

# Introduction to QbD and a Review of Current Regulatory & Industry Activities

*Andy Rignall, AstraZeneca*



IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

## Content

- An introduction to Quality by Design (QbD)
  - Foundations
  - Current Industry & Agency Activities
  - Key tools
  - Comparing the traditional and QbD approach
- Applying QbD concepts to Orally Inhaled or Nasal Drug Products (OINDPs), with focus on the the supplier/manufacturer interface
- Summary

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

## What is QbD - Foundations

- FDA Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21<sup>st</sup> Century (2002)
- ICH Quality Guidance Q8, Q9 and Q10
- PAT – Guidance for Industry
- Pharmaceutical Quality Assessment System

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight” Janet Woodcock 2005

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

## What is Quality by Design?

- A scientific, risk based, holistic and proactive approach to pharmaceutical development (Prasad Peri, RDD Europe 2007)
- 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 materials and process parameters on product quality is understood
- The process is evaluated and updated to allow for consistent quality over time
- Critical sources of process variability are identified and controlled
  - Appropriate control strategies are developed (Moheb Nasr, 2006)

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

## The QbD Submission

- Active ongoing dialogue with the regulatory agency during development with emphasis on science
- Highlight product and process understanding, risk and control strategy
  - A **quality overall summary** (QOS) containing the accumulated understanding of product and process, with the identified risks and how they are controlled
  - Detailed **pharmaceutical development** reports with visual representation of information to summarise formulation design space and support product knowledge/understanding
  - **Manufacturing and control** section which defines process design space and control strategy including process analytical technology
  - A **regulatory agreement** which will provide a framework for post approval change control and continuous improvements

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

## Pharmaceutical Development

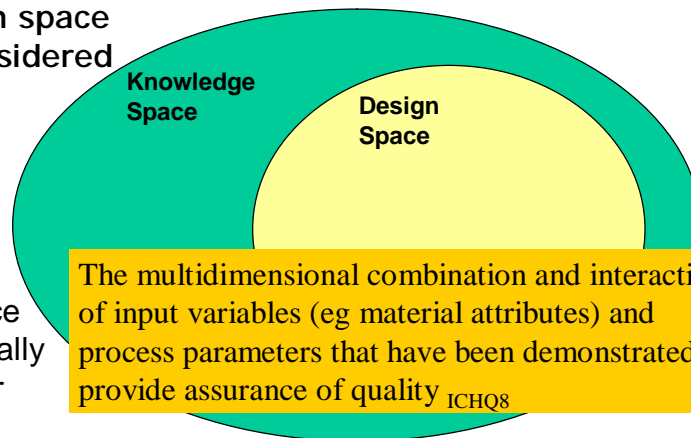
- Comprehensive understanding of the product and manufacturing process
  - How we developed the product and its manufacturing process
  - How we used prior knowledge, good science and risk based approaches to identify critical attributes during the development programme and develop robust strategies to control them (including PAT)
  - Establishment of our product and process design space and control strategy

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

# Design Space



Working within the design space is not considered a change

Working outside the design space would normally require prior approval



IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

## Current Activities (1)

- Numerous public meetings and scientific conferences/workshops to develop the idea's and discuss practical solutions to QbD implementation
-  FDA
  - Establishment and evolution of the Pharmaceutical Quality Assessment system (PQAS) & Manufacturing Sciences branch
  - CMC Pilot programme
-  EMA
  - PAT Team provide focus for assessment of QbD and PAT

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

## Current Activities (2)

- Industry groups and consortia developing the concepts further and working up case studies, with appropriate dialogue with regulatory agencies

– EFPIA PAT Team



– PhRMA working groups



– IPAC-RS & EPAG working groups, focussing on OINDPs



IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

From Moheb Nasr's Presentation at the "FDA Quality Initiatives Workshop" Feb 28, 2007

## QbD System



### Product & process design and development

Define desired product performance upfront; identify product CQAs

Design formulation and process to meet product CQAs

Continually monitor and update process to assure consistent quality

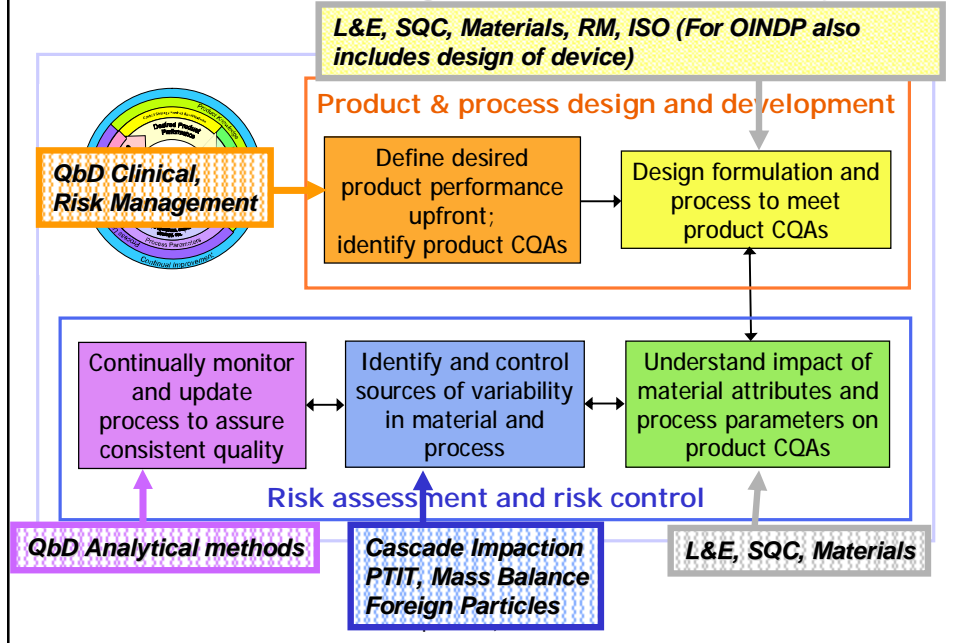
Identify and control sources of variability in material and process

Understand impact of material attributes and process parameters on product CQAs

### Risk assessment and risk control

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

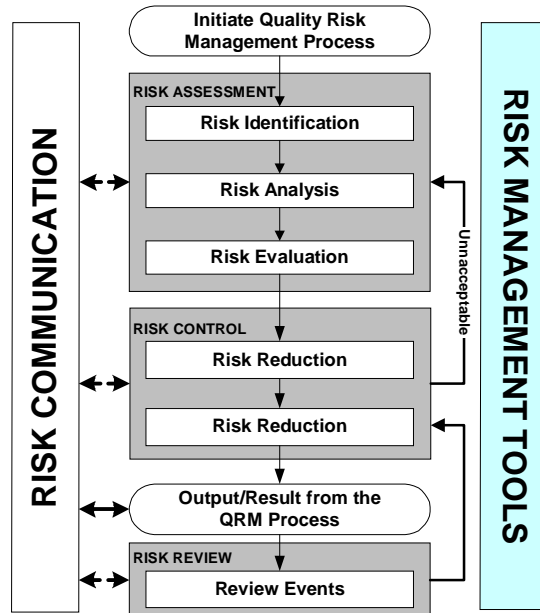
# IPAC-RS Working Groups in QbD System



## Key Tools: Quality Risk Assessment (ICH Q9)

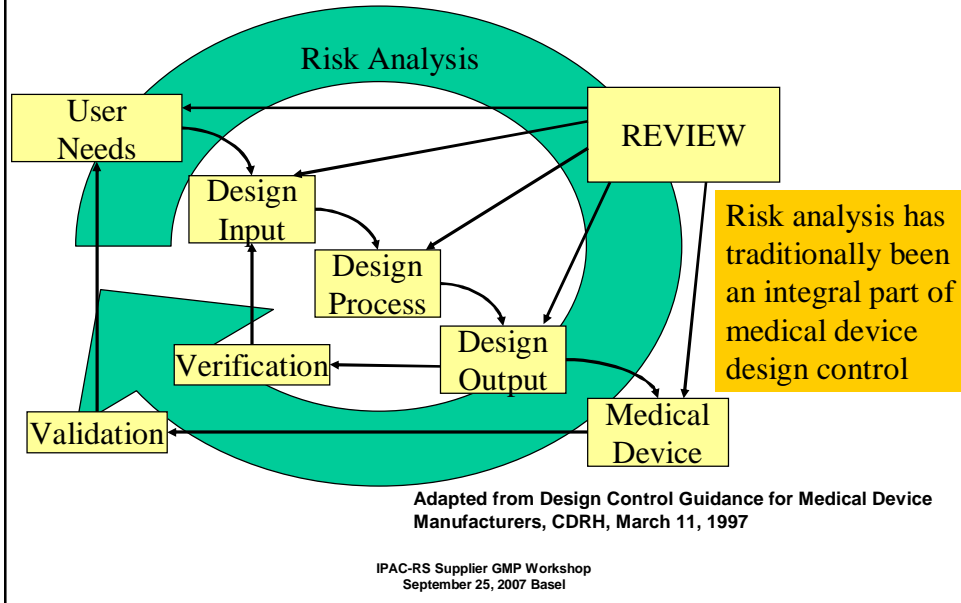
- Failure mode effect analysis
- Fault tree analysis
- Failure mode effects and criticality analysis
- Risk ranking

Potential Component	Potential Failure Mode	Potential Effect of Failure	Severity Class	Potential Causes	Occurrence	Current Controls
			High			
			Medium			
			Low			
			Very Low			

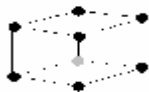


IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

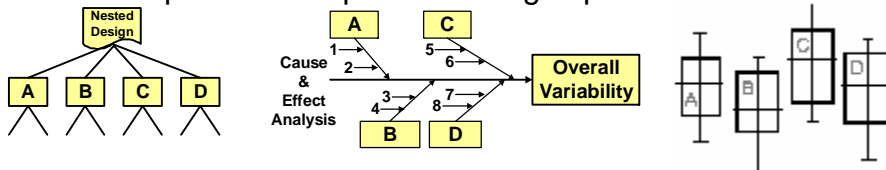
# Key Tools: Design Control



# Key Tools: Multivariate Analysis



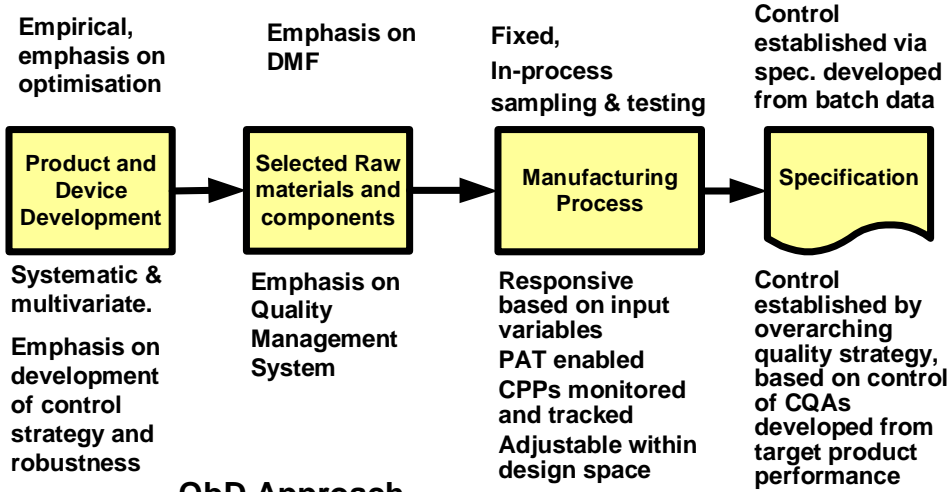
- To identify which excipient, active ingredient, component properties and manufacturing process parameters are critical to the quality of the final product, design of experiments (DoE) approaches will be required.
- Prior knowledge and quality risk management tools (see ICH Q9) will help to highlight the key areas to focus the DoE efforts
  - Cause & effect analysis, FMEA, FMECA, fault tree analysis
- Multivariate analysis may also be used to justify product and process design space



IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

# Traditional vs QbD Approach

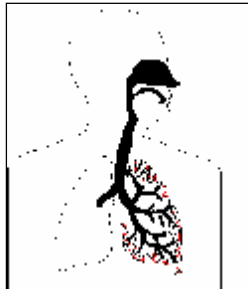
## Traditional Approach



## QbD Approach

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

# Orally Inhaled or Nasal Drug Products (OINDPs)



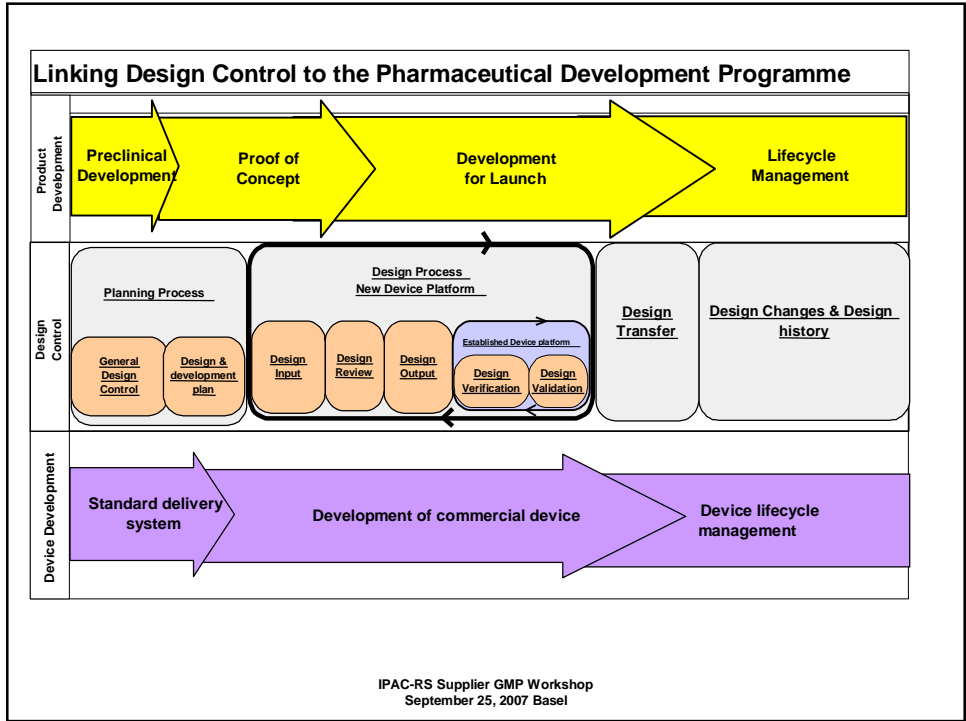
## Design factors

- Systemic vs topical, rescue vs maintenance
- Needs of the patient
- Chemistry, manufacturing & control requirements

## Complexity

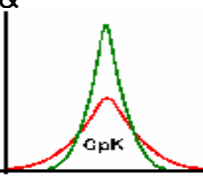

- Drug delivery achieved by a complex interaction between the formulation and the device
- Variability of input materials (excipients & API), device components and manufacturing process will all contribute to overall product variability

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

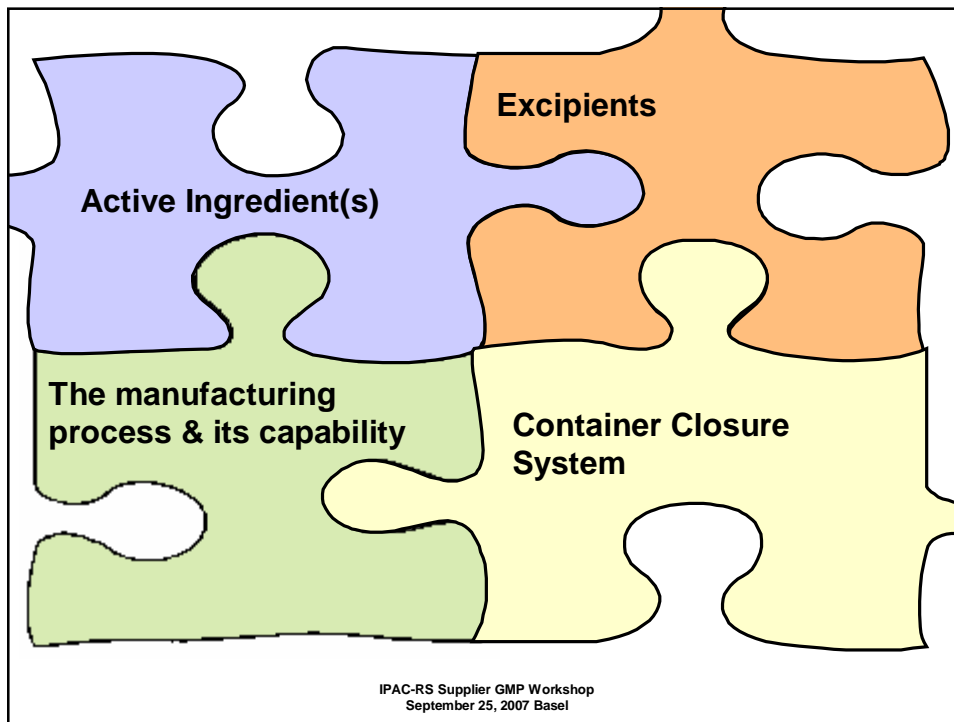


## Defining Product Quality Requirements

- Safe, easy to use & reliable in the patients hands
- Reproducible dose delivery
  - Ø Acceptable delivered dose uniformity and fine particle dose variability
- Chemically, physically & dimensionally stable, mechanically robust
- Acceptable impurity profile (including leachables)
- Capable manufacturing process with suitable control of critical parameters
- Acceptable worldwide

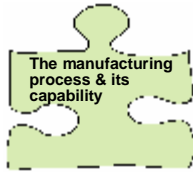
IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel



## Active and Excipients

- Goal is identification and control of critical quality attributes of API and excipients which have been demonstrated to effect product performance and therefore the subsequent safety, efficacy and stability
  - Physical properties: Particle size distribution (PSD), physical form (polymorph, hydration status, morphology) – See ICH Q6A
  - Chemical properties: Impurities, intrinsic stability
  - Compatibility with each other and engineering plastics, elastomers etc.

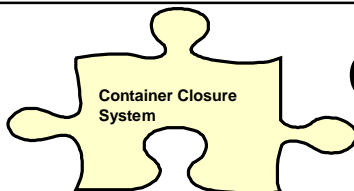
IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel



## Manufacturing process

- Developing an understanding how process parameters effect the product CQAs allows critical process parameters to be identified and control strategies established.
- Design of experiments (DoE) should be employed to explore the impact of critical process parameter changes and any combination/interaction effects.
- The outcome of the designed experiments aid the establishment of design space.
- From a component perspective, fabrication and use of ingoing components at the maximum and minimum of their permitted tolerances may be required.

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel



## Container/Closure System

- Integral part of an OINDP
- Critical factor in appropriate, targeted, delivery of the medicine
- Components often supplied and or assembled by 3<sup>rd</sup> parties
- Opportunity to share knowledge for inclusion in the development pharmaceuticals section of the filing.

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

## The role of OINDP Materials & Components



For OINDPs, the container/closure system features are likely to influence product performance – **Critical Quality Attributes**.

- How can manufacturing companies and component suppliers ensure that the component CQA's are identified and controlled?
- What is the best way to manage change?

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

## Design Dialogue

### OINDP Manufacturer

- Technical needs of the product & process
- Specific formulation attributes relevant to container/closure selection

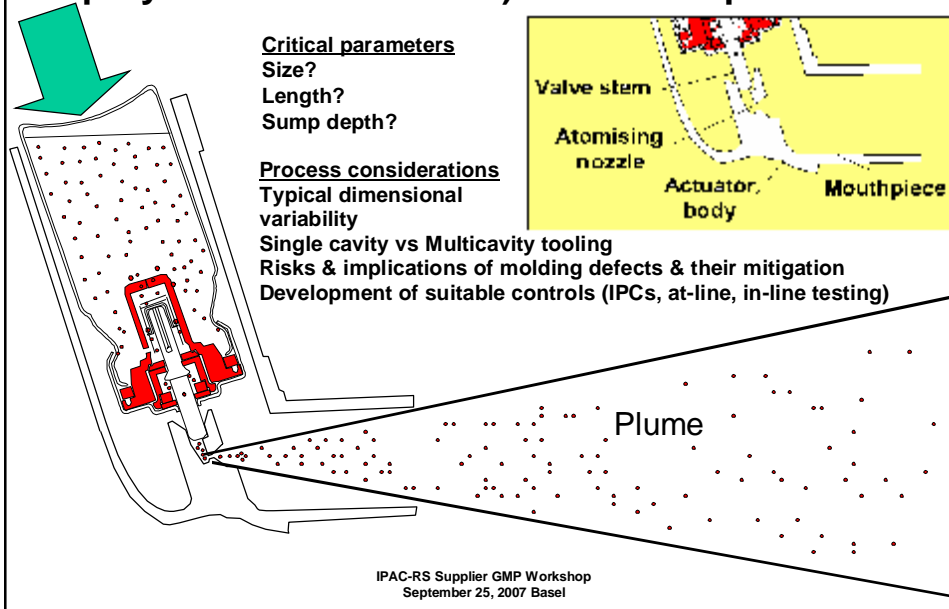
### Component Supplier

- Limits of design choices
- Processes & additives
- Known incompatibilities
- Where possible, an assessment of component variability

- Select high quality materials and components
- Agree control systems & procedures to maintain high quality

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

## Example: Effect of actuator design (particularly spray orifice dimensions) on aerosol plume.



## Specifications

- Specifications are only one part of the overall control strategy
  - Control of ingoing raw materials and components
  - Process analytical testing to monitor and control the critical process parameters
  - Science and risk based selection of specification parameters
  - Statistical approaches to delivered dose specifications such a parametric tolerance interval (PTIT) should be considered
- Ultimate goal is real time release
  - Potentially harder to achieve for OINDPs

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel

# Summary

- Quality by design concepts present opportunities for manufacturing companies and regulatory agencies
  - More regulatory flexibility
  - Shorter regulatory review cycles
  - Patients will see a consistent and high quality product
- A key element is demonstrating that all sources of variability are understood and controlled, hence
  - Good supplier relationships for the manufacture and control of components is completely consistent with the QbD philosophy
  - Manufacturers and suppliers should work together closely to ensure selection of suitable raw materials and components which are well designed and appropriately controlled
- QbD understanding is still evolving, with active industry and agency participation

IPAC-RS Supplier GMP Workshop  
September 25, 2007 Basel