



Quality by Design (QbD) for Orally Inhaled and Nasal Drug Products (OINDPs)

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IPAC-RS 2006 Conference
Inhalation and Nasal Drugs: The Regulatory Landscape

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Acknowledgements

- n Chi-Wan Chen
- n Christine Moore
- n Moheb Nasr
- n Prasad Peri
- n Guirag Poochikian

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Outline

- n General QbD Principles
 - n What is QbD?
 - n Why use QbD for OINDPs?
- n QbD Applied to OINDPs
 - n Product Design
 - n Formulation Design
 - n Container Closure System Design
 - n Process Design (micronization example)
 - n Design and Setting Specifications in the Future
 - n Agency Expectations
- n A blinded Case Study Where QbD Could have Helped

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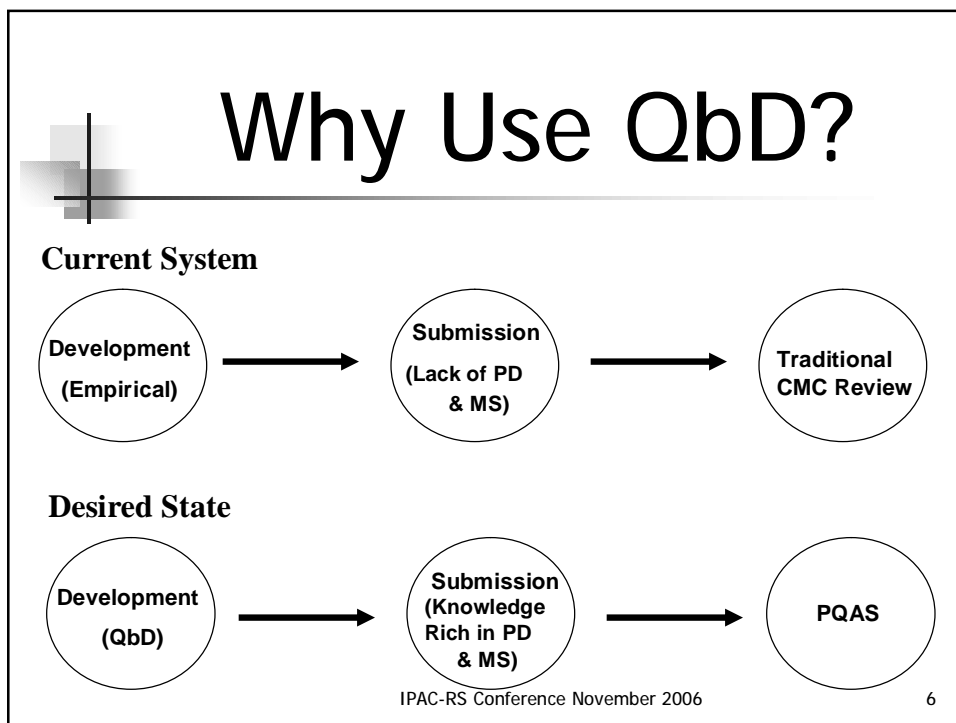
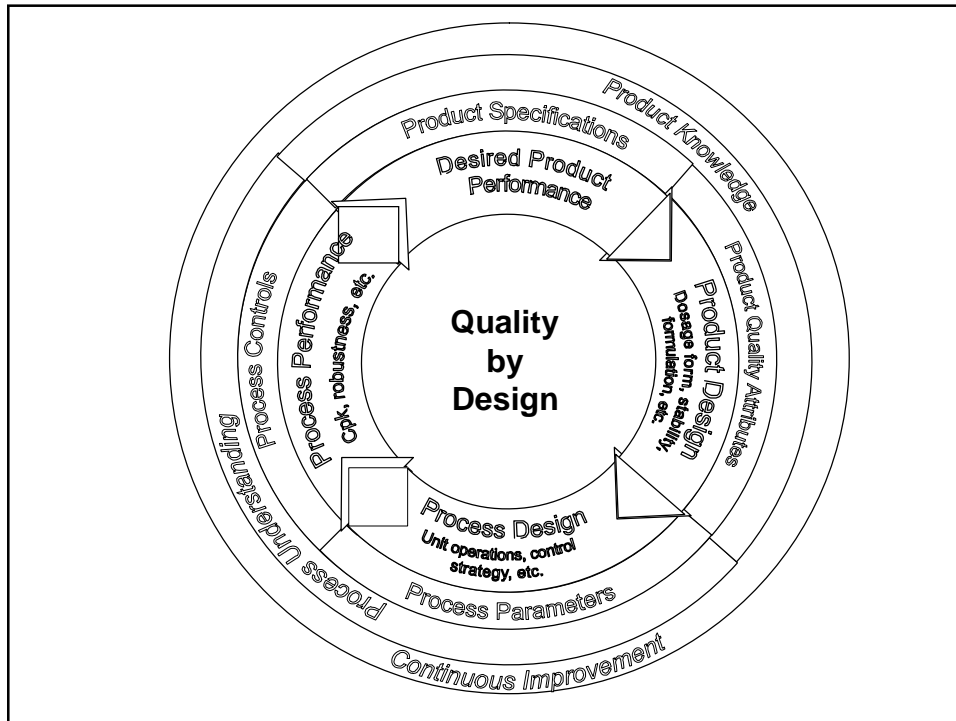


What is Quality by Design (QbD)?

- n **In a Quality-by-Design system:**
 - n The product is designed to meet patient needs and performance requirements
 - n The process is designed to consistently meet product critical quality attributes
 - n The impact of materials and process parameters on product quality is understood
 - n The process is evaluated and updated to allow for consistent quality over time
 - n Critical sources of process variability are identified and controlled
 - n Appropriate control strategies are developed

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Why Use QbD for OINDPs?

- n Critical quality attributes (COAs) for materials, products, and processes parameters (CPPs) are better understood (knowledge is power)
- n Controls are rationally designed to fit end use performance criteria in light of COAs and CPPs
- n The entire manufacturing system is more flexible; accounting for and responding to variability in materials, environment, and process, within a known design space.
- n More flexible regulatory framework which relies on the demonstration and use of knowledge
- n May reduce overall development time (time to approval + launch)
- n May reduce product failures after approval associated with variability in ingredients and process that would not otherwise have been considered.

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Dosage Form and Manufacturing Process Development

- n Start product design in early phases of development
 - n This may be an iterative/continuous process
- n Base critical quality attributes on desired/targeted product performance requirements
- n QbD is thorough understanding of product and process and implementation of that understanding
 - n QbD is more than traditional process and formulation optimization
 - n QbD is more than justification of COAs and CPPs

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Product Design

- n Utilize early phase data such as
 - n Optimum dose or dose range
 - n Therapeutic index
 - n PK / PD profile
 - n Site of activity (local) / absorption (systemic)
 - n If local; rescue versus chronic
 - n Physicochemical properties
 - n Prior knowledge
- n To define desired product characteristics and performance such as
 - n Delivered dose uniformity (DDU)
 - n Particle size distribution (PSD)

Formulation/Product Design

- n Drug Substance (DS)
 - n Identify Critical Quality attributes (CQAs) such as moisture content, polymorph form, surface morphology, PSD which affect downstream drug product performance of DDU, APSD, etc.
- n Delivery Platform
 - n MDI, DPI, Nasal Spray, Soln for Inhalation, etc.
- n Formulation/device subtype
 - n E.g., suspension versus solution MDI
 - n E.g., device metered versus pre-metered DPI
- n Limited excipient choices in all cases



Identify CQAs of Excipients

- n Propellant(s)
- n Ethanol
 - n Water content
 - n Impurities
- n Surfactants
 - n Surface active impurities
- n Lactose
 - n Hydrate form
 - n Surface morphology
 - n Water content
 - n PSD
- n Water, buffers, salts, preservatives, etc.



Formulation Development

- n DS and Excipients
 - n Selection of excipients based on compatibility and performance requirements
 - n Chemical and physical properties influence downstream process parameters and product performance
 - n Need to understand the impact of excipient and DS ***variability*** in order to adjust in-process and/or set appropriate controls. This is essential in QbD.



Container Closure System (CCS)

- n OINDPs are distinguished from other dosage forms by their incorporation of device components as part of the drug delivery system as an integral part of the drug product.
- n CCS design has always been critical for OINDPs
- n The degree of knowledge sharing between the NDA applicant and the CCS designer manufacturer correlates with success.



CCS Performance Goals

- n The following are desired throughout shelf life and for the life of each individual unit
 - n Reliable as well as accurate metering and delivery
 - n Stable and consistent
 - n Inert
 - n Mechanically robust
 - n User friendly yet child resistant
 - n Protection of the formulation
- n Manufacturable



CCS Development in QbD

- n Gather knowledge early with your CCS supplier(s)
- n Understand and agree to the design basis for every material used in the CCS for your OINDP. This includes:
 - n Metals
 - n Plastics
 - n Elastomers
 - n Fabrication methodology for each component
 - n Additives in plastics and elastomers
 - n Processing aids used in forming, cleaning, and assembly

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CCS Development in QbD

- n Understand sources of variability for each material, component, and processing used in the CCS for your drug product.
- n Evaluate the impact of this variability on CCS performance as it pertains to your drug product.
 - n Rational Design of Experiments (DOE)
 - n Determine who will do them (NDA applicant or supplier)
- n Work with your supplier(s) to ensure appropriate in-process controls for your CCS components
- n Collaboration with your CCS supplier(s) works to maximize the chances for success as part of a rational risk assessment program.

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Manufacturing Process Understanding

- n For each unit operation
 - n Understand how process parameters affect CQAs
 - n Conduct risk analysis/assessment to:
 - n Identify critical process parameters and materials attributes
 - n Develop risk mitigation strategies
 - n Establish appropriate control strategy to minimize effects of variability on CQAs
 - n Evaluate risk in terms of severity, likelihood and detectability

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Manufacturing Process Understanding

- n As an example, consider DS micronization
 - n Current recipe approach
 - n Fixed equipment, almost any change requires Agency approval
 - n Time, temp, humidity set at predefined ranges
 - n This approach is controlled but not robust
 - n Scales up and/or transfers poorly
 - n No response to input variability of non-micronized DS
 - n Tight controls over incoming non-micronized DS are usually necessary
 - n Problematic with planned site, equipment, and scale, changes
 - n Sensitive to variability without being responsive to it
 - n Data laden, but knowledge poor system

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Manufacturing Process Understanding

- n Alternatively, for a QbD approach
 - n Equipment is linked to principles of operation
 - n Time, temp, humidity effects are studied, known, and controlled as necessary within appropriate limits
 - n A QbD approach controls the DS to desired endpoints (PSD, polymorph limits, surface morphology, etc.) and is more robust
 - n Scales up and/or transfers to desired endpoints
 - n Responsive to input variability of non-micronized DS
 - n Tight controls over incoming non-micronized DS may NOT be necessary
 - n Less problematic with site, equipment, and scale changes
 - n Less sensitive to variability by being responsive to it
 - n Knowledge rich, more predictable system

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Dosage Form and Manufacturing Process Development– Design Space

- n ICH Q8 Definition
 - n The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality
 - n Design space is proposed by the applicant and is subject to regulatory assessment and approval
- n Concept applicable to new and legacy drug products
 - n Manufacturing experience and product knowledge

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Dosage Form and Manufacturing Process Development– Design Space

For example, this would include any necessary limits as follows:

- n Non-micronized DS
 - n PSD, morphology
 - n Other processing/equipment parameters which are critical to ensure the quality of the output micronized DS based on non-micronized DS inputs
- n Micronized DS
 - n PSD
 - n Polymorph
 - n Surface morphology



Designing/Setting Specifications in the Future

- n Relate specifications to critical quality attributes
 - n Provide scientific rationale to justify proposed acceptance criteria

FDA's Expectations

- n The current system is adequate for regulatory submission
 - n Quality is assured by testing and inspection
 - n Considerable regulatory oversight
 - n Substantial efforts and considerable waste
- n However, QbD is the desired approach
 - n QbD principles should result in a higher level of assurance of product quality
 - n Additional product and process understanding could lead to regulatory flexibility
- n Focus remains on availability of safe, effective and high quality pharmaceuticals

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Case Study Introduction

- n There are no examples of QbD submissions for OINDPs at this time
- n What follows is one retrospective analysis where a QbD approach may help to
 - n Reduce time to initial NDA approval
 - n Mitigate failures in response to
 - n Normal (i.e., expected or predictable) material and/or process variability
 - n planned changes such as site, equipment, etc.
 - n Unplanned changes in material, process, or beyond historically normal or expected variability

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Case Study: Metastable Reversion of Micronized DS Used in an MDI

- n During early development the applicant discovers that there is a drop in drug product fine particle mass (FPM) as collected on stages 3-5 of ACI associated with micronized DS physical instability
 - n 20% drop over several weeks at 40C / 75%RH
 - n Same drop over several months at 25C / 60%RH
 - n This initial trend is problematic. In both cases above, there is very little drop in FPM afterwards.

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Case Study Initial Approach

- n The firm is considering to address the problem for subsequent studies by storing the finished MDI for several weeks at 40C ambient RH before release testing
- n Is the proposed conditioning operation the only solution to the problem?
- n Is the conditioning operation robust?
- n How could have a QbD approach prevented this problem?
- n How could a QbD approach provide more robust solutions to the problem now?

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Case Study Issues

- n Many uncertainties persist
 - n Reliability and predictability are unknown
 - n Gaps in knowledge are not filled in
 - n The material attributes and/or process parameters that cause (or mitigate) the FPM reduction have not been elucidated
 - n The role of moisture the FPM drop is unclear
 - n The role of moisture on the observed process of FPM reduction in the canister was not clarified
 - n Other changes that several weeks at 40C may induce in the CCS and formulation are not yet known
 - n Valve function changes in response to elastomer aging
 - n Leachables may increase in response to the proposed operation

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Designing a Robust Process

		PROCESS UNDERSTANDING	
		Low	High
PROCESS CONTROL	Low	High potential for failures.	Problems detected through product testing, inspection, or in-use.
	High	Recipe type process with narrow operating and material ranges.	Robust & reproducible process.

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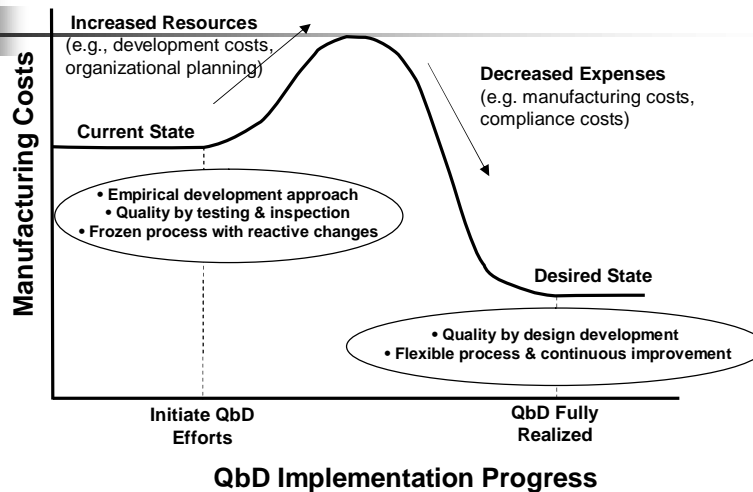
Case Study Resolution

- n Conduct lab scale studies
- n DOE
- n Possible results
 - n The proposed operation may be supported by thorough knowledge
 - n The need for (and effects of) several weeks of "hot storage" may be eliminated
 - n Control of material COAs (e.g., water content, feed PSD, etc.)
 - n Control of micronization CPPs

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Cost and Benefit of QbD



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Thank you.

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