“Design Space and PAT”
- Q8 ICH Draft Guidance on Pharmaceutical Development

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“This initiative is designed to establish product quality regulation founded on sound science and engineering principles for assessing and mitigating risks of poor product and process quality in the context of the intended use of pharmaceutical products.”
What is the ICH Q8 Guidance on Pharmaceutical Development?

- A draft guideline that describes the suggested contents for the 3.2.P.2 Pharmaceutical Development section of a regulatory submission for new drug products in the ICH M4 Common Technical Document (CTD) format.
- Most Recent Q8 Draft is Dated 18 November 2004
- Released for comment November 2004, U.S. comment period ended June 11, 2005
What is the ICH Q8 Guidance?

- Final version of Q8 will be a two part guideline:
  - Q8 Part 1 consists of the Core Document
    - Baseline Expectations, Optional Information, Regulatory Flexibility
  - Q8 Part 2 will contain details and recommended specific points to consider
    - Annexes relating to specific dosage forms
    - Appropriate examples of risk management
- Q8 will not be a “how to” Guidance
- Q8 will provide examples of the “Desired State” of process knowledge and pharmaceutical manufacturing in the 21st Century
What is the ICH Q8 Guidance?

- Q8 will focus on the drug product and the manufacturing process for the drug product
- Q8 will not focus on the API, Facility, Quality Systems
  - Other guidances address these issues ....e.g. Q7A for API
What is the ICH Q8 Guidance?

- Applicable to all drug products
  - minimal and optional information
- Not all development information will be “mandatory”
  - Guideline constructed to avoid potential misunderstandings that may evolve
  - Baseline information requirements will be clear
  - Applicant may choose to do more studies and/or share prior knowledge to justify a more flexible regulatory approaches
What is the ICH Q8 Guidance?

- Guideline describes one system with different levels of design focus
- The “process understanding – predictive ability” principles will be used as a means to create a continuous framework and to avoid “two different systems”
- Means to achieve enhanced knowledge of product performance e.g. by PAT, application of formal experimental design, Design Space, etc...
Why develop the ICH Q8 Guidance?

- Harmonised guidance on development submission content would be very helpful to address regional disharmony
  - US CTD focuses on future regulatory commitments
  - Sponsor generally doesn’t describe how they designed their product
    - Creates a “check-list” submission and review against guidance
    - Current ‘Development Report’ aimed at successful PAI
  - EU CTD has Development Pharmaceutics as a ‘cornerstone’ of submission

- Provide a framework to address the current limited regulatory incentive to truly understand our processes and products, and optimise them
There is a high level of uncertainty regarding pharmaceutical products and their manufacturing processes.
A “reactive” drug product development and manufacturing decision system

- Confounding of *Uncertainty, Variability and Risk*
  - Uncertainty = Risk
  - “event trees” not “decision trees”
  - “specifications are procrustean standards”
    - Procrustean - Producing or designed to produce strict conformity by ruthless or arbitrary means.
  - “testing to document quality”
  - “process validation is a well rehearsed demonstration....3 consecutive batches...”

- Multiple CMC review cycles for amendments and new product filings
- Product/process optimization discouraged
- Very low manufacturing efficiency and cGMP problems
The Current State - Drug Product Manufacturing & Regulatory Oversight

- Clearly, all the above contribute to the creation of hurdles for innovation and continuous improvement !!!!
Desired State - Drug Product Manufacturing & Regulatory Oversight

- As adopted by the International Conference on Harmonization (ICH) – Drug Product Manufacturing

  - Product quality and performance are achieved and assured by design of effective and efficient manufacturing processes
  - Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
  - An ability to effect continuous improvement and continuous "real time" assurance of quality
Desired State - Drug Product Manufacturing & Regulatory Oversight

- Regulatory Oversight
  - Regulatory policies and procedures are tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability.
  - Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product.

- Most Importantly - Facilitate risk based regulatory decisions
  - Critical variables – relevant specifications and controls that are designed to mitigate risk to patients (intended use of a product).
Key Definitions

- **Process Analytical Technology (PAT)**
  - A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of assuring final product quality.
Key Definitions

- **Design Space**
  - The design space is the established range of process parameters and formulation attributes that have been demonstrated to provide assurance of quality.
  - It forms the linkage between development and manufacturing design.

- Here is my science, here is my manufacturing scheme which was developed through my science, here is how they link together.....

- The concepts of design space and PAT are inherently & fundamentally linked!
An Illustration of Design Space...
**ICH Q8 Guidance - Vision**

- Marketing Application - Pharmaceutical Development Section (ICH Q8 Section 1, Introduction)
  - Appropriate place for companies to present the knowledge gained through the application of scientific approaches and risk management to the development of a product and its manufacturing process
  - This data can (and should) be updated to share knowledge gained over the life time of a product
  - Goal for reviewers and inspectors – Provide a more comprehensive understanding of the product and its manufacturing process.
ICH Q8 Guidance - Vision

 Establishment of Design Space (Section 2) through product and process design

  - Making changes to the formulation and manufacturing process during development generates valuable data that supports establishment of the design space.
    - It is implied that both positive and negative results are important to understanding the design space.
Establishment of Design Space (Section 2) through product and process design

- Minimum requirements are to provide data to support the proposed formulation and manufacturing process
  - Reports should identify properties of the active ingredient, excipients and manufacturing process that are critical and that present significant risk to product quality and therefore should be monitored or otherwise controlled.
**ICH Q8 Guidance - Vision**

- Applicants can choose to perform additional development studies that enhance knowledge of product performance over a wider range of attributes, processing options and process parameters.
  - Sharing such information with the regulatory bodies in the development report provides an opportunity to demonstrate an higher degree of understanding of manufacturing processes and process controls.
  - This effectively establishes the design space.
ICH Q8 Guidance - Vision

- This sharing of knowledge of the design space with the regulatory bodies will open the door to:
  - True risk based reviews and inspections
  - Manufacturing process improvements within the approved design space without further regulatory oversight
  - Real time quality control leading to a reduction in end product release testing.
Design Space and PAT

• Regulatory and Business Advantages of using PAT and Design Space
  • Working within the design space is not generally considered as a change of the approved ranges for process parameters and product attributes.
    – Result will clearly be less supplemental regulatory filings.
    – Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.
Regulatory and Business Advantages of using PAT and Design Space

- Will de-emphasize end product testing and may eliminate certain release tests.
  - Process knowledge can eliminate redundant testing for those attributes that are demonstrated to be controlled in-process
- Diminish the burden for validating systems by providing more options for justifying and qualifying systems intended to control critical attributes of materials and processes
Design Space and PAT

- Regulatory and Business Advantages of using PAT and Design Space
  - Can the Design Space concept be applied to currently approved products?
    - YES!!!....Data can be generated and submitted post approval
Design Space and PAT

FDA Acknowledged Challenges and Barriers to Implementation of Design Space and PAT

- Regulatory system emphasizes empirical quality standards vs. science-based standards
- Fear of punishment resulting from sharing of full spectrum of knowledge and data generated to implement the concepts
- Industry is well experienced in the "current state" of design and needs better guidance on risk management and quality systems

Industry Challenges

- Potentially higher upfront costs and expanded development timelines
**Design Space and PAT**

- Are the concepts being implemented at FDA?..Yes!

  - Reference.....Compliance Policy Guide 7132c.08 on Process Validation
    - Revised in 2004 and now includes the following caveat regarding the manufacture of conformance lots prior to approval:
      - Use of advanced pharmaceutical science and engineering principles and control technologies can provide a high assurance of quality by continually monitoring, evaluating and adjusting every batch using validated in-process measurements, tests, controls and process endpoints.
      - For manufacturing processes developed and controlled in such a manner, it may not be necessary for a firm to manufacture multiple conformance batches (validation batches) prior to initial distribution.
Design Space and PAT

Some Points of Caution

- PAT and Design Space cannot be implemented without the prerequisite scientific understanding of the manufacturing process.
- The transfer of laboratory methods to on-line methods does not necessarily represent the attainment of PAT.
References


Q8 ICH Draft Guidance on Pharmaceutical Development, Ver 4.3, November 18, 2004

Design Space and PAT

Thank you...Any Questions?

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