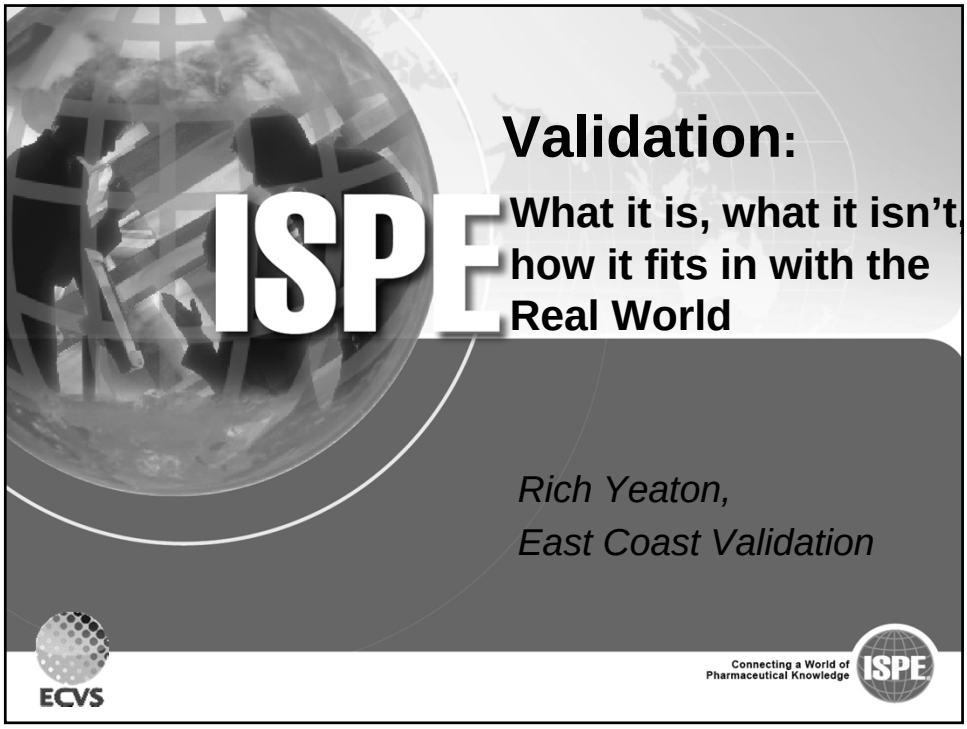


Outline

- Definitions
- Terminology
- Practices
- Current Trends
- Types of Validation
- Case Study

ECVS

Connecting a World of Pharmaceutical Knowledge ISPE

Validation - The Official Definition

"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes"

FDA Guideline on General Principles of Process Validation, 1987

Connecting a World of Pharmaceutical Knowledge ISPE

Validation – Unofficial Definition

- Proving that your stuff works
- Proving that you're in control
- Proving that you know what you're doing

Connecting a World of Pharmaceutical Knowledge ISPE

Validation – What it shouldn't be

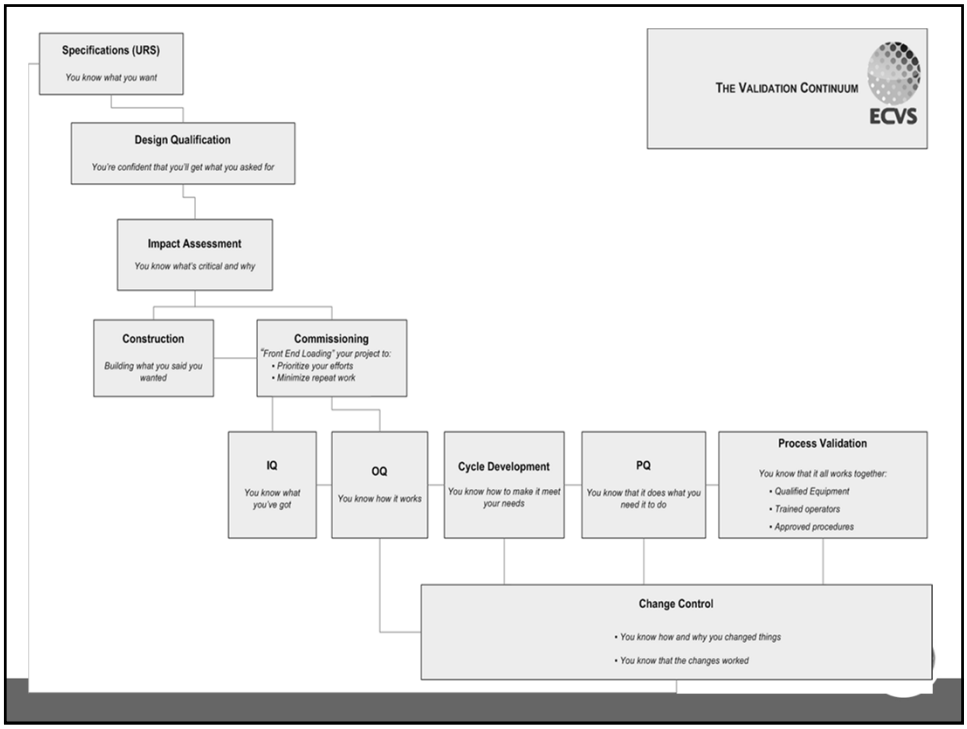
- Paperwork for the sake of paperwork
- A reason to not improve things

Connecting a World of Pharmaceutical Knowledge ISPE

Why Bother?

- The FDA expects it
- Customers expect it
- Legal liability
  - Demonstrates diligence
- You learn things

Connecting a World of Pharmaceutical Knowledge ISPE



More Definitions (1)

Acronym		Definition
URS	User Requirement Specification	You know what you want and why you want it
FRS	Functional Requirement Specification	Engineering (or the Manufacturer) knows how they're going to meet the URS
DQ	Design Qualification	You're confident that the design will meet your needs

ECVS

Connecting a World of Pharmaceutical Knowledge ISPE

More Definitions (2)

Acronym		Definition
IQ	Installation Qualification	Proving that you know what you've got Proving that you know what your system needs
OQ	Operation Qualification	Proving that you know how your system works
PQ	Performance Qualification	Proving that your system does what you need it to do, **Repeatably**

Connecting a World of Pharmaceutical Knowledge ISPE

More Definitions (3)

Acronym		Definition
IA	Impact Assessment	You know what's important, and why
	Commissioning	Getting your system working
CD	Cycle Development	"Tuning" your system to make it meet your needs

Connecting a World of Pharmaceutical Knowledge ISPE

More Definitions (4)

Acronym		Definition
PV	Process Validation	Proving that it all works together
	Change Control	Proving that you still know what's going on
FDA	Food and Drug Administration	The people you have to convince that you know what you're doing
QA	Quality Assurance	The people who get to deal with the FDA

Connecting a World of Pharmaceutical Knowledge ISPE

Process Validation

- This is the only type of validation mentioned in the CFR regulations
  - PQ, OQ and IQ are how the industry gets to PV

Connecting a World of Pharmaceutical Knowledge ISPE

Process Validation

- Trained Operators
- Approved Procedures
- Qualified Equipment

Process Validation

- 2011 Guidance document represents a significant clarification to the FDA's expectations for PV
- The industry is still figuring out how to respond

The FDA

- They're not the bad guys
- They're professional skeptics
  - All claims must be backed up with data
- They can smell fear

The FDA

- They won't tell you how to do things
  - They need to be convinced that your approach is valid
  - They need to be convinced that you're following your approach
- They like a good technical discussion
  - They will sometimes challenge a technical decision to see if the company is willing to defend their approach

Guidelines and Regulations

Guidelines **Regulations**

Outcomes of an FDA Audit

- No observations
  - This is the best you can expect
- Minor observations
- 483 Observations/Warning Letter
  - These are Public Domain documents
- Consent decree
- Batch seizure
- Padlock
- Criminal charges

User Requirements Specifications

- States what you want
  - Good idea to prioritize needs vs wants
- Should **NOT** talk about design
- Frequently larger (more detailed) than it needs to be

Functional Requirements Specifications

- This is the system design
- Can be drawings
- Can be custom documents or parts of existing Manufacturer's documentation
- FRS >> URS

Design Qualification

- "Maps" the URS to the FRS
- How will each URS spec be achieved?
  - It's a good sanity check
  - You don't want to try to validate things that aren't there
- I've found it helpful to write a URS as something to be executed against the FRS
  - Executed DQ becomes the RTM

Impact Assessment

- Identify major system components
- Direct vs indirect impact
- If it fails, how will we know?
- If you won't find out until it's too late, the component has Direct Impact
  - Direct Impact components must be accounted for during Qualification
  - You're prioritizing

Impact Assessment Generalizations

- Impact Assessment is Risk Management
  - You've got to be willing to defend your rationales
- Easy to overdo
  - Recommend keeping it at a high level
- "Why" is just as important as "what"

Connecting a World of Pharmaceutical Knowledge ISPE

Validation Practices

- Prospectively planned testing
- Acceptance Criteria established before execution
  - Link your Acceptance Criteria to your specs
  - This is one more reason to have clearly defined specs
- Data is recorded in realtime
  - FDA will want to know who collected what data, and when they it

Connecting a World of Pharmaceutical Knowledge ISPE

More Validation Practices

- "Clear" is more important than "pretty"
- Comments for clarification are good, but don't go overboard
- Your data could be reviewed two years later

Connecting a World of Pharmaceutical Knowledge ISPE

Deviations +/or Discrepancies (oops)

- Comments
- Discrepancies
- Deviations

Connecting a World of Pharmaceutical Knowledge ISPE

Comments

- For clarification
  - "Two years later" scenario
- To correct minor Protocol Generation Errors (PGEs)
- To document additional testing performed (that wasn't specified in the protocol)

Connecting a World of Pharmaceutical Knowledge ISPE

Discrepancies

- Documents when Acceptance Criteria are not met
- Can be resolved by:
  - Fixing/adjusting something and reexecuting
  - Explaining why the current results are really acceptable

Connecting a World of Pharmaceutical Knowledge ISPE

Deviations

- Documents when the protocol instructions were not followed
- These are most defendable when they're documented prospectively

Deviations and Discrepancies

- They're not necessarily bad
- The FDA expects to see them
- Resolutions must be supported by data
- You want a probable root cause
  - You can't keep trying until you get lucky

Things Happen

They need to be explained

Connecting a World of Pharmaceutical Knowledge ISPE

Theoretical example #1

- 2° - 8°C refrigerator 24 hour Empty Chamber Temperature Distribution study
  - Acceptance Criteria were 2° - 8°C
  - Results were 1°C – 5°C
  - Owner said that this was acceptable since the materials he intended to keep in the refrigerator wouldn't be adversely affected by the lower temperatures
    - Likely FDA response: Why did you set the Acceptance Criteria at 2° - 8°C?

ECVS

Connecting a World of Pharmaceutical Knowledge ISPE

Theoretical example #2

- 2° - 8°C refrigerator 24 hour Empty Chamber Temperature Distribution study
  - Acceptance Criteria were 2° - 8°C
  - Results were 1°C – 5°C
  - Adjusted refrigerator setpoint, reexecuted study, temperatures remained between 2° C- 8°C
  - This resolution is more defendable than Theoretical Example #1

Connecting a World of Pharmaceutical Knowledge ISPE

Real World Example

- 2° - 8°C refrigerator 24 hour Empty Chamber Temperature Distribution study
  - Acceptance Criteria were 2° - 8°C
  - Results ranged from -1°C to 12°C
  - We replaced the refrigerant and remapped
  - Results were between 2°C and 8°C
  - We suspected that the refrigerator had the wrong refrigerant

Connecting a World of Pharmaceutical Knowledge ISPE

The importance of data

- You **HAVE** to have data to support your conclusions
- 60°C WFI example
- It's not difficult to spend more time and energy rationalizing than reexecuting

Connecting a World of Pharmaceutical Knowledge ISPE

Current Trends in Validation

- Commissioning
- Risk Management

Connecting a World of Pharmaceutical Knowledge ISPE

Current Trends - Commissioning

- When equipment +/or systems are installed, there's a certain amount of "getting it to work" effort
- Intent is to capture data from this effort to minimize repeat work
- Everything gets commissioned
  - Only Direct Impact systems or components get validated

Connecting a World of Pharmaceutical Knowledge ISPE

Current Trends - Commissioning

- Hasn't lived up to its promise
  - People doing the Commissioning work need to have a clear understanding of expectations
- Requires a significant amount of up-front planning
- Companies have to be willing to fight human nature

Connecting a World of Pharmaceutical Knowledge ISPE

Current Trends – Risk Management

- An extension of Impact Assessment
- Partly a response to the complaint that the FDA is partly responsible for drug costs and lead times
- The FDA wants to see companies start in this direction
- ASTM E2500

Connecting a World of Pharmaceutical Knowledge ISPE

Change Control

- One of the biggest challenges in GMP operations
- You have to allow change, but you have to control it
- Evidence of lack of Change Control discipline is a common 483 cause

Connecting a World of Pharmaceutical Knowledge ISPE

Equipment Qualification

- Controlled Temperature Units
  - Refrigerators, freezers, stability chambers
- Production support equipment
  - Parts washers
- Production equipment
  - Reactors
  - Chromatography skids
  - UF/DF skids

Critical Utility Validation

- High Purity Water systems
  - Generation and distribution
- Process gas systems
- HVAC/Environmental Control
  - Temperature and RH control
  - Environmental classification

Critical Utility Validation –
Common Practices, Industry Standards and Acceptance Criteria

- Lots of things are Common Practice +/or Industry Standards, but aren't Regulatory Requirements
  - 316L Stainless steel
  - 40 ACH, 0.05" ΔP for Class 10000 rooms
- Be careful using these things as Acceptance Criteria
- When in doubt, refer to the URS and IA

Connecting a World of Pharmaceutical Knowledge ISPE

Noncritical (Indirect Impact) Utility Validation

- Examples
  - Plant Steam system
  - Potable water systems
- Not done as much as it was in the past
  - Benefit of documenting an IA
- Exception: Waste Treatment systems
  - May be validated to answer EPA questions

Connecting a World of Pharmaceutical Knowledge ISPE

Analytical Method Validation

- Done for lab methods used to make product quality decisions
  - TOC in WFI
  - Product purity
- This is a form of Process Validation
  - Trained personnel
  - Approved procedures
  - Qualified Equipment

Cleaning Validation

- How do you prove that your equipment is clean enough to use?
  - Batch to batch
  - Product to product
- How clean is clean enough?

Definition of Cleaning Validation

- Process Validation
  - Trained Operators
  - Approved Procedures
  - Qualified Equipment

Cleaning Processes

- Clean In Place (CIP)
- Clean Out of Place (COP)
- Parts Washers
- Manual Cleaning
- Facility Cleaning

Cleaning Acceptance Criteria

- How clean is clean enough?
- FDA does not provide much specific guidance
  - Practical, Achievable, Verifiable
  - Scientifically Sound
- "In God We Trust; All Others Must Have Data" *Mike Herman, former boss*

Cleaning Acceptance Criteria

- Must be based on a scientific rationale
- "Why" is more important than "What"
- You need your R&D people involved

Validation Standard Answer #1

- "It Depends"
- The point is that Acceptance Criteria must be based on the specifics of the process

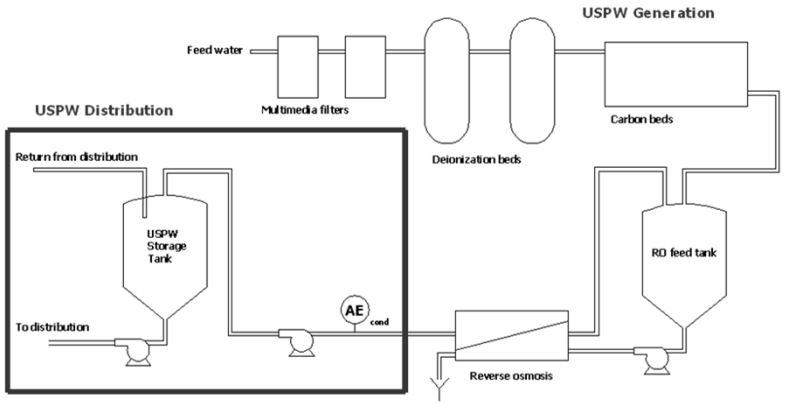
Connecting a World of Pharmaceutical Knowledge ISPE

High Purity Water System Validation

- Water is the most utilized ingredient in virtually all pharmaceutical manufacturing
  - Product formulation
  - Media and buffer batching
  - Cleaning
- Most operating companies distinguish between generation and distribution

Connecting a World of Pharmaceutical Knowledge ISPE

Generalized High Purity Water System



Alert and Action Levels

- **Alert**: parameter still within spec, but close enough to warrant attention
  - Responses could include additional testing, equipment inspection, sanitization
  - Should be described in SOPs
  - Need to demonstrate that SOPs are being followed

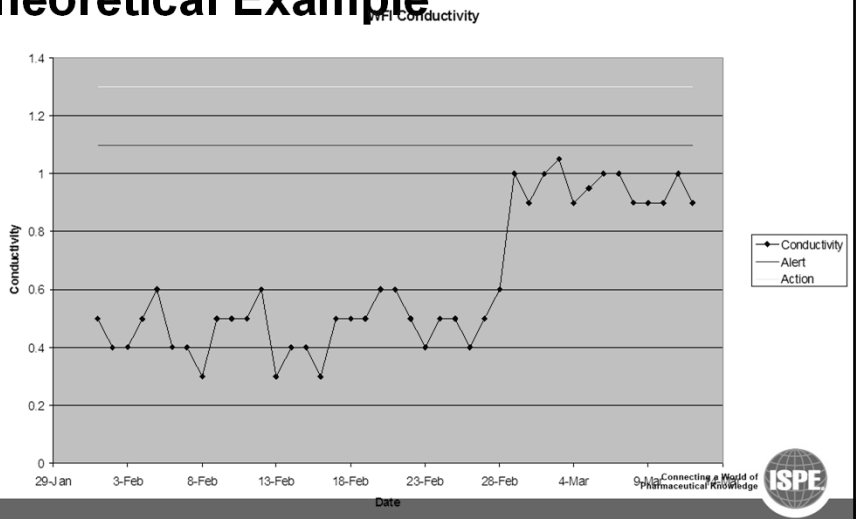
Alert and Action Levels

- **Action:** parameter close to or out of specification
  - Production may have to be quarantined until investigation and Corrective Actions are complete
  - Batch Record Deviation probably required

Alert and Action Levels

- Both must be based on data
  - Refine as more operational data is obtained

High Purity Water System Quality Trend – Theoretical Example



High Purity Water System Design Expectations

- Slope: >1/8 of an inch per foot
- Flow velocity: > 6 FPS – to ensure continuous turbulent flow
- Materials of Construction:
  - Primarily selected to be inert/not add anything to the product
  - Provide temperature and chemical resistance with smooth, clean surfaces that minimize nutrient accumulation

NOTE: These are not hard and fast requirements, but common practices. Different approaches are acceptable but must be defendable with data.

Case Study

Cleanroom Suite Qualification

Connecting a World of Pharmaceutical Knowledge ISPE

Background

- A Medical Device manufacturer built a new facility that included a Cleanroom suite consisting of five ISO Class 7 and Class 8 rooms
- The new facility was built in response to FDA concerns with the client's existing cleanrooms
- We knew that the FDA would be looking very closely at the Cleanroom validation

Connecting a World of Pharmaceutical Knowledge ISPE

60

Cleanroom Validation Approach

- Installation Qualification (IQ)
  - We're showing that we know what we have
  - We're showing that we know that the suite was built properly
- Operational Qualification (OQ)
  - We're showing that the suite works
- Performance Qualification (PQ)
  - We're showing that the suite meets our needs on an ongoing basis

Connecting a World of Pharmaceutical Knowledge ISPE

61

Cleanroom Validation Step 1

- Developed a User Requirements Specification
- Stated client's requirements for control of:
  - Temperature
  - RH
  - Total Airborne Particulates (TAPs)
  - Airborne and Surface Viables

Connecting a World of Pharmaceutical Knowledge ISPE

62

Cleanroom URS *(continued)*

- Outlined what the IQ, OQ and PQ would be testing
- Listed what was required in the Turnover Package (TOP)

Cleanroom URS

- Kept it to 13 pages in length
  - Including the Approval, TOC and Revision History pages
  - We focused on stating what performance we needed, not how to achieve the performance
  - KISS principle

Cleanroom IQ Verifications

- Identified critical components; verified nameplate information
- Engineering drawings
- TOP contents
- Cleanroom MOC
- Cleanroom entered into client support systems
- Utility connections
- HEPA Filter Certifications
- BMS Configuration

Connecting a World of Pharmaceutical Knowledge ISPE

65

Cleanroom OQ Verifications

- Client SOPs for:
  - HVAC equipment operation
  - HVAC equipment PM
  - Gowning
  - Cleanroom access control
  - Cleanroom cleaning
  - ΔP Monitoring
  - Environmental Monitoring

Connecting a World of Pharmaceutical Knowledge ISPE

66

Cleanroom OQ Verifications

- Critical and Test Instrument Calibration
- Air Balance Report Review
  - Air Changes per Hour (ACH)
- Smoke studies
  - Visual confirmation of ΔPs
- Alarm and Interlock Operation
- Baseline E/M Study
  - Demonstrated that the Cleanrooms could achieve required conditions in the At Rest state

Connecting a World of Pharmaceutical Knowledge ISPE

67

Cleanroom PQ

Demonstrated that the Cleanroom suite worked as a system: that when

- trained personnel
- follow approved procedures
- to operate qualified equipment

the Cleanrooms reliably maintained the required Environmental Conditions

Connecting a World of Pharmaceutical Knowledge ISPE

68

Cleanroom PQ

- Phase 1
  - Three 2-hour sessions of simulated manufacturing activities
  - Performed E/M at all sampling locations
- Phase 2
  - Performed weekly E/M for one quarter
  - Rotated through sampling locations
  - Established E/M Alert and Action levels

69

Cleanroom PQ

- Phase 3
  - Performed weekly E/M for three additional quarters
  - Rotated through sampling locations; concentrated on “challenge” spots
  - Determined Ongoing Monitoring sampling plan and E/M Alert and Action levels based on this full year’s data

70

Validation Report Organization

- Concise Summary Report
- Executed protocol
- Deviations and Discrepancies
- Associated documentation/exhibits
  - HEPA Certification Reports
  - Calibration documentation
  - Air Balance Reports

Connecting a World of Pharmaceutical Knowledge ISPE

71

Cleanroom Validation Outcome

An uneventful audit.

Connecting a World of Pharmaceutical Knowledge ISPE

72

Key Lessons

- A prospective, concise specification is extremely valuable
  - During startup
  - During Validation
  - During an Audit
- When feasible, include copies of documents referenced during execution with the Validation Report
  - "The auditors don't have a lot of time or patience"
    Paul Strouth, Organogenesis Validation Manager

Connecting a World of Pharmaceutical Knowledge ISPE

73

Questions?

Feel free to contact
Victoria Hayes or Rich Yeaton
at 603 421 2748 or
hayes@eastcoastvalidation.com
yeaton@eastcoastvalidation.com
with any followup questions

Connecting a World of Pharmaceutical Knowledge ISPE