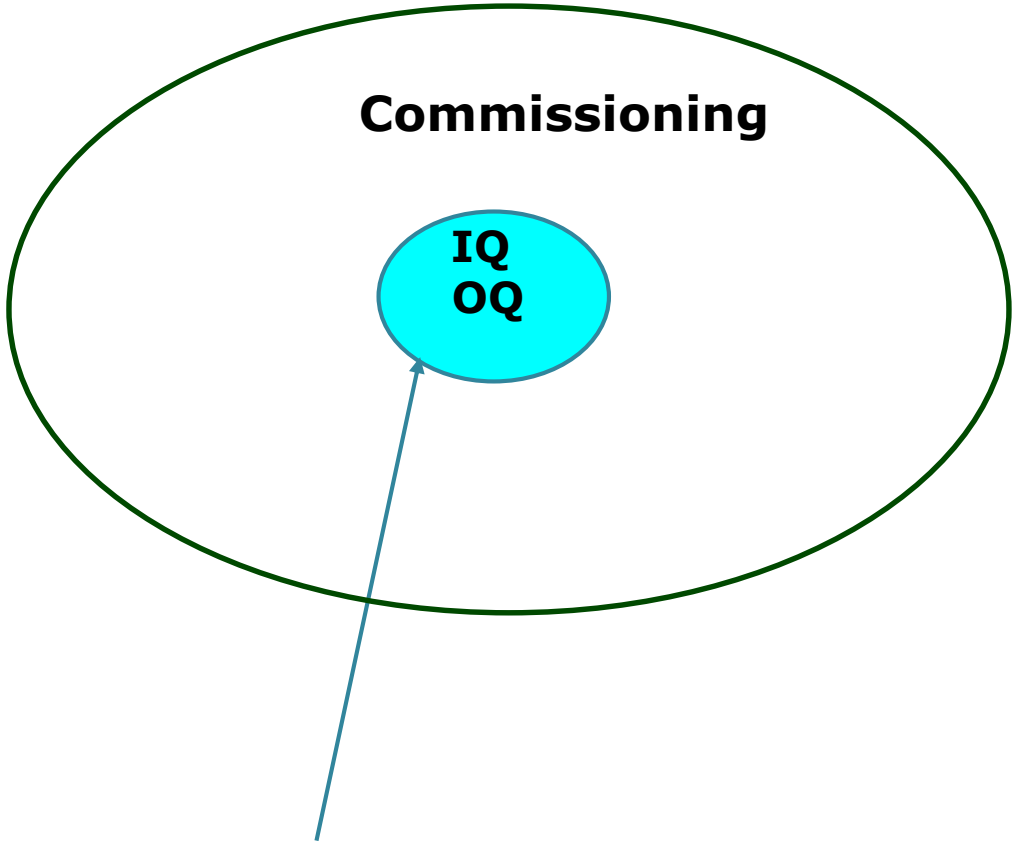
- ASTM E2500 calls for “Verification” that equipment and systems are “fit for purpose” in light of risk assessment
- Risk assessment can focus qualification activities on reducing real risks
- Risk assessment results in a significant reduction in effort for qualification
- ISPE Baseline Guide Vol. 5 Commissioning and Qualification provides a risk assessment system based on “impact” and “criticality” – which is aligned with the qualification structure common in many companies

Risk Processes and Qualification

- The objective of all of these approaches is to focus effort on those activities that will help to assure product quality.
- This class will present the C&Q approach with examples of an alternate risk approach.

Step 1 - Commissioning

- Find flaws
- Assure performance
- Get "as-built" info
- Get data for IQ/OQ
  - IQ = did they build what we specified?
  - OQ = does it do what we wanted it to do?



What is Qualification?

Commissioning + Enhanced Documentation = Qualification

Documents that verify that the commissioning was done correctly

- User Requirements and Functional Design are OK
- Sign-off by QC and Engineering

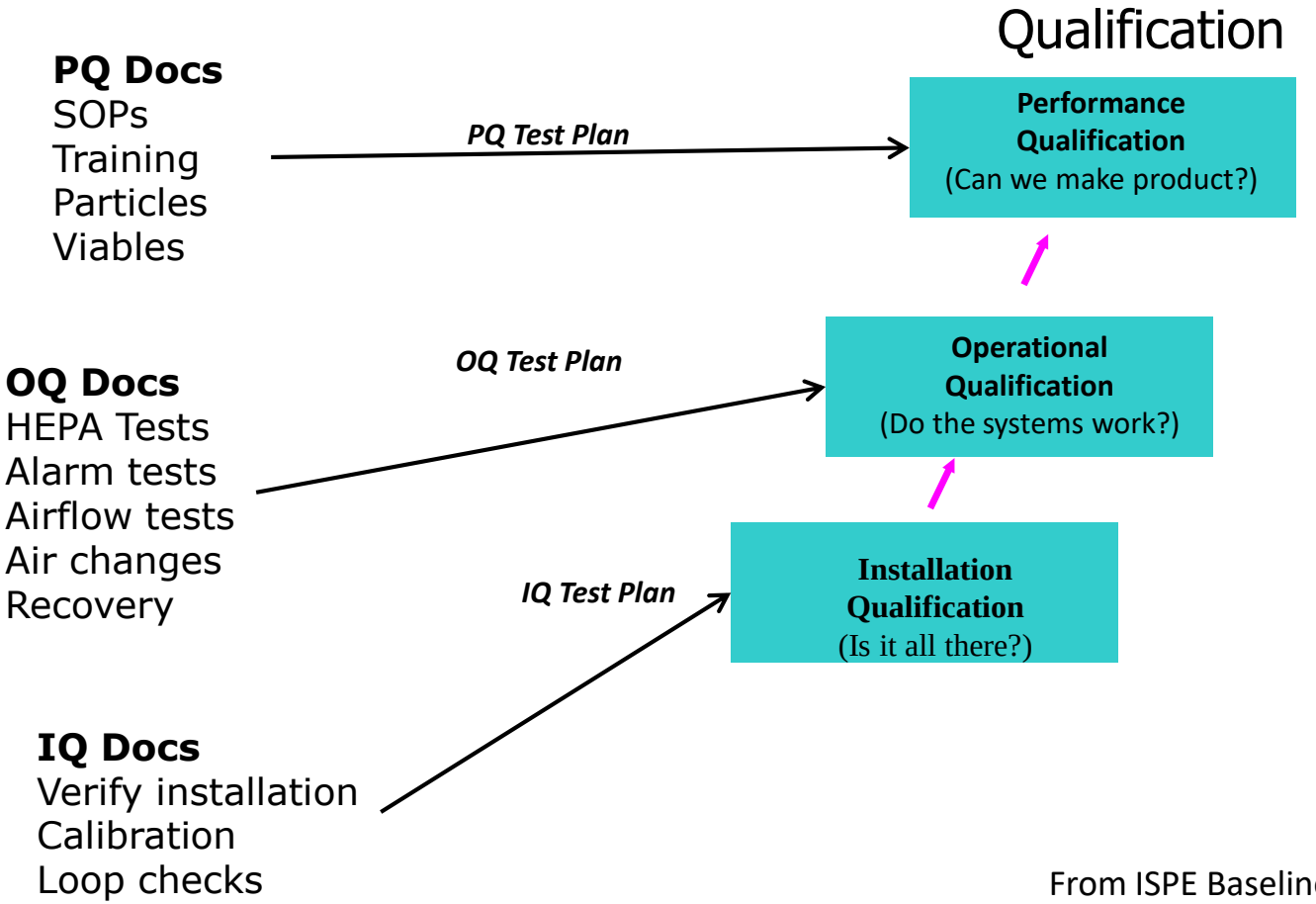
Not a re-commissioning!!!

- Do it once, then verify that performance requirements are satisfied

We Qualify Environmental *Performance*

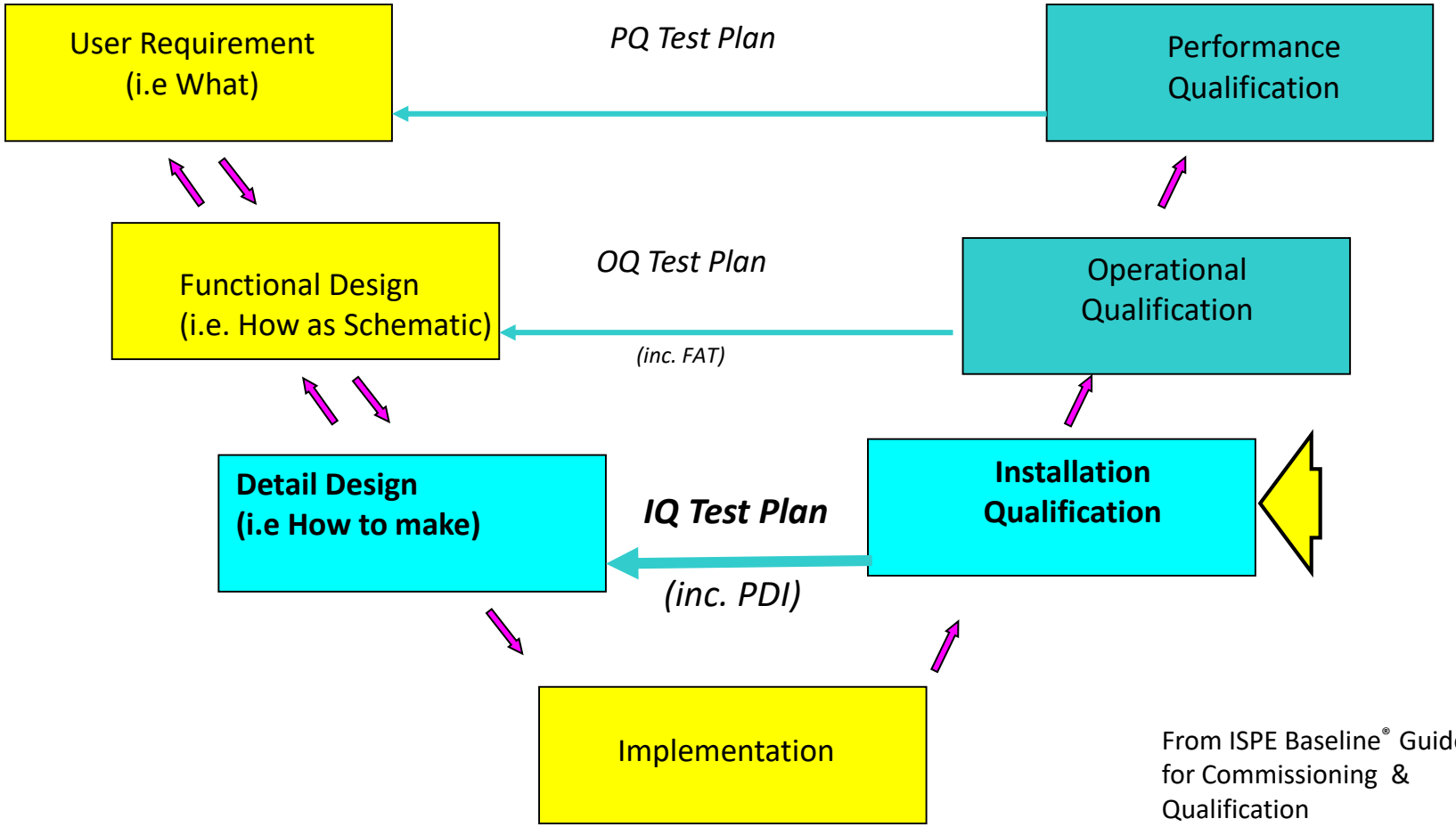
- Make sure we achieve User Requirements
- Critical component accuracy, repeatability, specification
- Critical parameter values
  - Acceptance Criteria
- Total Particulate
- Viable Particulate
- Surface Viables

What? No Validation?



From ISPE Baseline® Guide for Commissioning & Qualification

What to Qualify – IQ
(or What Should be in Detail Design)



From ISPE Baseline® Guide for Commissioning & Qualification

Some IQ Activities

Verify installation matches design documentation

- P&IDs
- AFDs
- Filter installation
- Equipment
- Controls
- Room Construction
- Update or correct

Verify documentation is complete

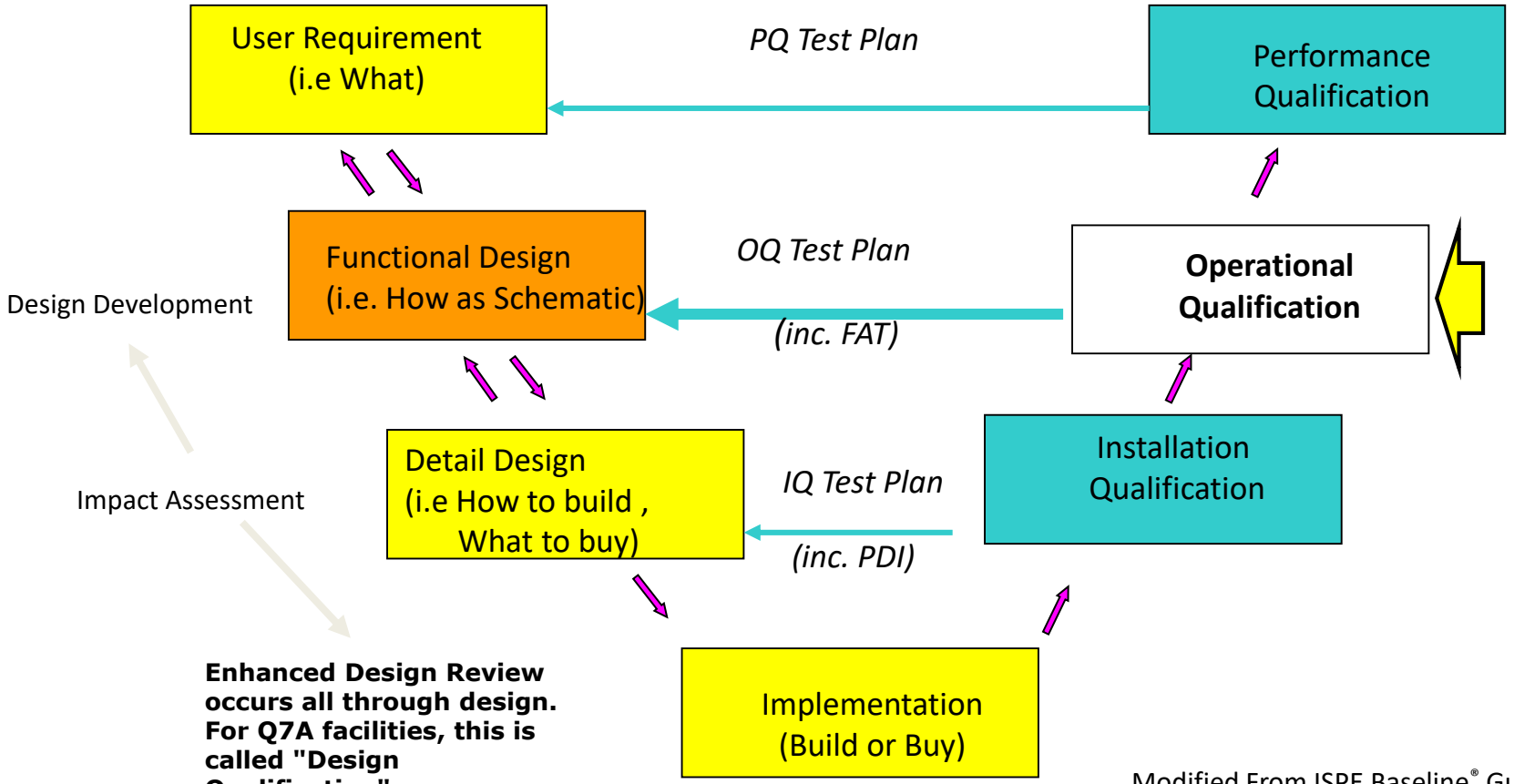
- Commissioning
- Submittal Data
- Cleaning

Verify installation is complete

Verify that cleaning is complete

Initiate facility change control

What to Qualify – OQ
Do We Satisfy Functional Design?



Modified From ISPE Baseline® Guide for Commissioning & Qualification

Some OQ Activities

- Final Air Balance Verification
  - Factory Acceptance Test results
- Room integrity test (if negative DP or DP< 0.5Pa)
- Functional Test EMS (alarms, alerts, indicators)
- Update as-built P&IDs (AFD too)
- Classified room air change calculations and/or recovery tests (attach to airflow balance report)
- HEPA Filter Integrity Tests (FIT)
- Class 100 ISO-5 airflow patterns
- General air patterns in Grade B (Gr7) rooms

Some More OQ Activities

- Temperature mapping
  - Storage area on a hot/cold day (high/low)
  - At product exposure sites
  - Under HEPA hoods
- Gowning room temperature, RH, recovery at maximum occupancy; PCF at rest
- Room pressure map on layout (if DP is critical)
- Minimum DP with one airlock door open (to find alarm set point - should be >0)
- Classified room particle counts at rest
- Finalize SOPs to reflect OQ data
- Training on SOPs

Airflow Pattern Tests

- Airflow pattern tests are common and expected in class 100 Grade A (5) zones
- Suggested for classified rooms
- Video is the accepted standard
- Need to explain what the viewer sees
- Correlate to a filter face velocity and a work space velocity

Keys to a Successful Airflow Video

- For unidirectional hoods and barrier/isolators, perhaps local protection
- Title shots to show what you are looking at, with dates
- Show camera locations on layout
- Visible smoke - close to neutral buoyancy unless cross-flow hood
- Wand design - not a hose, but a multiple point wand (T or L shaped with long handle) to provide a 2-dimensional flow visualization - practice!!!
- Use spurts of smoke to give idea of airflow velocity

Keys to a Successful Airflow Video
Continued

- Camera angle… move as needed (tape from inside room if possible)
- Back lighting and dark background increase visibility of smoke
- Tape the facility unoccupied
- Tape again with operators doing normal (& abnormal) routine interventions
- Include ALL possible interventions. Where an intervention shows a problem that airflow can't solve, change operator's procedures or tools
- Periodically retest to confirm no change (2-5 years?)

Review and Approve Results

- Organizations involved
- Real time, during execution
- After execution, videos
- Report

Videos and report

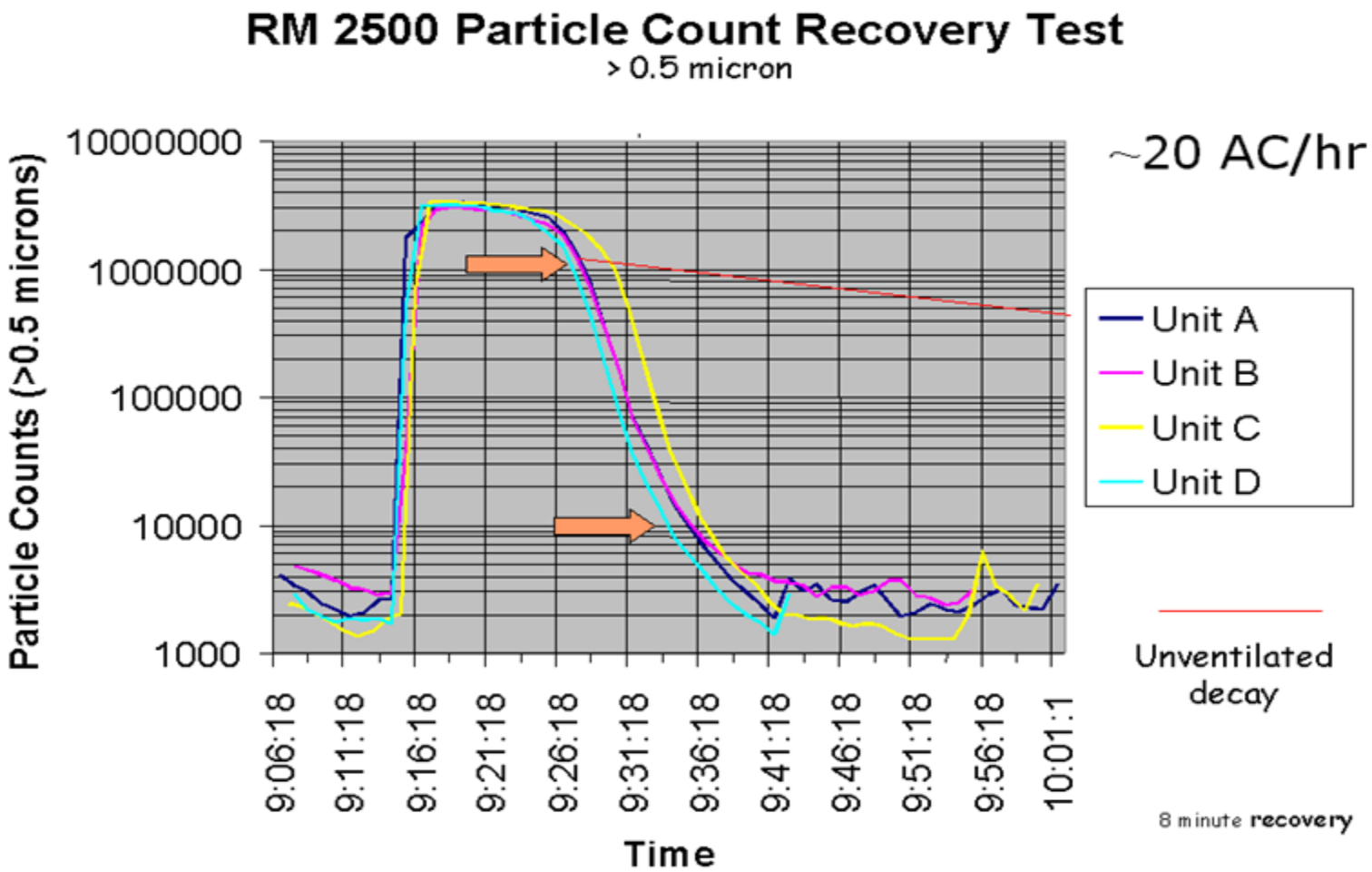
Ensure

- That the video is indexed clearly so a specific intervention can be found quickly
- Ensure the report includes an evaluation of the impact of aseptic interventions
- Alignment between the video and report
- If relevant: SOPs covering interventions are aligned with visualization

Recovery Test – Smoke Up the Room

Be sure to turn off the smoke detector system!!!

Recovery Test Using Theatrical Smoke Generator With Propylene Glycol



This room recovered fast because of good air supply distribution and low returns

Particle Monitoring in ISO-5

- FDA wants periodic Environmental Monitoring in ISO-5
- CONTINUOUS particle monitoring in ISO-5 is preferred
  - To detect inappropriate interventions
  - Locate where you WILL get an alarm if process deviates
  - Within 1 foot of critical zone(s)
  - Low enough to be meaningful, high enough not to get particles that are leaving the critical zone.

What Does ISO 14644-3 Cover?

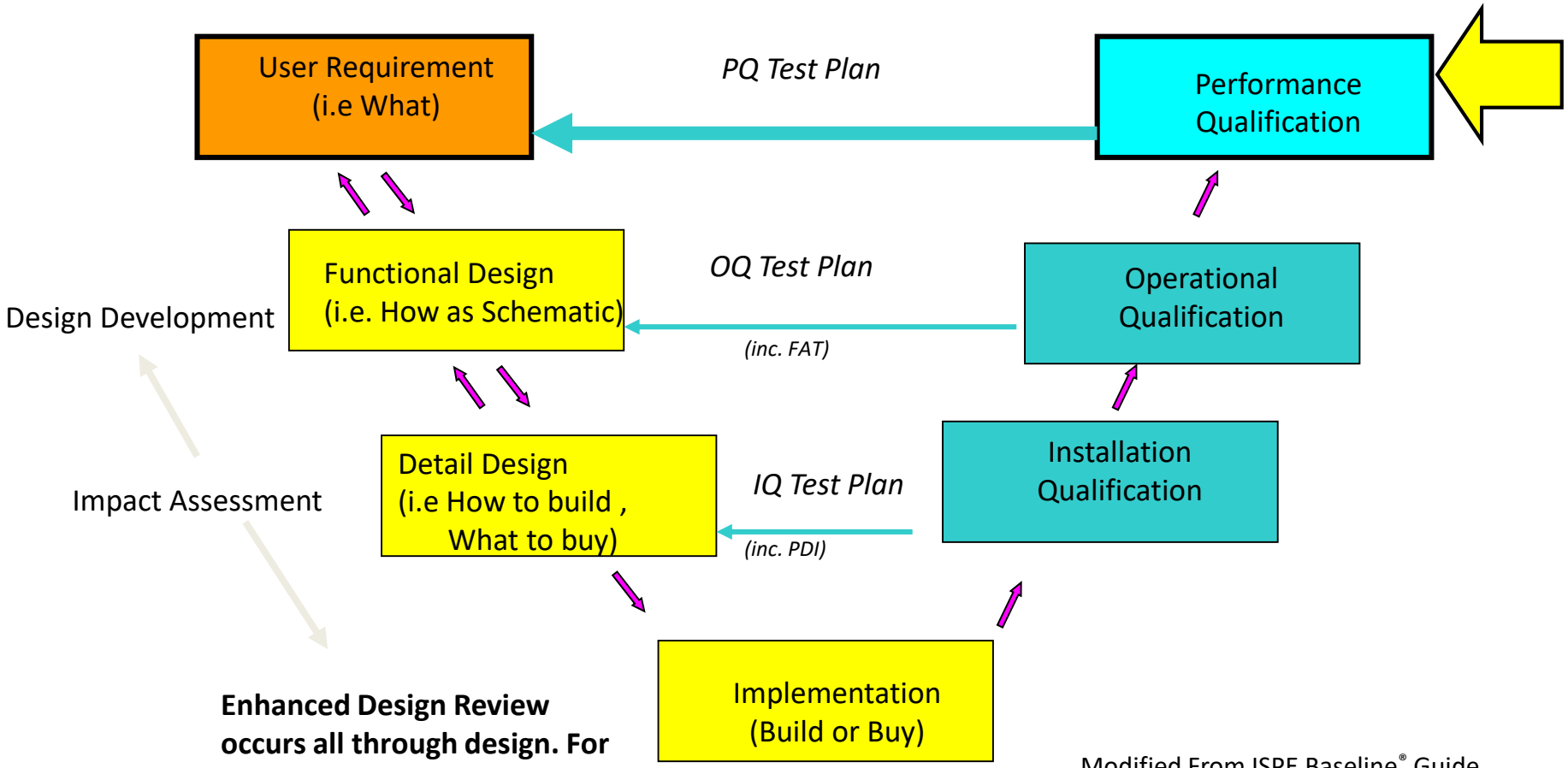
CLEANROOM TESTING:

- Airborne particle counting
- Airflow test
- Air pressure differential test
- Installed filter testing
- Flow visualization
- Airflow direction test
- Temperature test
- Humidity test
- Recovery test
- Containment (room integrity) test

What to Look for in HVAC Controls OQ

- Critical Parameters and Acceptance Criteria values identified and monitored
- Alarms work and are recorded
- Records are non-volatile
- Calibration error factored in
- Access and Security
  - Change control in place

What to Qualify – PQ
(Can We Use it to Make Product?)



Enhanced Design Review occurs all through design. For Q7A facilities, this is called "Design Qualification".

Modified From ISPE Baseline® Guide for Commissioning & Qualification

Some PQ Activities

- Temperature and RH at climatic extremes (stored or exposed product)
- Critical parameter values OK in production mode
- "Normal" and extreme values of T, RH (other CRITICAL PARAMETERS) to determine action levels
- Normal critical parameter levels to determine *"maintenance alert"* alarms (to engineers, not to GMP)

More PQ Activities

Validate frequency of data logging

- DP changes fast, room T and RH change slowly, product T changes even slower
- Don't choke the system with extraneous data

Brownouts and power outage

- Operator procedures, time limits

Verify DP alarm time delays in operation

- At extreme particle counts in lower class room, set time delay less than time to reach action levels in the cleaner room.

HEPA Testing

- Class 100 (Grade A) twice/year
- Class 10,000 (Grade B) twice/year
- Class 100,000 (Grade C/D) perhaps once a year if supported by data
  - Test 2/year until trends identified

Summarize!

CALIBRATION REPORT SUMMARY							
Component Parameter - HVAC TEMPERATURE				Date 1 July 2001 Signature_____			
Temperature loops	Critical?	Location	SOP Number	Date	Performed By	Equipment	Next Calibration
TE -14, TT-14, TI-14	Y	Bldg 100/4 Col A5	SOP 145567	21-Jun-01	Jones, ID 144567	Acme Quik-Cal, GW33445786	21-Dec-01
TE-17, TT-17, TI-17	Y	Bldg 100/4 col A5	SOP 145567	21-Jun-01	Jones, ID 144567	Acme Quik-Cal, GW33445786	21-Dec-01
TE-21A, TT-21A, TI-21A	N	Bldg 100/4 col C3	SOP 145567	23-Jun-01	Jones, ID 144567	Acme Quik-Cal, GW33445786	23-Jun-02
TE-21B, TT-21B, TI-21B	N	Bldg 100/5 col B3	SOP 145567	23-Jun-01	Jones, ID 144567	Acme Quik-Cal, GW33445786	23-Jun-02
Temperature Alarms							
TA-14	Y	Bldg 100/4 contrl rm	SOP 145567A	21-Jun-01	Jones, ID 144567	Acme Quik-Cal, GW33445786	21-Dec-01
TA-17		Bldg 100/4 contrl rm	SOP 145567A	21-Jun-01	Jones, ID 144567	Acme Quik-Cal, GW33445786	21-Dec-01
Temperature Recorders							
TR-01	Y	Bldg 100/4 contrl rm	SOP 145589	21-Jun-01	Jones, ID 144567	Fluke 28, Prop tag GW002	21-Dec-01
TR-023	N	Bldg 100/4 contrl rm	SOP 145589	21-Jun-01	Jones, ID 144567	Fluke 28, Prop tag GW002	21-Jun-02

ONE copy of each SOP in the file.

Eqpt tag number refers to S/N and calibration record.

One copy of eqpt calibration record in the file.

Don't mix critical and non-critical if a LOT of items.

Beware of the Dark Side

.

There is a galaxy of paperwork on the Dark Side, Luke.

Join me and you can rule it all!

Summary

- Qualification Starts at Design
- Maintenance starts at Design too
- Focus Qualification on areas of real risk
- Be familiar with systems and risk
- Document and Summarize
- K.I.S.