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# Clarifying and Understanding ICH Guidelines

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# Outline

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- ◆ **FDA GMP Initiative**
- ◆ **Recent ICH Quality Guidelines**
- ◆ **ICH Q8**
- ◆ **ICH Q9**
- ◆ **ICH Q10**

# FDA GMP Initiative

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- ◆ “seeks to **integrate quality systems and risk management** approaches into the existing programs and encourages adoption of modern and innovative manufacturing technology.”
- ◆ “intended to enhance the **integration of pre-approval review and cGMP programs** and achieve more consistent application across agency organization components.”
- ◆ “use **existing, and emerging science and analysis** to ensure that limited resources are best targeted to address important quality issues, especially those associated with predictable or identifiable health risks.”

*Lester M. Crawford, FDA Deputy Commissioner, August 21, 2002*



# Proposes Flexible Regulatory Approach

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- ◆ **FDA evaluates category of risk, based on:**
  - Product, process and facility
  - Controls to assess & mitigate risk
  - Quality system implementation
- ◆ **FDA determines 'risk category' and will modify level of oversight accordingly for:**
  - Post-approval change review
  - GMP inspections
- ◆ **This will lead to:**
  - Removal of barriers to continuous improvement
  - Efficient use of resources by industry & regulators

# ICH Quality Vision

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- ◆ Developed in Brussels in July 2003
- ◆ *“A harmonised pharmaceutical quality system applicable throughout the lifecycle of the product, emphasizing an integrated approach to risk management and science.”*
- ◆ Defined in:
  - Quality by Design (Q8)
  - Quality Risk Management (Q9)
  - Quality Systems (Q10)

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# ICH Q8 Pharmaceutical Development

# Other Names

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- ◆ **Quality by Design (QbD)**
- ◆ **CTD-Q Section 3.2.P.2**
- ◆ **P2**
- ◆ **Pharmaceutical developmental report**
- ◆ **Development pharmaceuticals**
- ◆ **Development pharmaceuticals and manufacturing science**

# Structure

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## Two-Part Guideline

### ◆ Part 1

- Core document
- Baseline expectations
- Optional information
- Regulatory Flexibility

# Structure (cont.)

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## ◆ Part 2

- Annexes relating to specific dosage forms
- Appropriate examples of risk management

# Why Is the Guidance Needed?

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- ◆ Approach inconsistent across the three regions
- ◆ Help reviewers gain a better understanding of **key** product and process attributes
- ◆ Help field investigators during the inspection process
- ◆ Increased knowledge of manufacturing science and technology lead to greater regulatory flexibility
- ◆ Guideline describes **what** should be discussed but not **how** to do it

# Philosophy

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- ◆ **Product** quality and performance assured by effective and efficient manufacturing process
- ◆ **Product** attributes based on mechanistic understanding of how formulation and process impact performance
- ◆ Ability to effect Continuous Improvement and continuous real time assurance of quality
- ◆ Regulatory policies recognize level of knowledge and understanding that promotes improvement

# Scope

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- ◆ For contents of Module 3 of CTD-Q (part of M4)
- ◆ Drug substances and products “...as defined in the scope of ICH guidances Q6A New Chemical Entities (NCE) and Q6B Biological/ Biotechnological (Biotech)”
- ◆ ***Does not apply*** to clinical trial material, but “principles ...are important to consider...”

# What is the Goal?

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- ◆ A systematic process of building desirable quality attributes into a “**product**” to assure its performance
- ◆ Design features that deliver with confidence the intended product quality and performance as it relates to the safety and efficacy of drug throughout product life cycle\*

\*Initial development through marketing and product termination

# How to Achieve Goal?

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## Pharmaceutical Development

- ◆ Information on development studies conducted to establish that the dosage form, formulation, manufacturing process and quality attributes are appropriate for the product
- ◆ Information to identify and describe the critical parameters that can influence product quality and performance

# Further Resolution Needed

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- ◆ **Need clarity on definitions of:**
  - **Design Space**
  - **Regulatory Flexibility**
  - **Critical**

# ICH Q8: Opportunity for Change

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DIA Annual Meeting 2005

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# ICH Q9 Quality Risk Management

# Scope

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Provides a framework that **may be applied to all aspects of pharmaceutical quality**, including:

- ◆ Development
- ◆ Manufacturing
- ◆ Distribution
- ◆ Inspection
- ◆ Submission/review processes

# Scope (cont.)

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Throughout the **lifecycle** of:

- ◆ Drug substances and drug products
- ◆ Biological and biotechnological products
- ◆ Use of raw materials, solvents, excipients, packaging and labeling materials

# Principles

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- ◆ The evaluation of the quality risk should ultimately **link** back to the **potential harm** to the patient
- ◆ The **level** of effort, formality and documentation of the quality risk management process should be **commensurate with the level of risk**

# What is Risk Management?

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- ◆ Risk Management is NOT about:
  - making do with insufficient time, money, or people,
  - providing an excuse not to do the right things,
  - deciding what to do based on what might be observed during an inspection.
- ◆ Risk Management does NOT provide an excuse to be out of compliance with applicable regulations.

# What is Risk Management?

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- ◆ **Risk Management IS about:**
  - **Knowing the manufacturing and business processes**
  - **Understanding what's truly important**
  - **Not spending time on a low risk activity**
  - **Focusing resources on the things that are really important**
  - **Focusing our efforts and resources on the things that provide quality assurance to our customers**

# Risk Management Process

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- ◆ Risk assessment
  - Risk identification
  - Risk analysis
  - Risk evaluation
- ◆ Risk control
  - Risk reduction
  - Risk acceptance

# Risk Management Tools

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- ◆ Failure Mode Effects Analysis (FMEA)
- ◆ Failure Mode, Effects and Criticality Analysis (FMECA)
- ◆ Fault Tree Analysis (FTA)
- ◆ Hazard Analysis and Critical Control Points (HACCP)
- ◆ Hazard Operability Analysis (HAZOP)
- ◆ Preliminary Hazard Analysis (PHA)
- ◆ Risk ranking and filtering
- ◆ Supporting statistical tools

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# ICH Q10 Quality Systems

# Objective

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- ◆ To establish a guideline describing the modern quality system needed to establish and maintain a state of control that can ensure the realisation of a quality drug product and facilitate continual improvement over the product life cycle
  - Not a global GMP guideline!
  - Augments existing GMPs with modern quality systems elements

# Scope

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- ◆ Drug substances (small and large molecule)
- ◆ Drug products
- ◆ Throughout the product lifecycle
  - Process development
  - Technology transfer
  - Routine manufacturing

# Background

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- ◆ **Divergent approaches to quality systems across regions**
  - **Suboptimal deployment of resources**
  - **Impact on availability of medicines**
  - **Delays in implementing innovation and continuous improvement**
  - **Delays in new product launches**
  - **Inconsistent approaches to facility inspections**

# Potential Benefits

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- ◆ Harmonize the concept of quality systems between the three regions
- ◆ Encourage improvement of manufacturing processes
- ◆ Demonstrate industry and regulatory commitment to robust quality systems and technical innovation
- ◆ Facilitate innovation and continuous improvement
- ◆ Provide the quality systems link between development and manufacturing

# Potential Benefits (cont.)

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- ◆ Facilitate management commitment to quality
- ◆ Encourage a science and risk based approach to quality decisions
- ◆ Encourage a preventive action culture
- ◆ Improve quality monitoring and review

# General Principles

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- ◆ Understand and satisfy patient needs
- ◆ Promote a paradigm shift for GMP compliance
- ◆ Embrace both ICH Q8 and Q9 as integral elements of the Pharmaceutical Quality System
- ◆ Promote continual improvement based upon process understanding and risk management

# Quality Improvements

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- ◆ **The biggest opportunities lie in improving the overall system**
- ◆ **Identify and remove barriers**

# Questions or Advice

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