Introduction to Validation
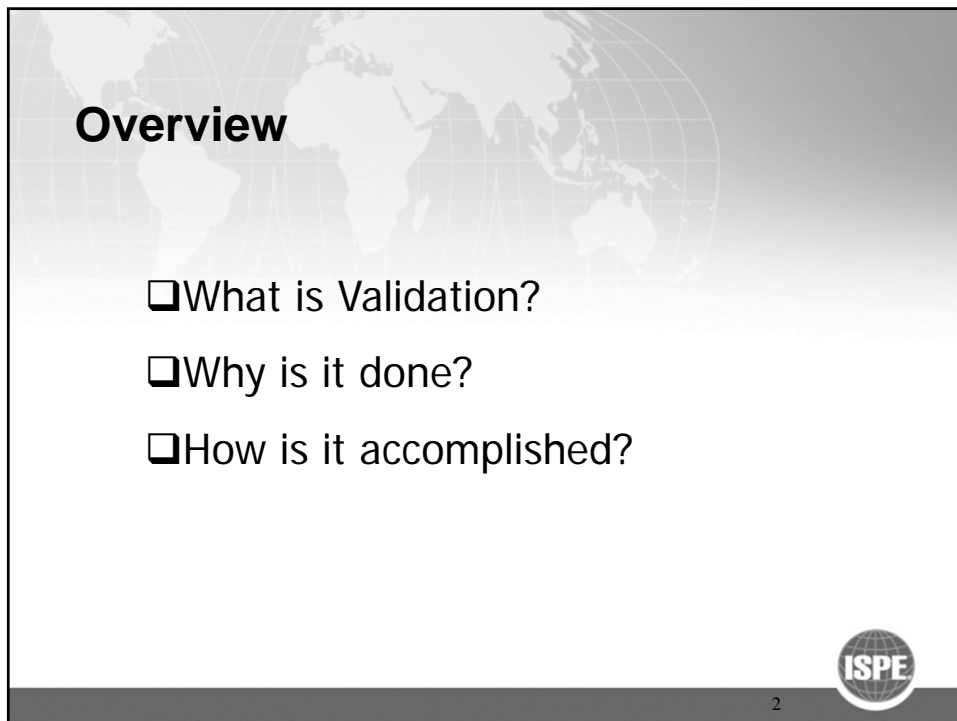
Jack Campion, P.E.
June 20, 2013

genzyme
A SANOFI COMPANY

Connecting a World of
Pharmaceutical Knowledge   ISPE

Overview

❑What is Validation?

❑Why is it done?

❑How is it accomplished?

2

What is Validation?

- "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"

  - FDA Guidance: *Process Validation: General Principles and Practices*
  - January, 2011

3

Other ways to describe Validation…

- A sequence of complementary activities that include verifications, tests, and documentation

- An extension of Good Engineering Practices that includes review and approval by an independent quality organization

4

More ways to describe Validation…

- A state of being, which if unchanged, assures that a pharmaceutical manufacturing system will consistently produce quality medicines
  - Part of the lifecycle of pharmaceutical manufacturing systems starting with the conceptual elements of process design and ending with the cessation of production

ISPE

5

One Last way to describe Validation…

- A mindset that assures that systems are designed, constructed, and can be robustly operated to produce quality medicines

ISPE

6

Sidebar: What is the Product?

What are the "pre-determined specifications and quality attributes"?

- Safety
- Efficacy
- Identity
- Potency
- Purity

A. Measureable by analyzing the final product itself

B. Inferred by a **validated process**

→ In part, the *product IS the process*

ISPE

7

Why is Validation done?

We validate the production process because, in part, the process defines the product and assures its quality attributes.

ISPE

8

Regulatory Requirement

- *From the January 2011 Guidance:*
- Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)), which states the following:
- A drug…shall be deemed to be adulterated…if… the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice….

ISPE

9

Unpacking the Definition of Validation

"documented evidence"	*If it's not documented it's just a rumor*
"high degree of assurance"	The risks to product quality have been assessed, the process has been tested, and the remaining risk has been found to be acceptable
"specific process"	"System" inclusions and exclusions are well defined (hardware, software, procedures, environment). Critical Attributes are clear and measureable.

ISPE

10

Unpacking, continued…

"consistently produce"	Documented evidence of <u>repeatability</u>
"pre-determined specifications and quality attributes"	"In the beginning there was a URS…and on the 6th day there were test protocols"

11

The Process is comprised of Systems …

We validate the production **process** by validating the **systems** used in the production process

Which systems?

"…the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding…"

What could be in a system?

12

What could be in a manufacturing system?

- Hardware
- Control elements
- Software
- Analytical Equipment
- Procedures
- Facilities & Environment
- Supplies

ISPE

13

Validation
"How To"

ISPE

14

How to Validate in Three Easy steps!!

From FDA Guidance: *Process Validation: General Principles and Practices*
January, 2011

B.   Approach to Process Validation

For purposes of this guidance, *process validation* is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes process validation activities in three stages.

- Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

- Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

- Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

This guidance describes activities typical of each stage, but in practice, some activities might occur in multiple stages.

15

How to Validate in Six Easy Steps!!

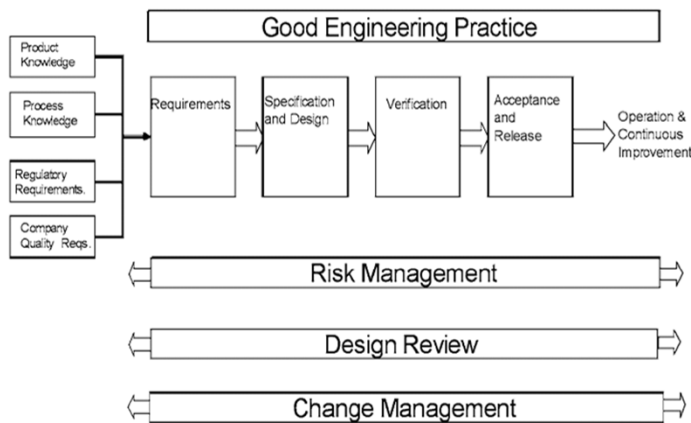**From ASTM E2500-07 Standard Guide**

FIG. 1 The Specification, Design, and Verification Process

16

**Involvement in the early stages
Begin with the End in Mind**

1. Review the design for "verifiability" & "testability"; make recommendations to the project leaders
2. Participate in system boundary definition;
    a. Draw system boundaries on P&IDs
3. Develop a timeline (schedule) for the entire project

ISPE

17

Begin with the End in Mind, *cont'd.*

4. Determine the documentation needed from designers and vendors for validation and include it in the contracts; use a documents requirement matrix
5. Include FATs and SATs into vendors' contracts
    a. Tests should address the owner's operational and performance acceptance criteria

ISPE

18

Definitions – CQA & CPP

Critical Quality Attribute (CQA)	A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
Critical Process Parameter (CPP)	A process parameter whose variability impacts a quality attribute and therefore needs to be controlled to ensure the process produces the desired quality.

ISPE

19

Definition – Process Validation

1. Broad term for the overall FDA requirement described in January 2011 Guidance

   - Incorporates all steps leading to licensure

2. Conventional term to describe the first production of product batches or lots using the new or modified process

   - Batches are marketable upon acceptance by the licensing agency

   - Called "Process Performance Qualification" in 2011 FDA Guidance

ISPE

20

The Chain of Validation Documentation

1. *Requirements*
2. *Criticality*
3. *Acceptance Criteria*
4. *Risk*
5. *Test Plan*

ISPE

21

The Chain of Validation Information:

1. *Requirements Definition*
   - User Requirements Specification (URS)
   - Identify "operability" "inspectability" "cleanability" and "maintainability" requirements

ISPE

22

The Chain of Validation Information:

- *2. Criticality Assessment*
  - List Critical Quality Attributes (CQA) of the *product*
  - List corresponding Critical Process Parameters (CPP) of the *process*
    - List where, when & how they are measured in the process
  - Identify how information must be recorded – manually and/or automatically

- *3. Acceptance Criteria (AC)*
  - Based on CPPs

ISPE

23

The Chain of Validation Information:

- *4. Risk Assessment**
  - Use a cross-functional team
  - Use a trained <u>process</u> RA facilitator
  - Challenge the AC; identify the tests

- *5. Validation Plan*

  - Encompasses Commissioning, Qualification & *Process Validation*
  - *Vesper, James L. "Risk Assessment & Risk Management in the Pharmaceutical Industry, Clear and Simple" © 2006

ISPE

24

Protocols

1. Installation
2. Operational
3. Performance
4. Process

- "Verification" "Qualification" "Validation"

ISPE

25

"Verification"

- A term introduced by the ASTM E2500-07 Standard Guide as follows:

  "a systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other."

- a.k.a. Commissioning & Qualification (C&Q)
- a.k.a. Integrated C&Q

ISPE

26

"Verification" continued…

- May or may not include Performance Qualification (PQ)
- Conventionally does <u>not</u> include *Process Validation* (a.k.a. "Process Performance Qualification")
- *Note: The terms "Installation Qualification" & "Operational Qualification" are <u>not mentioned</u> in the January 2011 guidance. They are still used but less than in the past.*

ISPE

27

Performance Qualification (PQ)

- The challenge of a system under real or simulated conditions (e.g. water batches), including minimum and maximum CPP's
- Typically the final stage of cleaning and sterilization process validation
- For other processes, typically used as a precursor to *Process Validation*
- *Note: The term PQ is <u>not found</u> in the January 2011 guidance. It may or may not satisfy the "Process Performance Qualification" requirement.*

ISPE

28

Process Validation

- a.k.a. "Process Performance Qualification" (PPQ) from January 2011 FDA Guidance
- Traditionally three "batches" or "lots" of material produced by the process using all of the now-validated systems
- This material can be marketed upon approval of the changed process or licensing of the manufacturing facility

ISPE

29

Final Advice

1. Explicitly base validation policies, procedures and plans on industry guidance and standards
2. Explain the rationale for all intended validation activities, i.e. what makes sense and why
3. Use the Chain of Validation Information to build in traceability back to the user requirements

ISPE

30

Final, Final Advice

3. Use risk assessment to scope the validation of each system, i.e. the "risk-based approach"

4. Build in flexibility wherever possible as to methods and acceptance criteria – you will be held to what you said you would do!!

ISPE

31

Questions ??

ISPE

32