Quality by Design for Orally Inhaled Drug Products

Lawrence X. Yu, Ph.D.
Director for Science
Office of Generic Drugs
Food and Drug Administration

PQRI Workshop on Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products, March 9-11, 2009

Opinions expressed in this presentation are those of the speakers and do not necessarily reflect the views or policies of the FDA

Credits

- Sau Lee, Ph.D.
- Robert Lionberger, Ph.D.
- Wallace Adams, Ph.D.
- Prasad Peri, Ph.D.
- Bing Li, Ph.D.
- Dale Conner, Pharm.D.

What is Pharmaceutical Quality?

- Janet Woodcock
  - Free of contamination and reproducibly delivering the therapeutic benefit promised in the label to the consumer

Pharmaceutical Quality

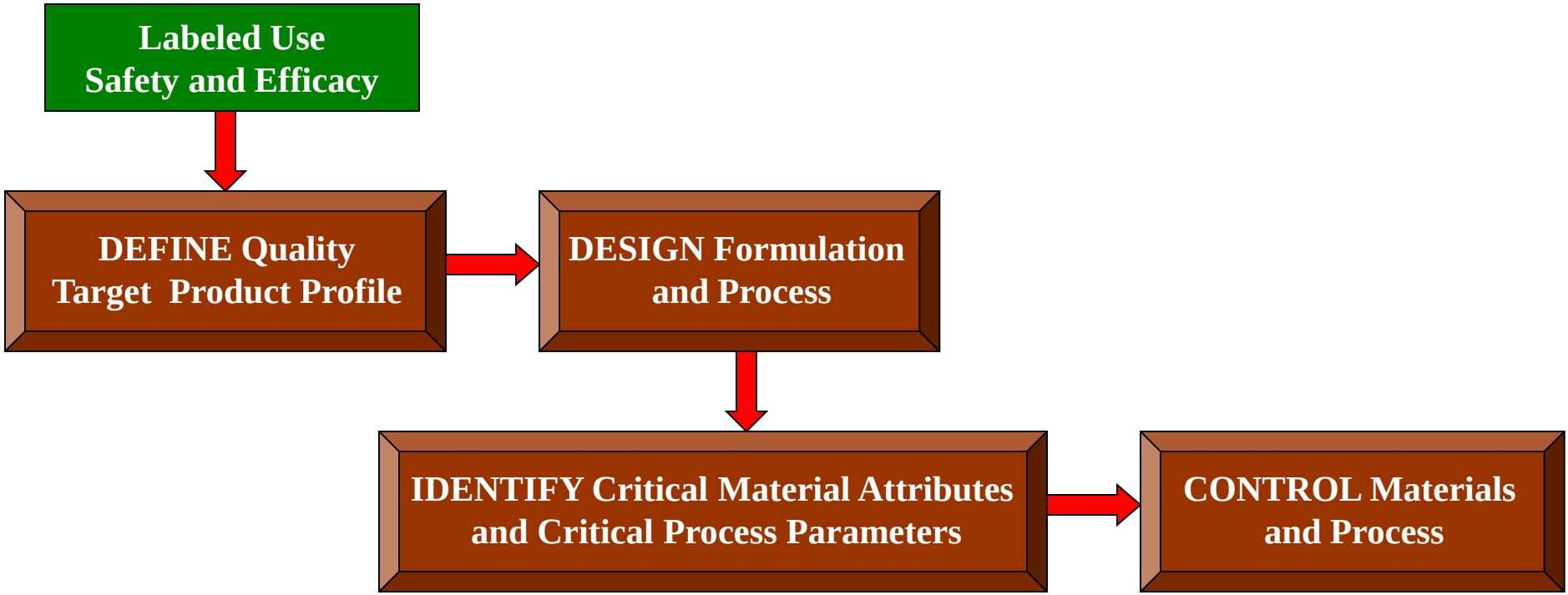
$= f$ (Drug substance, excipients, manufacturing, and packaging)

- Quality cannot be tested into products; quality can only be built into products

What is Quality by Design?

- ICH Q8(R1)
  - The pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management
- Quality by Design Tools
  - Design of experiments (DoE)
  - Risk assessment
  - Process analytical technology (PAT)

What Constitutes QbD?



TARGET → DESIGN → IMPLEMENTATION

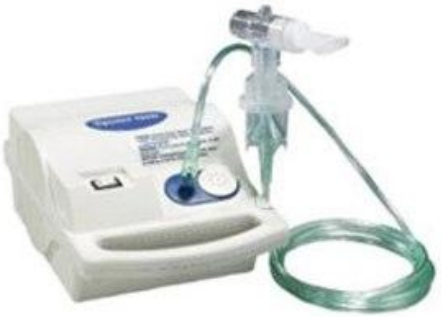
L. Yu. *Pharm. Res.* 25:781-791 (2008)

Orally Inhaled Drug Products

- Propellant driven metered dose inhalers (MDIs)
- Dry powder inhalers (DPIs)
- Nebulizers

MDI

DPI (Advair Diskus)



Nebulizer

Dry Powder Inhalers

- Contain micronized drug attached to larger carrier particles (i.e., lactose) or micronized drug particles agglomerated into soft pellets
- Employ the patient's inspiratory effort to provide energy for drug delivery (passive DPI system)

Pre-metered Single Dose Unit

Handihaler

Pre-metered Multiple Dose Unit

Diskus

Drug Reservoir

Twisthaler

Why is QbD More Significant to Orally Inhaled Drug Products?

- Inhalation manufacturing often exhibits low process capability
- Product is a device in association with a formulation
- Product handling may affect received dose
- Environmental effects may influence product manufacture and use
- Low testing efficiency of aerodynamic particle assessment methods
- Lack of clear in vitro - in vivo correlations

N. Bowles et al. Drug Delivery to the Lungs 18, The Aerosol Society, Edinburgh, UK, 2007:75-78

Quality Target Product Profile

- A prospective summary of the quality characteristics of a drug product that will best ensure the desired safety and efficacy.
- Guide to establish formulation strategy and keep the formulation effort focused and efficient

What Does Quality Target Product Profile Include?

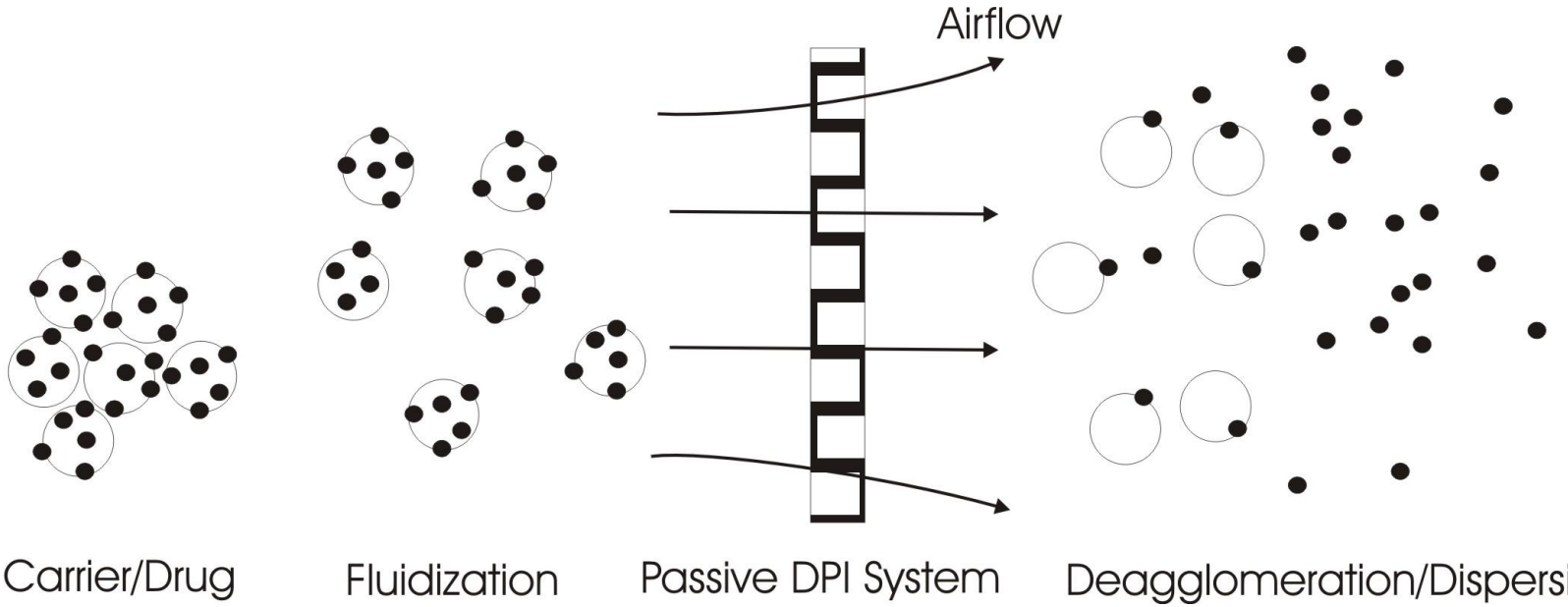
- Intended use in clinical setting
  - Route of administration, dosage form (delivery system), and container closure system
- Quality characteristics of drug product
  - Appearance, identity, strength, assay, uniformity, purity/impurity, stability, and others
- Active pharmaceutical ingredient release or delivery and attributes affecting pharmacokinetic characteristics (efficacy & safety)

Quality Target Product Profile for DPIs

- In vitro performance
  - Emitted dose
  - Aerodynamic particle size distribution
  - Delivered dose uniformity
- Product stability and purity
- Patient usability/acceptability
- Local and systemic delivery
  - Pharmacokinetic and pharmacodynamic measurements

Formulation Considerations

- Formulations of the currently approved DPIs
  - Micronized drug attached to larger carrier particles (i.e., lactose) or
  - Micronized drug particles agglomerated into soft pellets

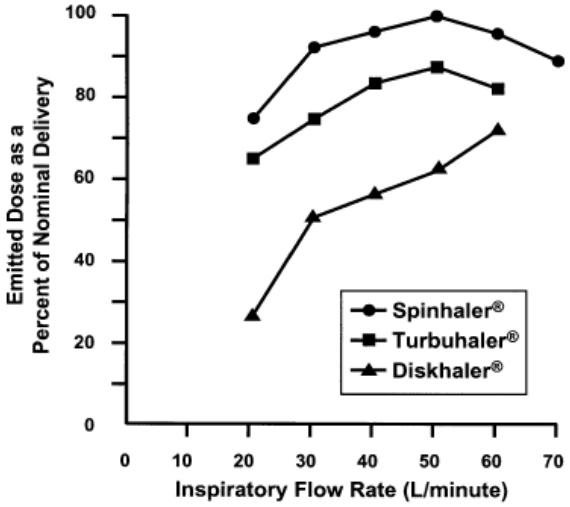


Formulation Considerations

- Physicochemical properties of drug and excipient(s) particles
  - Particle size and shape
  - Density
  - Surface properties
  - Solid (polymorphic) form
- Particle interactions
  - Drug-drug interactions
  - Excipient-excipient Interactions
  - Drug-excipient Interactions

Device Considerations

- Device resistance
  - Depends on the internal geometry and dimension
  - Influences achievable flow rates through the device



A.H. de Boer et al. *Int. J. Pharm.* 130: 231-244(1996)

Device Considerations

- Device materials
  - Understand the sources of extractables and leachables
  - Compatible with formulation
    - Electrostatic effects between the device and dry powders
- Patience usability
  - Device operation
  - Drug metering
  - Device resistance

Development of Equivalent DPIs

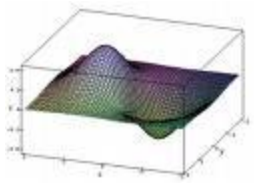
- Constraints for formulation design
  - Q1 the same; Q2 the same preferred
  - Manufacturability
- Constraints for device design
  - Similar shape
  - Equivalent design and operating principle
  - Comparable device resistance

Process Development

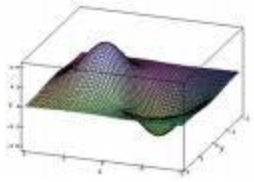
- Understand impact of material attributes and process parameters on product CQAs and the target quality profile
- Identify critical process parameters and input material attributes that must be controlled to achieve product CQAs.
- Use risk assessment to prioritize process parameters and material attributes for experiment verification
- Combine prior knowledge with experiments to establish a design space or other representation of process understanding

Process Identification and Understanding: Concept

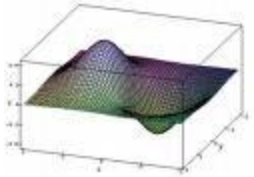
INPUTS (X)



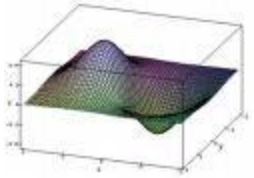
Process



Equipment



Material



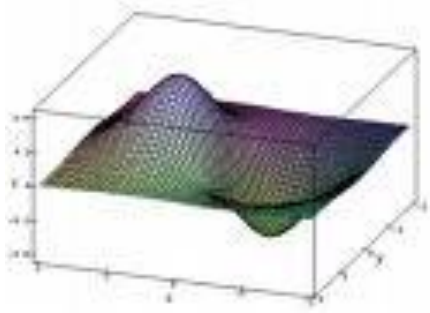
Environment

$Y = f(X)$

Priori knowledge
Risk Assessment
Design of Experiments

Inputs to the process control variability of the Output

Y



OUTPUT

Design Space

- Design Space
  - The multidimensional combination and interaction of input variables (eg. material attributes) and process parameters that have been demonstrated to provide assurance of quality
- Regulatory Implication
  - Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval

Delivered Dose Uniformity

- Delivered dose uniformity
  - Within a container for multiple dose products
  - Between containers
  - Between batches
- Delivered dose uniformity testing documented in the
  - FDA Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products - CMC Documentation (Draft, October 1998)
  - Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - CMC Documentation (Final, July 2002)

IPAC-RS (1998-2003)

- Nonparametric limit tests
  - Counts the number of determinations in a sample within and outside certain pre-fixed limits
    - "NMT 1 of 9 determinations outside 80 - 120% of label claim
    - 0 outside 75 - 125% of label claim"
- Too stringent to encompass all product types
  - High potential for failing good batches
  - OINDP cannot routinely meet expectations in draft Guidances, *e.g.,* many products have been approved with exception to DDU tests acceptance criteria in published Guidances

http://www.fda.gov/ohrms/dockets/ac/03/slides/3996s1.htm

2005 FDA Advisory Committee for Pharmaceutical Science Meeting

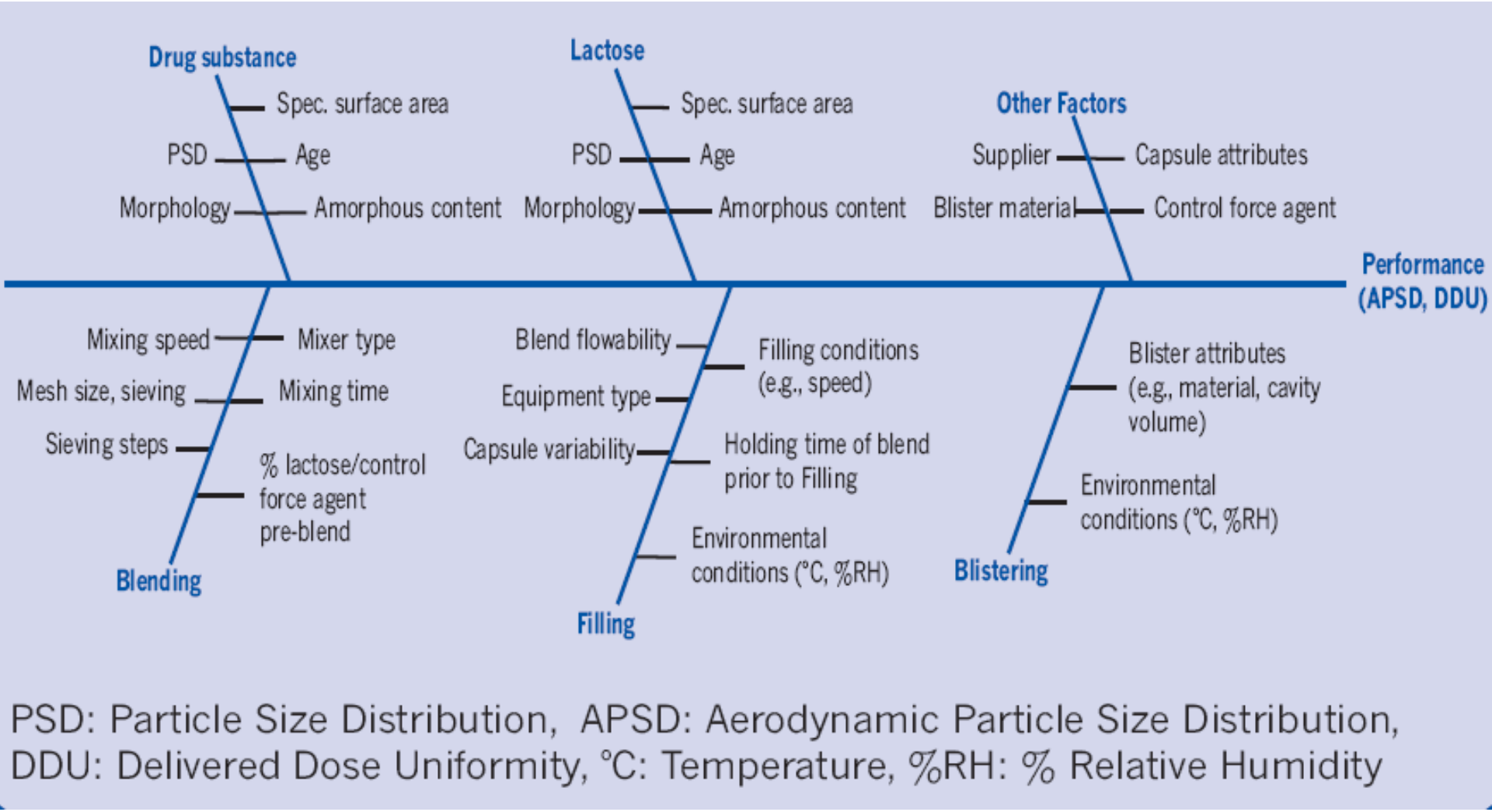
- FDA presented a proposal for delivered dose uniformity testing
  - Goalposts are 80% to 120% of label claim
  - 87.5% coverage within the goalposts
- IPAC-RS
  - Implementation of PTI test in this manner results in a coverage requirement that is greater than the design point (95.8% for “10/10/30/30 - 87.5%” test)
  - Even higher coverage is required when the mean is off target

http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4187s1_Slide%20Index%20Day%201.htm

2005 FDA ACPS Meeting Outcome

- FDA emphasized a Quality by Design approach that calls for product and process understanding:
  - Clinical relevant specification
  - Understanding leads to good control of variability
- IPAC-RS
  - The FDA October 4, 2005, proposal is tighter than the 1998 MDI/DPI draft guidance test

Cause Effect Relationship



PSD: Particle Size Distribution, APSD: Aerodynamic Particle Size Distribution, DDU: Delivered Dose Uniformity, °C: Temperature, %RH: % Relative Humidity

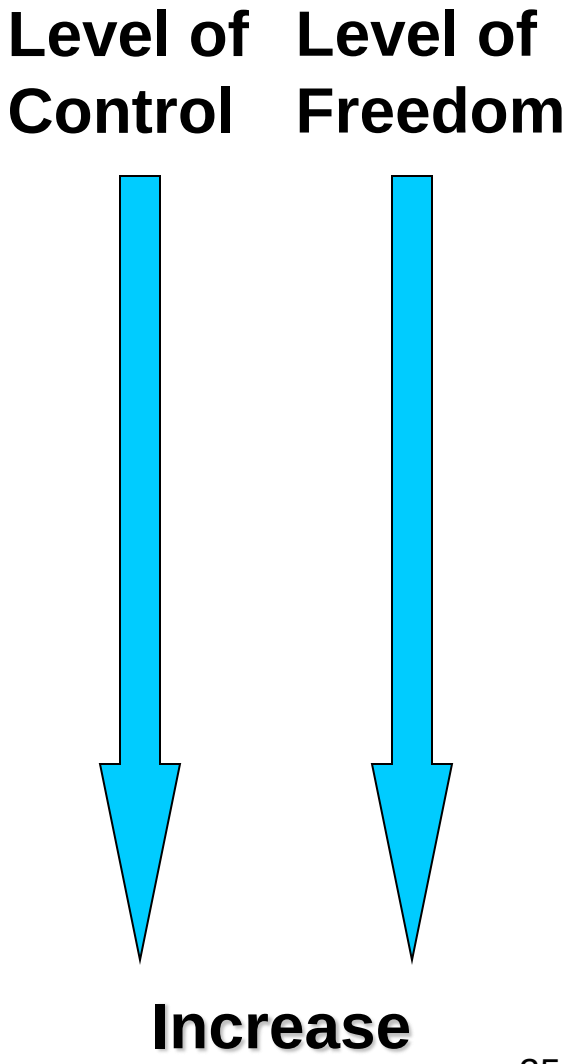
Armanni et al. http://www.ipacrs.com/PDFs/Posters/RESP_On-screen%20version_IPAC2008%20Poster.pdf

Control Strategies

Level 1: Extensive end product testing + Fixed Critical Process Parameters (CPPs)

Level 2: Reduced end product testing + Flexible manufacturing process within fixed design space

Level 3: PAT, Real-time automatic "engineering control"+ Flexible manufacturing process



Level 1 Control

API, fixed particle size
MCC, grade specified
Croscarmellose Na
Mg stearate

Fixed order of addition
Fixed load level
Fixed # of revolutions

Blend Uniformity Testing

Fixed pre-compression force
Fixed compression force
Fixed press speed
Fixed feeder speed

Drug product

Test
Appearance
Identity
Assay
Uniformity
Impurities
Tablet weight
Hardness
Friability
Dissolution

Level 2 Control

WDS = Within Design Space

API, particle size WDS
MCC, particle size WDS
Croscarmellose Na
Mg stearate

Fixed order of addition
WDS load level
WDS # of revolutions

Blend Uniformity Testing

WDS pre-compression force
WDS compression force
WDS press speed
WDS feeder speed

Drug product

Test
Appearance
Identity
Assay
Uniformity
Impurities
Tablet weight
Hardness
Friability
Dissolution

Testing may be reduced if predicted from input and process parameters

Level 3 Control

UFC = Under Feedback Control

API, Flexible particle size
MCC, Flexible particle size
Croscarmellose Na
Mg stearate

Drug product

PAT

"PAT"

"" = . . .

Flexible order of addition
Flexible load level
UFC # of revolutions

UFC pre-compression force
UFC compression force
UFC press speed
UFC feeder speed

Control Variability

- There is uncharacterized variability in the excipients and process
  - Level 1 handles variability by excessively testing
  - Level 2 handles variability by limited testing and establishing design space for critical material attributes and process parameters
  - Level 3 is a robust process that can ensure quality in the presence of uncharacterized variability

Conclusion

- Quality by Design
  - is the basis for science-based regulatory decisions
  - sponsors need to share Pharmaceutical Development information in the application
- Generic Inhalation Products
  - Many opportunities to use QbD to develop equivalent drug products