Introduction to ISPE GUIDE: SCIENCE AND RISK-BASED APPROACH FOR THE DELIVERY OF FACILITIES, SYSTEMS, AND EQUIPMENT

&

Overview of Amgen’s CQP Commissioning and Qualification Program

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Agenda

- Introduction and Overview of ISPE GUIDE: *Science and Risk-Based Approach for the Delivery of Facility Systems and Equipment (FSE)*

- Overview of Amgen’s CQP Commissioning and Qualification Program

- Questions ??
Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment
A paradigm shift is occurring in the global pharmaceutical industry. The pharmaceutical industry, in conjunction with ISPE is applying an all-encompassing approach to qualification and toward using focused methodologies to assess the scope of qualification.

A science and risk based approach to Qualification of applicable systems and facilities consists of:

- The identification and control of risks to product quality
- Formality and documentation commensurate with risk
- The use of Good Engineering Practices (GEP) to verify installation and operation of systems
- Verification that system performance meets product and process user requirements

**Think about it:**
If everything is critical, then nothing is.
Qualification – A Broken Process

- IQ/OQ had become more intensive than PQ.
- Organizations refused to leverage commissioning.
- Automated systems and the controlled equipment were qualified separately and inefficiently.
- Deviations for trivial items diluted Q-unit attention.
- “Change-is-bad” attitudes driven by cost/time.
In the Beginning…

A number of seminal documents established the principles of a RBA:

- ISPE Baseline Guide 5 (2001)
- ICH Q8 Pharmaceutical Development (2008)
- ICH Q9 Quality Risk Management (2006)
- ASTM E 2500 (2007)
10 Principles for Risk-Based Qualification

1. Focus on that which affects product quality
2. Process User Requirements key to acceptability (IQ/OQ subordinate to PQ)
3. Risk assessments and process knowledge used to identify critical elements
4. Only critical features/functions to be qualified
5. All activities must contribute value
6. Risk-based asset delivery – not “cookbook” requirements
7. Value-added documents based on technical merit
8. Use of supplier documentation
9. Test planning (and one-time testing)
10. Foster innovation – all change is not bad

ISPE White Paper “Risk Based Qualification for the 21st Century”
March 2005
Scope of BG 5 vs. FSE GUIDE

BG 5 Guidance

- Design Development
- Enhanced Design Review

New Risk-based Approach

- Design Development
- Design Review
- Verification Testing
- Performance Testing

Engineering Change Management
QA Change Control

PQ
Process Validation

IQ & OQ

Verification vs. as Qualification

FAT Verification Work

SAT Verification Work

Basis for Suitability: Process Requirements, Risk Control

Commissioning Verification Work

Qualified as Suitable For Intended Use

Figure 2 from “Solving the Terminology Conundrum”
Pharmaceutical Engineering, July/August 2008
Qualification – “Traditional” vs. RBA

**Traditional Approach**
- (Product) User Requirements not Formally Documented
- Protocols Developed from “Templates”
- IQ/OQ Protocols “Preapproved”
- Commissioning not Leveraged
- Engineering and “Validation” Personnel Often Distinct
- Emphasis on Documents – Not System Performance

**RBA Based on ASTM E 2500**
- Process Requirements Documented, Approved
- Risk Assessments Determine Critical Aspects of Design
- Engineering Testing (“Commissioning”) Verification
- All Documents with Technical Merit Used as Evidence of Fitness for Use
- Emphasis on Meeting Process Requirements
Eyes on the Prize

Time & $$$

= to

Focus on Critical Quality Issues

Actual photo of an Abbott Laboratories risk based revalidation paperwork for a legacy control system (on right) vs. previous revalidation “testing everything”
FSE- Rationale for the New ISPE GUIDE

Presents a **structured lifecycle approach** to the delivery of facilities, systems and equipment which support these regulatory initiatives

Designed to **improve** the way in which the industry **delivers regulated manufacturing capacity**

- Improve the ability to **meet documented process requirements**
- **Control risks** within the manufacturing process
- **Produce high quality** products which **consistently** meet product user requirements.

The GUIDE describes the **Principles** required when applying a science and risk based program.
Structure of FSE GUIDE

- Good Engineering Practice
  - Requirements
  - Specification and Design
  - Verification
  - Acceptance and Release

- Risk Management
  - Design Review
  - Change Management

Reference: Figure 1: ASTM E2500-07, pg 3
## FSE GUIDE Overview

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Note: Automation dealt with throughout each chapter
Introduction

This Guide is a key part of the validation life cycle approach to quality assurance to ensure the manufacture of safe and effective products. The Guide is designed to improve the way in which industry delivers regulated manufacturing capacity:

- to documented process requirements
- control risks within the manufacturing process
- produce high quality products
- consistently meeting product and process requirements
Background

- The successful delivery of manufacturing facilities (including small, large, new, expansion, or renovation type projects) regulated by various authorities, poses significant challenges to manufacturers, engineering professionals, and equipment suppliers.

- These facilities are required to meet all applicable GxP regulations, and to comply with all other relevant local and international governing codes, laws, and regulations.

- This Guide has been published in support of the principles provided in these publications and to provide specific implementation guidance on meeting the expectations of global regulators as embodied in the ICH documents, as applied to the design and delivery of regulated facilities.
Relationship of this Guide to International GMP Regs and ICH Guidance Docs

- US GMPs
- EU GMPs
- Japan GMPs

ICH 08, 09, 10 Guidance

This Guide

How to perform key elements of Science and Risk-based approach and determine ‘Suitability for Intended Use’. 
Scope

– Planning, specification, design, and delivery of facilities/utilities/equipment and associated automation (harmonized) with GAMP 5
– All pharmaceutical manufacturing
– Addresses the verification (or qualification) portion of the validation life cycle on which process validation is built
– New commercial manufacturing and modification to existing regulated mfg facilities
Purpose

• Objective is to facilitate the translation of the scientific product and process knowledge into a documented specification, design, and verification of equipment/systems/utilities which are fit for intended use, and minimize risk to patient safety and product quality.

• Approach is built on science based quality risk management, and concepts of Quality by Design.
Encourage the industry and individual organizations to reassess the terminology, practices, and roles and responsibilities involved in delivering new manufacturing capacity to focus on the criteria required to establish suitability for intended use.
Key Concepts

**Science Based Quality Risk Management**
- Describes the importance of a QRM program
- Documented risk assessments focused on risk to patient
- Focus on identifying, assessing and controlling risk

**Product and Process Understanding**
- Resulting from scientific investigation
- Enhanced continually during ongoing operations
- Begins with knowing the product CQAs and associated CPPs (ICH Q8R2)

**Focus on Achieving Fitness for Intended Use**
- Verification activities focused on confirming that CAs of equipment/systems and associated meet acceptance criteria
- Verification inspections and tests are not limited to CAs
Key Concepts (cont.)

Flexible Approaches to Specification and Verification

- Several approaches to structure the documents, inspections, and testing activities
- Demonstration of fit for intended use and sufficient to meet regulatory expectations

Clarification of Roles and Responsibilities

- The roles of Quality Unit and SME are described in the context of the scope of activities covered by this Guide. Subject Matter Experts (SMEs) are defined as those individuals with specific expertise in a particular area or field.
- The Quality Unit has a key role within the quality management system governing facilities, systems, and equipment. In addition to acting as a Subject Matter Expert (SME), the Quality Unit is responsible for overseeing quality and compliance.
Role of the Quality Unit

A key focus of the Quality Unit is identifying and approving those aspects that are required to manufacture a quality product, and to ensure that appropriate procedures are followed to ensure that risks to the patient in the manufacturing systems are adequately controlled.

The QRM approach recognizes that the GxP regulations provide the Quality Unit with the responsibility for ensuring controls to assure drug product quality.
The Risk-Based Verification Process

R&D
interdiscipl. expert team

Product & Process Knowledge (initial CQAs, CPPs)

initial Risk Assessment

Appropriate tool

List of Critical Aspects (CQA, CPP)

Verification Plan

Verification Testing, (Design to Performance) to confirm Critical Aspects meet Acceptance Criteria

Acceptance & Release

GEP, Project Quality Management

Appr. by Q Unit

Appr. by Q Unit

Review all completed verification test documentation by second, independent SME

Appr. by Q Unit

CPP: Critical Process Parameter
CQA: Critical Quality Attribute
Verification – ASTM E2500-07

- It is a life-cycle approach – not a check at the end of the process
- It is based on the process and product knowledge, regulatory, and quality standards
- Verification approach must be documented – Verification Plan(s) (approved by quality unit)
- Acceptance criteria must be established
- Documented confirmation that the equipment/system is fit for intended use
- Acceptance and release must be documented (approved by the quality unit)
Overview of Amgen’s CQP Commissioning and Qualification Program

Special Thanks to:
Ronald Brunelle - Quality Assurance Director
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Why do this

Goal

– Simplify Validation
– Better, Cheaper, Faster

Industry Guidance Utilized

– ASTM E2500
– ICH
Agenda

• Introducing Change
• Highlights of the Program
• Lessons Learned and Next Steps
Introducing Change
From Impact Assessments to System Boundaries

- C&Q impact assessments time consuming
- Impact assessment giving inconsistent results across sites
- Component and system impact assessments not helpful in the risk based ASTM 2500 model
Boundary Diagrams

- **Boundary diagrams** were created for all systems in Amgen
- Allowed a consistent manner for systems and component assessments
- No need to perform the C&Q impact assessment process
- Set the stage for Risk Based approach to qualification
Change from Impact categorization to “Levels” – Mindset Change

- **Level 1** - Equipment assets within a system where operation or maintenance activities can affect the **critical quality attributes, the critical aspects, or the critical process parameters** of the product the system delivers.

- **Level 2** - Equipment assets within a system where operation or maintenance activities can have an **adverse business impact**.

- **Level 3** - Equipment assets not included in the definitions of level 1 or 2.
Cold Rooms – System 810

Notation:
The system boundary suggested is as shown on the drawing. The flowchart shows the standard list of sub-systems and equipment. Items not shown on the hierarchy are considered a spare part or consumable to a sub-system listed.

Critical Quality Attributes/Process Parameters (CQAs/CPPs):
The potential CPPs are listed below. For the physical system being evaluated, the SCBD user is responsible for determining which (if not all) CPPs are needed to ensure the system produces the desired quality:
- Temperature
- Humidity/Moisture

Instruments directly associated with these attributes shall be classified as level 1.

Assumptions:
The assumptions made when defining the classification level 1 equipment are as follows: Cold rooms used in the storage of controlled materials are classified level 1. The example shown indicates a control system independent of the CPP monitoring system. The evaporator location has a direct impact to the temperature map of the room. Additionally, the CQAs and CPPs are routinely monitored through the calibrated monitoring system. Through this monitoring, any non-Level 1 equipment failure would be detected.
Highlights of The Program
The ASTM 2500 Standard

- A science and “risk-based” approach to assure that GMP equipment & systems are:
  - Fit for use
  - Perform satisfactorily

- Amgen interpretation and application of:
  - ASTM-2500
  - ICH Q9
  - EU Vol. 4 Annex 15
  - FDA Process Validation Guidance
  - ISPE Guide: SCIENCE AND RISK-BASED APPROACH FOR THE DELIVERY OF FACILITIES, SYSTEMS, AND EQUIPMENT
Amgen Document Hierarchy plays key role in change

**Policy:**
Governing principle/position that mandates or restricts action.

**Standard:**
Operational principles that are typically translated into other required / controlled documents (SOPs) for how to / execution information

**Procedure:**
Instructions for performing tasks, activities or practices that includes the identification of roles and responsibilities.
Using the Document Hierarchy

Integration of Engineering and Quality can be achieved through Document Hierarchy
GEP Framework – 5 SOPs

Design Review

Engineering Change Management

Engineering Quality Systems

Automation Project Delivery

Commissioning Planning and Execution
GEP Framework

Commissioning Planning and Execution

- Sample Summary Reports
- Sample Commissioning Plan/Template
- Sample Commissioning Specifications
- Facility commissioning sample report
- HAVC System commissioning sample report
- Pipe System commissioning sample report
- Process Equipment and Automation guidance
- BMA/BAS System Commissioning sample report
- Security System Commissioning
Verification: Activities within any of these processes
Qualification Process and Quality Oversight

- Requirements
- Specifications and Design
- Build / Construct
- Verification
- Accept and Release

Risk assessment controls confirmed
Strategy scope and acceptance criteria for risk controls
Risk assessment controls identified
Approvals of program standards, GEPs, SOPs
Quality Oversight model at full maturity of the Engineering, Automation and Quality processes.

Plan
- User Requirements
- Quality Risk Assessments
- Commissioning Plan
- FAT
- Receipt Verification & Installation Verification
- Commissioning Tests - Automation checkout, Performance tests, SAT
- Qualification
- Summary Report
- Performance Testing / PQ

Design
- Validation Plan
- Design Reviews
- Development Testing
- ✔️ Quality Pre and Post Approval

Build
- ✔️ Quality Review
- ✔️ Quality Approval

Test
Amgen Relational Model for Qualification

- **User Requirements**
- **Risk Assessment**
- **Commissioning / Testing**
- **Qualification Report**
- **Performance Qualification**

**SME's**
- Process
- Product
- System
- Regulatory
- Quality
- Vendors

**System Specifications**

**Design Review**

**Vendor Assessment**

- Vendor Documents
- Good Engineering Practices
- Change Management

Traceability

Feed into ongoing maintenance management systems
Lessons Learned - Wins

- One site inspection by agency - the process not challenged
- Resulted in focus of Quality on critical aspects
- Different groups understand and appreciate roles and interactions more clearly
- Faster implementations and more robust systems have been recognized
- System based vs. component based thinking
Lessons Learned - Challenges

- Expectations around documentation practices
- GEPs not well established and understood
- Comfort zones are challenged and resistance varies
- Use escalation process for resistance
Maturing the Process

- Engineering is intensifying their practices and delivery models to provide more robust systems
- Alignment of procedures and practices between groups (Engineering, Automation, Validation)
- Understanding and accountability of SME Role
- Legacy systems applicability
- Intensify training for risk assessments
- Individual site assessments to ensure maturity progression
Benefits Beyond Large Capital Projects

Additional Value
- Change Control Assessments
- Failure Event Impact Assessments
- Preventive Maintenance
- Others?

Adopted Practices
Questions
Thank You!

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