

Quality by Design for OINDP

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Evolving Regulatory Environment

- FDA Critical Path Initiative
 - cGMPs for the 21st Century
 - PAT Guidance
 - Pharmaceutical Quality Assessment System
- ICH Quality
 - ICH Q8: Pharmaceutical Development
 - ICH Q9: Quality Risk Management
 - ICH Q10: Quality Management Systems

Why is FDA driving industry to re-evaluate the CMC development and control strategy for pharmaceutical products?

What will this mean for OINDP?

QbD, PAT, CQA, so many acronyms!!! What do they all mean?

How will NDAs change in the future?

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cGMPs for the 21st Century

- Outlines a quality systems approach
- Emphasizes quality by design (QbD)
- Encourages development of innovative manufacturing technologies, including PAT
- Reinforces science & risk-based principles

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Quality by Design

- The product is designed to meet patient needs and performance requirements
- The product is designed to consistently meet product critical quality attributes
- The impact of starting raw materials and process parameters on product quality is understood
- The process is evaluated and updated allow for consistent quality over time
- Critical sources of process variability are identified and controlled
 - Appropriate control strategies are developed

Moheb Nasr (2006)

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Key Elements of QbD

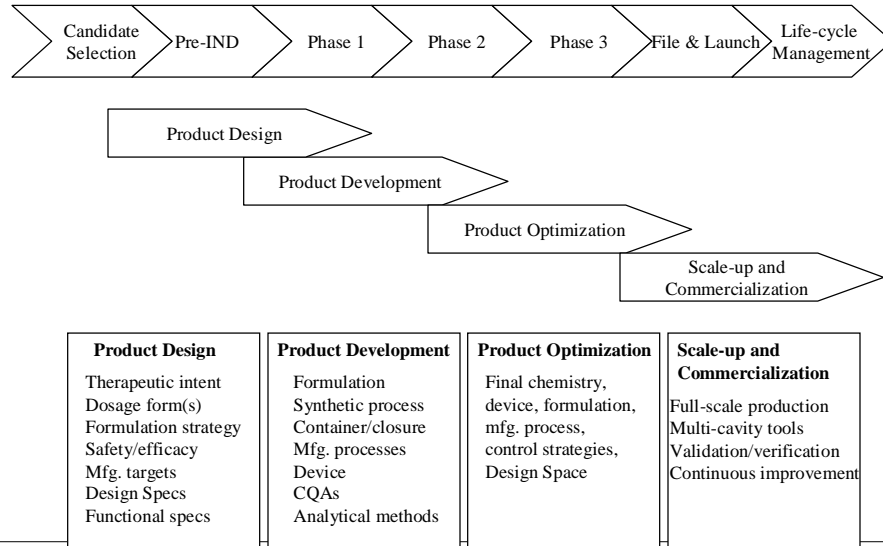
- Patient focused systematic development
- Process Analytical Technology (PAT)
- Risk Management/Structured Methodologies
- Open and frequent communication
- Knowledge-rich submissions

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Patient Focused Systematic Development



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Process Analytical Technology (PAT)

- System for designing, analyzing, and controlling manufacturing through
- Timely measurement of critical quality and performance attributes of
- Raw and in-process materials and processes
- With a goal of ensuring final product quality

FDA PAT Guidance (2004)

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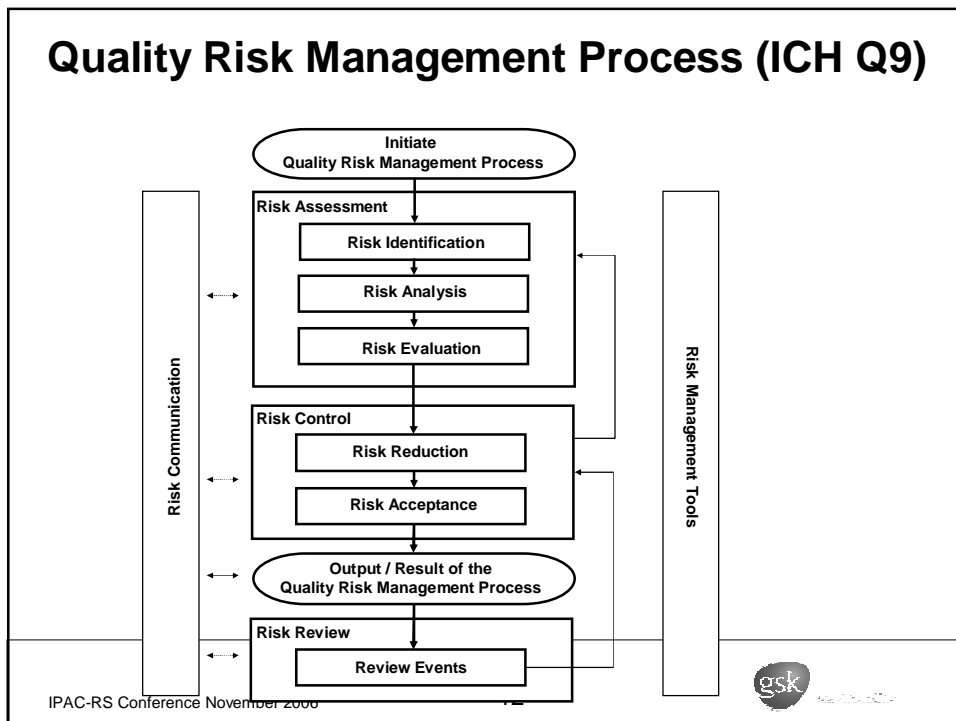
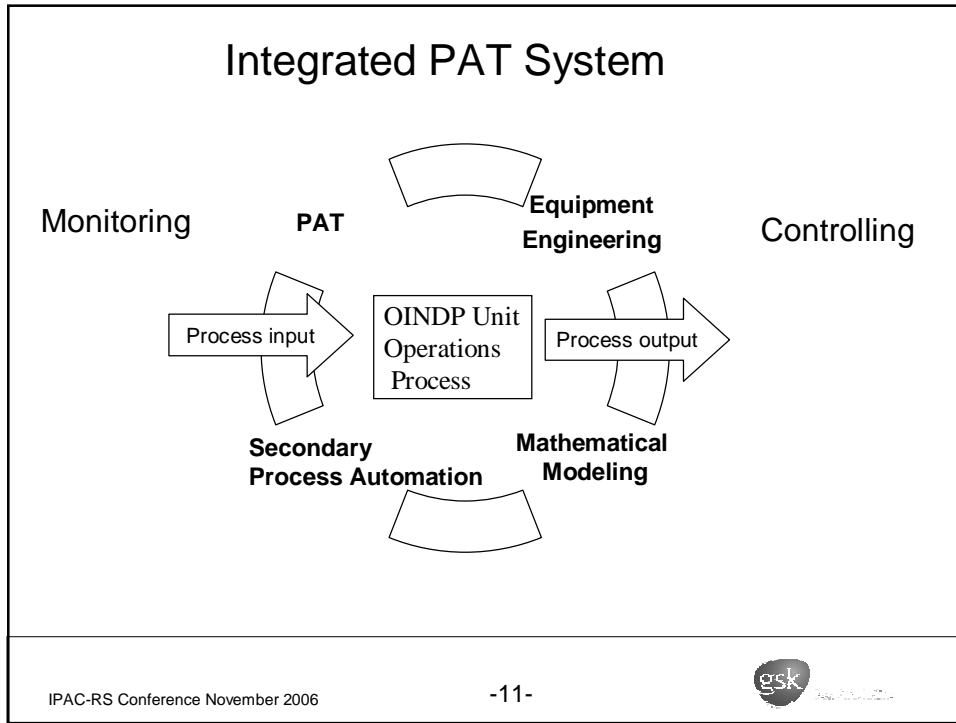


Process Understanding

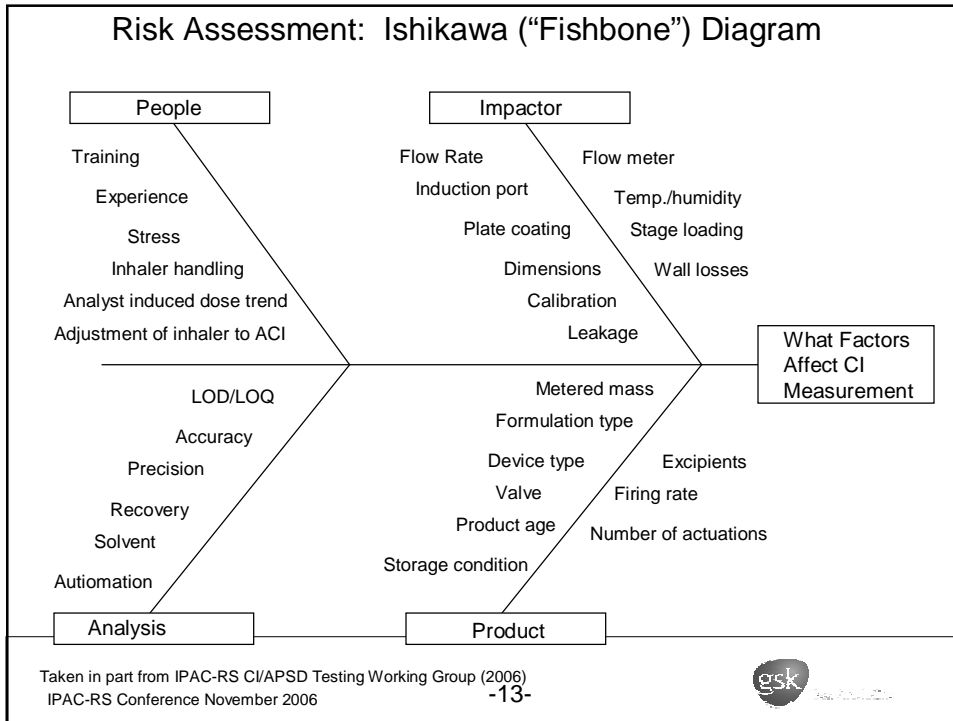
- Critical sources of variability identified and explained
- Variability is managed by the process
- Product quality attributes can be accurately predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions.

Purpose of PAT

- Increase process understanding
- Identify and control critical process parameters
- Facilitate introduction of new mfg. technologies
- Increase efficiency of processes
- Enhance product quality

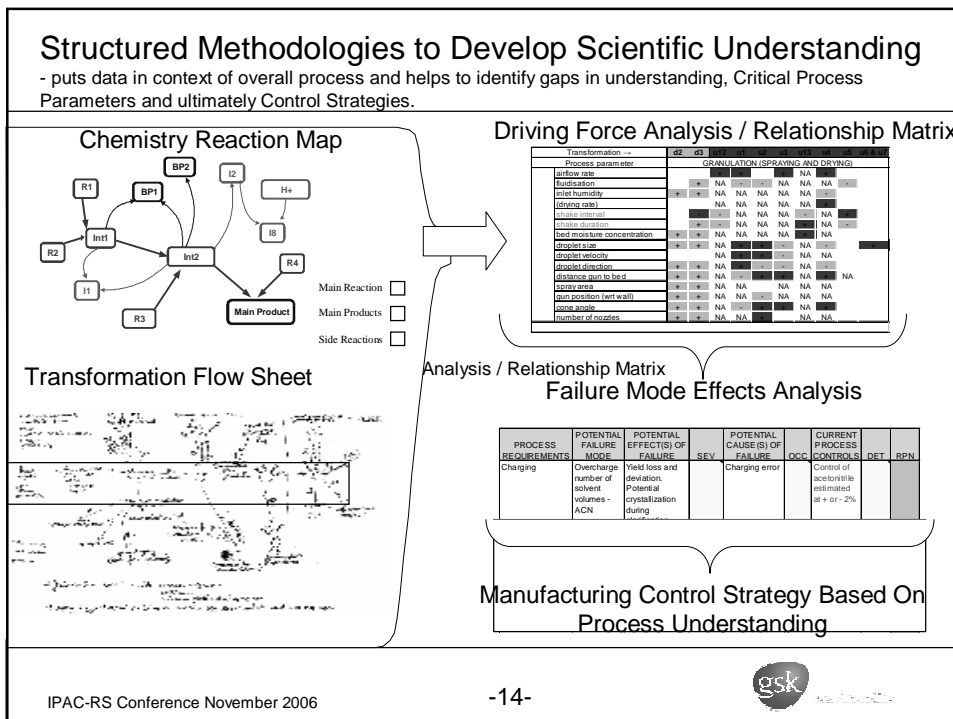


Risk Assessment: Ishikawa ("Fishbone") Diagram

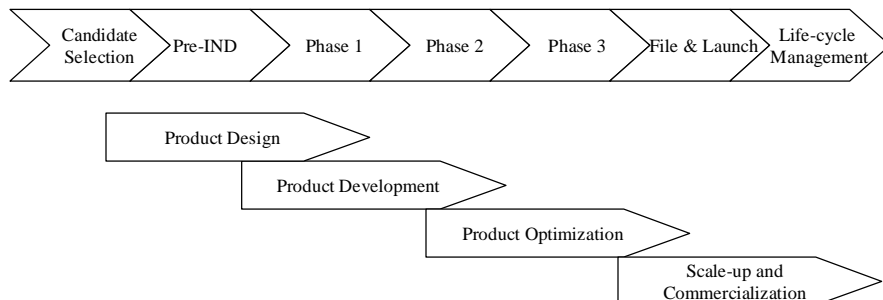


Structured Methodologies to Develop Scientific Understanding

- puts data in context of overall process and helps to identify gaps in understanding, Critical Process Parameters and ultimately Control Strategies.



Patient Focused Systematic Development



Product Design	Product Development	Product Optimization	Scale-up and Commercialization
Therapeutic intent Dosage form(s) Formulation strategy Safety/efficacy Mfg. targets Design Specs Functional specs	Formulation Synthetic process Container/closure Mfg. processes Device CQAs Analytical methods	Final chemistry, device, formulation, mfg. process, control strategies, Design Space	Full-scale production Multi-cavity tools Validation/verification Continuous improvement



Product Design: Design and Functional Specs

Design Specs

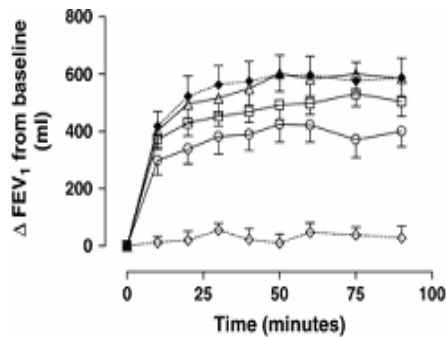
- β agonist
- MDI
- Contains 1 month supply
- Dose counter
- Reliable
- Minimal L&E
- Robust mfg. process
- Partial real-time release
- Etc.

Functional Specs

- Δ FEV1 > 400mL
- Dose on target (LC \pm 3%)
- Dose uniformity (<4% RSD)
- APSD ~ 6 μ m
- Leachables < X μ g
- Content uniformity (<1% RSD)
- PAT control of content
- 6 σ process
- Etc.



Product Design: Therapeutic Intent vs. Particle Size



Change in FEV1 response vs time profiles

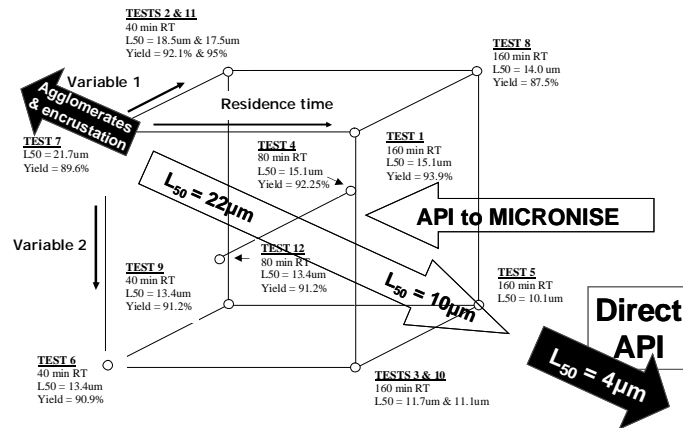
Placebo (*dashed line, open diamonds*) and albuterol metered-dose inhaler 200 µg (*dotted line, closed diamonds*) are shown on both graphs. Monodisperse albuterol aerosols are shown as follows: 1.5 µm (*circles*), 3 µm (*squares*), and 6 µm (*triangles*) at a 15-µg dose (*open symbols*). Data are presented as means (of 12 patients) of the maximal change in each patient's individual FEV1 response (from baseline value)

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Product Development: Understanding API Crystallization



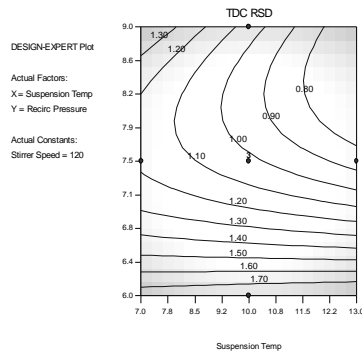
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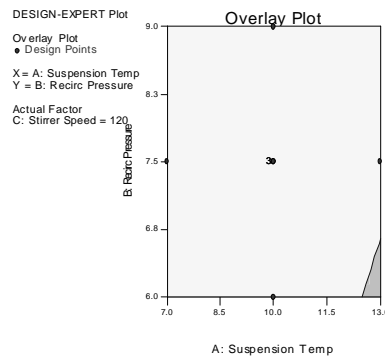


Product Optimization: Manufacturing Process

Robustness Map



Process Map

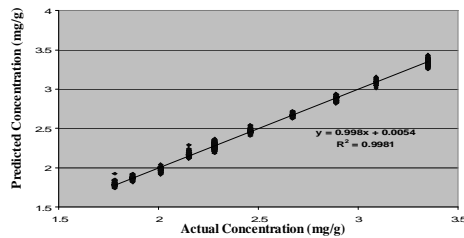


More curvature seen at higher pressures

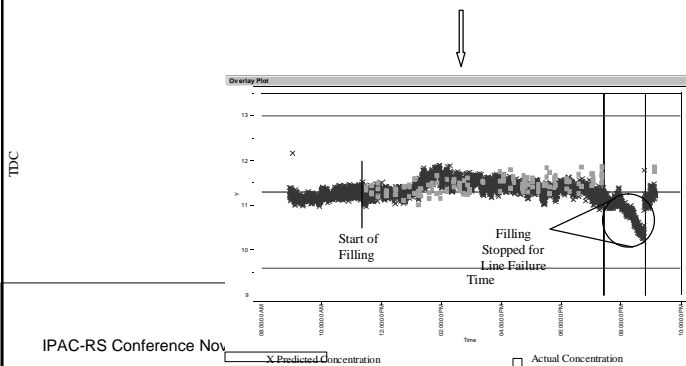
High temperature, low pressure region produces product outside of desirable range



Commercialization: Process Measurement Technologies Suspension Concentration Monitoring



PLS Prediction Model



Full Batch Prediction



Open and Frequent Communication

- Ongoing dialogue throughout development and during review
- Focus on product and process understanding, risk, and control strategies
- Consider “PAI style” scientific review meetings at various points during development, review, and product lifecycle
- Sets the stage for submission content and review
- Positive correlation between frequency and quality of interaction and 1st action approvals¹

1 Independent Evaluation of FDA's First Cycle Review Performance – Retrospective Analysis Final Report
Prepared by Booz Allen Hamilton Inc. (January 2006)

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Knowledge-Rich Submissions

- High-level summary of process and product understanding, risks, and control strategies (e.g., comprehensive QOS)
- Detailed development report (including DoE's, FMEA's, predictive modelling, etc) to underpin the high-level summary (e.g., Pharmaceutical Development)
- Clearly written, complete, and easy to understand and review
- Graphical summaries instead of “data dumps”, even for stability
- Design space & control strategy definition
- Regulatory Agreement to facilitate change control and continuous improvement

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Benefits to QbD – “Regulatory Flexibility”

- “Fit for purpose” specifications & control strategies
- Opportunities for real-time release
- Use of Design Space for manufacturing and testing flexibility
- Use of “process signatures” to qualify post-approval expansion of Design Space
- Reduction in supplements

What Does QbD Mean for OINDP?

- Improved product understanding
- Improved process control
- More predictable quality
- Increased efficiency of development, approval, and lifecycle management

Regulatory Implications

- Less emphasis on end-product testing
- Fewer “standard” specifications
- More flexible control strategies
- Faster more predictable approvals
- Post-approval flexibility with facile continuous improvement
- Fewer compliance issues

Regulatory Uncertainties

- PQAS is new and many reviewers reassigned
- FDA still recruiting staff with required expertise
- Time required for training, alignment, & organizational learning
- Resources & guidance limited
- Potential for more questions with more information
- Differences in regional expectations

Conclusion

- QbD is a work in progress for industry and regulators
- Important to engage and participate in the evolution of QbD
- Transition from prescriptive guidance to conceptual guidance is beneficial for OINDP
- A QbD approach for OINDP will provide significant benefits to industry and regulators

Acknowledgements

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