Importance of ICH Guidance in Fulfilling Process Validation Requirements
Process Validation

- **PROCESS VALIDATION** is the collection and evaluation of data, from the process design stage throughout commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products. (FDA Guidance to Industry January 24, 2011)
Why Process Validation?

- “Quality of the product cannot be assured by simply inspecting or testing in-process and finished products.” It must be built into the product-process a-priori. (the need for QbD)
- “Focusing exclusively on the qualification effort without understanding the process and ensuring the process is maintained in a state of control may not lead to adequate assurance of quality.” (knowledge and monitoring in addition to qualification)
The Stages of Process Validation

• Three Stages of Process Validation
  – Stage 1 - Process Design Stage (process is defined based on development and scale-up)
  – Stage 2 - Process Qualification Stage (Design is confirmed as being capable of reproducible production)
  – Stage 3 - Continued Verification and improvement (Continuously gaining assurance the process remains in a state of control)
The Life Cycle Approach to Process Validation

Planning & Design *(ICH Q8)*

Continuous Verification & Improvement *(ICH Q9)*

Implementation & Qualification *(ICH Q9)*

ICH Q9, CAPA, PAT & Change Control

ICH Q10
The Quality System

ICH Q8

ICH Q9

ICH Q10

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Stage 1: Process Design

• Understanding the science
• Understanding the risk
• Building quality into the process
• Establishing Control Strategy
Stage 2: Implementation and Process Qualification

- Implement the process and Facility
- Qualification of utilities and equipment
- The Process Performance Qualification (PPQ) protocol
- Protocol execution and report
Stage 3: Continued Process Verification

• Monitoring appropriate parameters to ensure process in a validated state of control.
• Proper maintenance of the facility, utilities, and process equipment
• Use CAPA, PAT and Change control as well as data collected in monitoring to ensure the process remains in a state of control and continually improve it.
International Conference on Harmonization (ICH)

• Issues guidance to assist member countries in harmonizing their compliance requirements
• Outlines approaches and possible requirements to comply with GMP requirements
• The regulatory agencies of member countries participate in developing the guidance and implement them.
• The guidance also outline tools and information useful for fulfilling the requirements of Process Validation
ICH-Reorganization

• October 2015 reorganization
• Legal entity under Swiss Law
• New Name “International Council for Harmonization”
• Making it a truly global initiative, expanding beyond the current ICH members
• Mission did not change but now all regulatory agencies of the world can participate
ICH Q8

• Titled: Pharmaceutical Development
• Pharmaceutical development aims at:
  – Designing a quality product, and
  – Designing a manufacturing process to consistently deliver intended product performance.
• Use information gained from development studies as well as previous manufacturing experience to establish the design space, specifications, and manufacturing controls (the need for knowledge management).
ICH Q8

• Information from development studies are basis for Quality Risk Management (QRM)
• Quality cannot be tested in the product instead it should be built in by design (QbD)
• Design space (DS) is proposed by applicant and approved by regulators. Working within DS is not a change.
ICH Q8

• **Importance in Validation**
  – Mostly applicable in Stage 1 (process design)
  – Can be used as part of CAPA in stage 3 proactively (continued verification and improvement)
  – Define the important processing parameters
  – Define the design space
ICH Q8

• **Importance in Validation (Cont.)**
  – Identify product CQAs
  – Identify the CPP that affect the CQAs
  – Help define the control strategy
  – Implement QbD during the process design stage to ensure lowest risk process is developed
ICH Q9

• Titled: Quality Risk Management
• Quality risk management is an important component of a robust quality system.
• Risk is the combination of the probability of occurrence of harm and the severity of that harm.
• Mitigating the risk to the patient is of prime importance.
ICH Q9

• Risk to patient manifests itself through product quality.
• The level and extent of actions to be taken to eliminate or minimize actual or potential risk must be appropriate to the magnitude of the problem and commensurate with the level of risk anticipated.
ICH Q9

• **Importance in Validation**
  – In stage 1 used to develop low risk designs
  – In stage 2 used to define critical vs. noncritical systems and instruments for PPQ studies
  – In stage 2 used to define critical parameters which require testing during qualification
  – In stage 3 used to assess criticality of observed trends
  – In stage 3 used to assess criticality of deviations and determine level and extent of action to be taken as part of CAPA
ICH Q10

- Titled: Pharmaceutical Quality System
- Describes an effective quality management system
- Takes into account ISO principles and GMP principles.
- Complements ICH Q8 and ICH Q9
- Implementation of ICH Q10 throughout the product lifecycle facilitates innovation and continued improvement.
ICH Q10

• Quality System supports development and manufacture of drug products
• It applies in the development, technology transfer, manufacturing, and product discontinuation
• Describes QS elements and management responsibilities
• Objectives are product realization (design implementation and production initiation), maintaining a state of control, and continual improvement.
ICH Q10 - Enablers

• Knowledge management:
  The systematic approach to acquiring, analyzing, storing, and disseminating information related to the product, its manufacturing process and its components.

• Quality Risk Management
  Proactively identifying, evaluating and controlling risk to product quality
Pharmaceutical Quality Management System-ICH Q10

• Contents:
  – Definition of management responsibilities
  – Process performance and product quality monitoring
  – Corrective and preventive action (CAPA)
  – Change Management
  – Management review
Pharmaceutical Quality Management System-ICH Q10

• Contents:
  – Performance Indicators to assist in monitoring the process
  – Quality Manual
    • Describes the quality Policy
    • Defines the quality system process
    • Describes the quality system
    • Management responsibilities
Management Responsibility

- Commitment to quality
- Establish a Quality Policy
- Quality Planning
- Resource Management
- Internal Communication
- Management Review
- Extension to outsourced material
Continual Improvement of The Process Performance and Product Quality (Stage 3 of PV)

• Continual Improvement is achieved through implementation of the four quality elements, these are:
  – Monitoring (process & product quality)
  – CAPA
  – Change Management System
  – Management Review
ICH Q10

**Process Validation**

- Process Design Stage
- Process Qualification Stage
- Continued Verification Stage

- **Development**
- **Tech Transfer**
- **Implementation**
- **Commercial Operation**
- **Discontinued**

**Management Responsibility**

**Enablers:**
- Knowledge Management (Q8) - Design Reviews
- Quality Risk Management (Q9)

**QS Elements:**

**Quality System Ties it all Together**
ICH Q10

• **Importance in Validation**
  – In stage 1 used to manage knowledge of the process design
  – In stage 1 used in managing changes as process being developed
  – In stage 2 provide procedures and defines required management oversight to the PPQ development and execution
  – In stage 3 manage the monitoring of process to ensure state of control is maintained
ICH Q10

• Importance in Validation
  – In stage 3 outlines management review and its importance thus ensuring continuous improvement
  – In stage 3 defines CAPA implementation to maintain state of control and continually improve the process/product
  – In stage 3 used to manage changes to insure maintenance of a state of control
  – In stage 3 process and product quality monitoring procedures and approaches
ICH Q11

• Titled: Development and Manufacture of Drug Substances

• Provides clarification on the principles and concepts described in ICH Guidance on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality System (Q10) as they pertain to the development and manufacture of drug substance.
ICH Q11

• Defines two possible approaches to drug development/drug manufacturing process:
  – Traditional
    • Defined set points and ranges, control strategy based on demonstrating process reproducibility
    • Disadvantage: Rigid
  – Enhanced
    • Risk and science used to understand process parameters impacting CQA develop appropriate control strategies applicable over the lifecycle of the drug substance which may include the establishment of design space(s).
    • Advantage: Flexible manufacturing and Flexible regulatory approaches
Definitions

- CQA: Critical Quality Attribute - typically include those properties or characteristics that affect identity, purity, biological activity and stability.
- CPP: Critical Process Parameters – typically include processing parameters that have an impact on the Critical Quality Attributes such as material characteristics and processing steps conditions. These should be monitored, “alarmed”, and controlled to ensure the process produces the desired quality.
Definitions

- QTPP: Quality Target Product Profile - A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.
Quality Risk Management (QRM)

- QRM, as described in ICH Q9 can be used in a variety of activities (Associated with Process Validation):
  - Assessing options for the design of the manufacturing process
  - Assessing quality attributes and manufacturing process parameters
  - Increasing the assurance of routinely producing batches of the intended quality.
Knowledge Management

• Knowledge management as described in ICH Q10 can facilitate manufacturing process development (stage 1 in Process Validation):
  – Identify and utilize sources of information which include prior knowledge and development studies.
    • Prior knowledge can include established biological, chemical and engineering principles, technical literature, and applied manufacturing experience.
    • Data derived from relevant prior knowledge, including platform manufacturing can be leveraged to support development of the commercial process and expedite scientific understanding.
Knowledge Management

• Knowledge management as described in ICH Q10 can facilitate qualification of the process (stage 2 in Process Validation):
  – Retrieve protocol
  – Identify previous qualification issues encountered with similar equipment, systems or processes
Knowledge Management

• Knowledge management as described in ICH Q10 can facilitate insuring a state of control and process improvement (stage 3 in Process Validation)
  – Recognize and retrieve historical data for the process—e.g. define processing limits
  – Identify possible solutions for processing problems—e.g. support CAPA
  – Needed for continuous improvement of the process—e.g. recognize reoccurring problems to address
Approach to Development

• ICH Q8 recognizes that there are many strategies for product development.

• ICH Q11 extends the statement to process development. Manufacturing process development must include, at a minimum (stage 1 of Process Validation):
  – Recognizing CQAs of the drug substance having impact on its quality
  – Define appropriate manufacturing process
  – Defining control strategy
Approach to Development

• Enhanced approach will also include:
  – Identifying, through prior knowledge, experimentation and risk assessment, the material attributes (e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters that can have an effect on drug substance CQAs
  – Determining the functional relationships that link material attributes and process parameters to drug substance CQAs
  – Using the enhanced approach in combination with QRM to establish an appropriate control strategy which can, for example, include a proposal for a design space(s).

___________________________________________________
All needed in Stage 1 or PV
Linking Material Attributes and Process Parameters to CQA – Developing DS

- Identify potential sources of process variability
- Identify the material attributes and process parameters likely to have the greatest impact on drug substance quality. This can be based on prior knowledge and risk assessment tools
- Design and conduct studies (e.g., mechanistic and/or kinetic evaluations, multivariate design of experiments, simulations, modelling) to identify and confirm the links and relationships of material attributes and process parameters to drug substance CQAs
- Analyze and assess the data to establish appropriate ranges, including establishment of a design space.
Manufacturing Process Development

• Define Quality Target Product Profile (QTPP) and CQA

• Use ICH Q9 to:
  – Assess process design alternatives
  – Assess quality attributes and manufacturing process parameters

• Use knowledge:
  – Prior knowledge
  – Development studies
Approach to Development

• Identify CQAs
• Define an appropriate process to obtain CQAs
• Develop a control strategy to ensure process performance and drug substance quality
• Using prior knowledge, risk assessment and experimentation identify material quality issues affecting CQAs. Identify the functionality relating material quality to CQAs.
• Define Design Space
Approach to Development

- Link CQAs to CPPs (which must be controlled)
- CPPs can be materials or processing parameters.
- Identify relative importance through Risk Assessment
- Use knowledge to develop control strategy to reduce variability
Control Strategy

• Control over materials attributes, in designing the manufacturing process (appropriate processing sequence to do the job), in-process parameters, and final product.

• Ensure product CQAs are always within appropriate limits

• Single point vs. multipoint control of CQAs
ICH 11 and Process Validation

• Data collected in support of PV for Biotech processes, aseptic processes and sterilization steps is included as part of the marketing application.

• The appropriate number of production batches to complete PPQ depends on several factors, including but not limited to:
  – Complexity of process
  – Level of process variability
  – Amount if experimental data or process knowledge available
ICH 11 and Process Validation

• Use continuous process verification in process validation protocols
• Use continuous process verification for manufacturing process changes to continually improve the process through the product life cycle.
• Would be applicable for determining useful life of chromatography columns
ICH 11 and Process Validation

• Use of data from small-scale studies in support of applications and to supplement process validation data in biological processes*.

• Can use small scale studies instead of PV for certain studies* (e.g. viral removal).

• Validation studies must demonstrate ability of the process to remove product related impurities, process related impurities, and potential contaminants including biological ones.

*Must demonstrate small-scale model represents commercial scale
ICH 11 and Process Validation

• Suitability of control strategy should be demonstrated.

• PPQ should be completed and data included in application

• Full scale PPQ should have data derived from the final manufacturing process and site(s) used to produce product
Lifecycle Management

- The quality system should be used throughout the product lifecycle.
- This be accomplished through knowledge management from development through the commercial life of the product.
- Such a lifecycle management promotes continual improvement throughout the lifecycle.
ICH 11 and Life Cycle Management

• Development to continue throughout the life cycle.
• Periodic evaluation of the process performance and the effectiveness of the control strategy.
• Successful process validation and continued improvement of the process requires an effective control strategy.
ICH 11 and Life Cycle Management

• An effective Knowledge Management (KM) strategy is a must for successful compliance. KM to include but not limited to process development, tech transfer, PPQ, change control, etc.

• Knowledge should be shared across sites involved in the manufacture of the product

• Change management should be established a-priori.
ICH 11 and Life Cycle Management

• Use knowledge gained from other products and/or from new innovative technology to:
  – Adjust control strategy to ensure product quality
  – Improve the process performance and the product quality

• Changes to the process must be evaluated from the point of view of their impact on the product quality and possible risk to the patient.
ICH 12

• Titled: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

• Currently concept paper approved and in step 1

• Provides guidance on a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle.
ICH Guidance Progress

Q8 Pharmaceutical Development

Q9 Quality Risk Management

Q10 Pharmaceutical Quality System

Q11 Development and Manufacture of Drug Substance

Q12 Pharmaceutical Lifecycle Management
Summary

• ICH guidance namely ICH Q8, Q9, Q10, and Q11 provide considerable guidance outlining the how-to for process validation.
• ICH Q8 is mostly focused on product development but the concepts in it have been extended to process development (stage 1 in PV) in ICH Q11.
• ICH Q9 discusses quality risk management which is applicable to all three stages of PV.
• ICH Q10 Pharmaceutical Quality System is applicable in all stages of process validation and defines management responsibilities.
Summary

• ICH Q11 ties ICH Q8, Q9, and Q10 together and has specific guidance on how to complete the process qualification exercise.

• The proposed ICH Q12 is meant to complement all four guidance and provide the mechanism for product/process life cycle management.

• ICH Q12 is the next element in the succession of the Guidance issued to date by ICH to ensure compliance with GMP and facilitate Process Validation.