

Quality by Design

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CDER/OPS

New Drug
CMC

Generic
CMC

Biotech
CMC

Microbiology
CMC

Chemistry Manufacturing and Controls (CMC)

Outline

- n Desired State
- n Product Quality vs. Batch Quality
- n Specifications
- n Quality-by-Design
- n Regulatory Flexibility

The Desired State: A Mutual Goal of Industry, Society, and the Regulators

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

Consequences of Current State

- n High cost and low efficiency of manufacturing
- n Sub-optimal assurance of quality
- n Drug shortages due to inability to manufacture
- n Need for intensive regulatory oversight

Characteristics of Desired State

- n Manufacturers have extensive knowledge about critical product and process parameters and quality attributes
- n Manufacturers strive for continuous improvement
- n FDA role: Initial verification, subsequent audit
- n No manufacturing supplements needed

Desired State

- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Continuous "real time" assurance of quality

<http://www.fda.gov/cder/gmp/21stcenturysummary.htm>

FDA "Desired State"

Extensive Product Testing
Little Process Understanding



High Process
Understanding and Control

Obviated
End Product Testing

Increasing Desirability



Pharmaceutical Quality

n The state of having an acceptably low risk of failing to achieve the desired clinical attributes.

n Product Quality

n Batch/Lot Quality

Describing Product Quality

n Specifications (e.g.,)

n Strength

n Purity

n Moisture Content

n Dissolution

n Sterility



n State Function for Quality

n $Q = \int (\text{Strength, Purity, Moisture, etc...})$

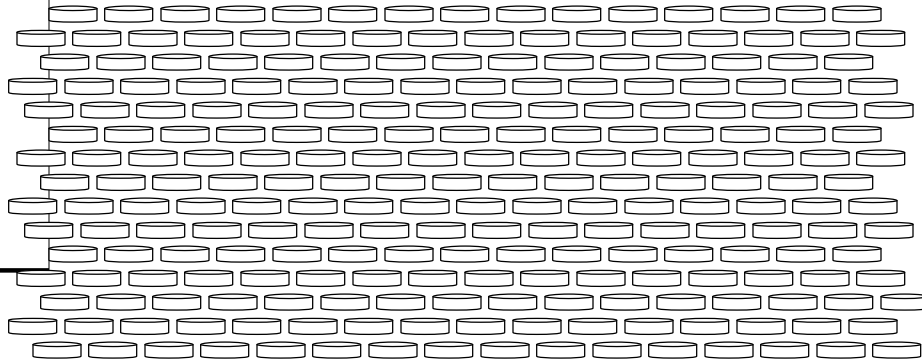
QbD Specifications

- n Specs are prospectively designed based on clinical needs and performance requirements
 - n Patient Population (peds, geriatric, etc.)
 - n Route of Administration
 - n Dosage Form
 - n Solid Oral
 - n Dermal Patch
 - n Inhaled
 - n Rate of release
- n Testing is not the only way to assure conformance

Assuring Batch Quality

- n End Product Testing
 - n Evaluates conformance of individual units to specifications, therefore...
 - n Need to use a statistically meaningful number of samples (costly!)
 - n Even so... not so good.
- n $Q(\text{pass, fail}) = \prod(\text{spec}_A)(\text{spec}_B)(\text{spec}_C)\dots$
 - n $\text{spec}_A(\text{pass, fail}), \text{spec}_B(\text{pass, fail}), \dots$
 - n Risky business (false positives or negatives)

Unit Quality à Batch Quality?



 Good

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 Bad

 Tested 13

Is This Assuring Batch Quality?

n Prospective Process Validation

- n Correlates manufacturing process to quality metrics
- n Locks in the manufacturing process
- n Requires assurance that the process doesn't drift over time
- n Not responsive to "the unexpected"
- n How much validation is enough?

This is Assuring Batch Quality

n Quality-by-Design

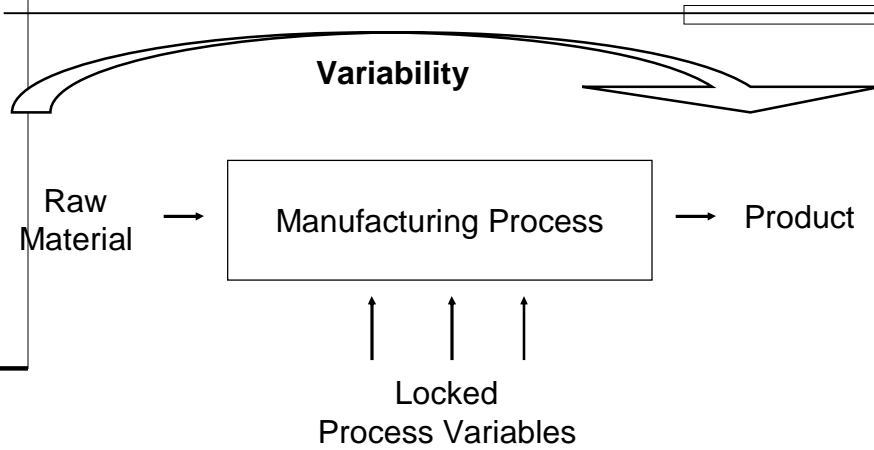
- n Process is designed to ensure consistent product quality
 - n Impacts of material- & process-variability on quality are understood
 - n Variability is managed by the process
 - n Risk-based focus on quality control

A Tool For Assuring Batch Quality

n Process Analytical Technology

- n Incorporates quality metrics into the manufacturing process
- n Continuous Quality Verification
- n Flexible manufacturing process
- n Responsive to variability

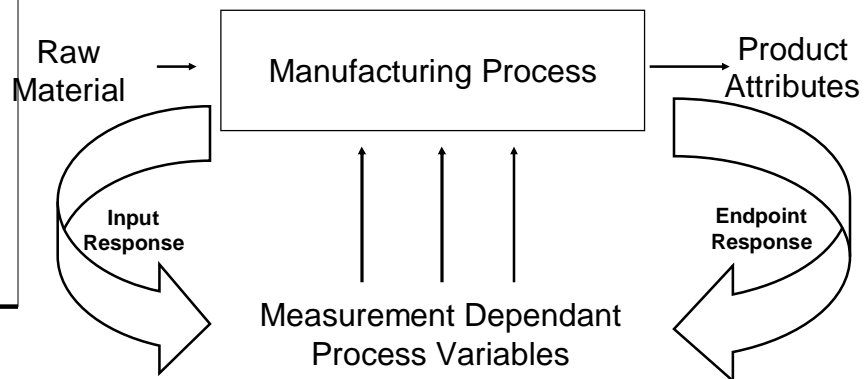
Traditional Paradigm



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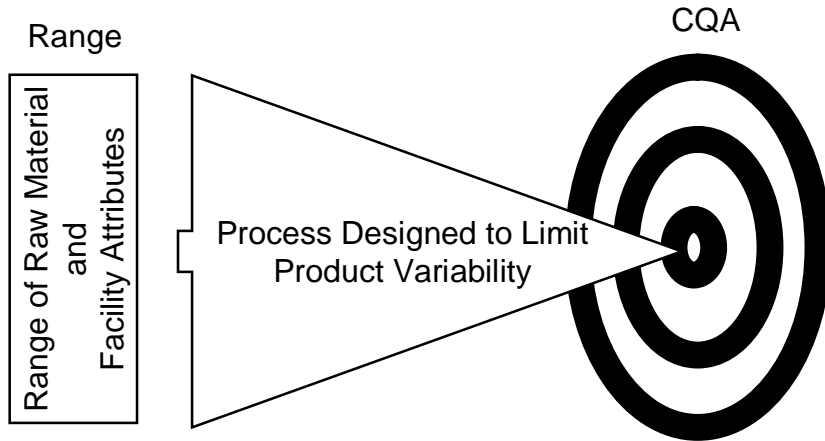
Dynamic System



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Target Critical Quality Attributes



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Regulatory Flexibility

- n Manufacturers will be afforded regulatory flexibility commensurate with their:
 - n Level of product & process understanding
 - n Ability to predict the impacts of changes
- n Post-Approval Changes w/o Supplements

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Composite material design:

**Eliminates 1,500 aluminum sheets
and 40,000 - 50,000 fasteners**

40,000 lbs lighter than A330

20% fuel savings

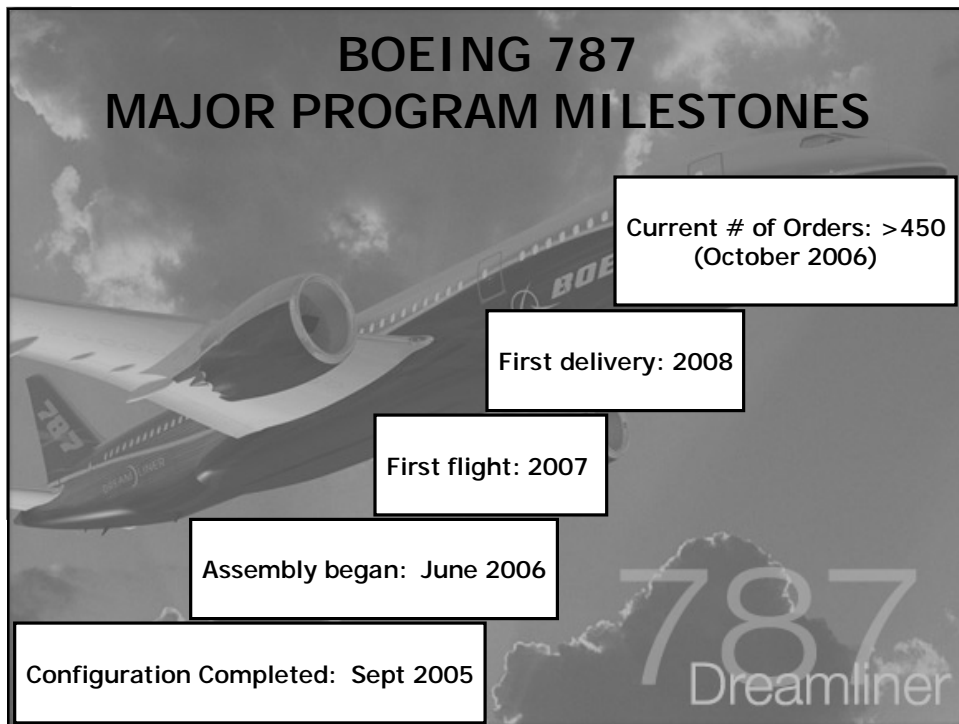


Advanced electrical architecture:

35% less power drain on engines

Eliminates 60 miles of copper wire

787
Dreamliner



How can pharmaceutical development knowledge help?

- n Demonstrate quality was designed in
- n Specifications based on mechanistic understanding
- n Continuous "real time" assurance of quality
- n Flexible continuous improvement?

Summary

- n Quality-by-Design includes
 - n Design of product quality specifications
 - n Design of a robust manufacturing process that inherently ensures product quality
- n Quality-by-Design allows
 - n Improved quality assurance
 - n Increased manufacturing flexibility
 - n Reduced post-approval supplements

Quality & Success

- n Success is a journey, not a destination

 - n Quality-by-Design is a
Quality Assurance strategy
not destination.

 - n Do what you say
Say what you do
- Thank you!

Bonus Material

What is a specification?

n ICH Q6a

- n A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described.

n What is to be tested?

- n Most of the time we rely on a sample of the finished product
- n Is this the best approach?

Consider Batch Specification

- n Applications generally contain specification that carefully describe the test procedure and result criteria for collection of dosage units, a specimen:
 - n 20 tablets for assay
 - n 30 tablets for uniformity of content
 - n 24 tablets for dissolution
- n Does this characterize the batch?
- n Where can we find help with this?

Regulation on Selection of “Units”

- n 21 CFR 211.165(d)
 - n “...adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release”
- n Is there anything about batch variability?

Regulation on Variability

n 21 CFR 211.110(b)

- n Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate

n What does USP say about those samples?

USP General Notices, 29th Revision

n “These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of a specimen”

n “These procedures should not be confused with statistical sampling plans”

n “Treatments of data handling are available from organizations such as ISO, IUPAC, and AOAC”

n What does this say about USP used for batch release?

USP General Notices, 29th Revision

- n Data derived from manufacturing process validation studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch
- n What does this say about how not to characterize a batch?

Where do we go for help?

- n World's single largest purchaser
- n Long history of good and bad experiences
- n Lives depend on the quality of products they receive
- n Moved away from a focus on sampling and inspection of finished material
- n Moved toward defining measurement of desired attributes during processing
- n US Department of Defense

Mil-Std-1916, April 1996

- n Sampling inspection by itself is an inefficient industrial practice for demonstrating conformance to the requirements of a contract and its technical data package
- n Suppliers can reduce risks by employing efficient processes with appropriate process controls
- n An effective process control system may also be used to provide information to assess the quality of deliverables submitted for acceptance

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Mil-Std-1916, April 1996

- n Suppliers are encouraged to use process control and statistical control procedures for their internal control and to submit effective process control procedures in lieu of prescribed sampling requirements to the Government for approval
- n How does this compare to the terms “Release Testing” and “Specification”?
- n What about “Real Time Release”?
- n What does USP say about every test result?

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USP General Notices, 29th Revision

- n it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution
- n What else does USP say?

USP General Notices, 29th Revision

- n Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs
- n ...release specifications and compliance with good manufacturing practices generally, are developed and followed to assure that the article will indeed comply with compendial standards until its expiration date
- n ...any specimen tested as directed in the monograph for that article shall comply

Separation of Spec and Test?

n Real Time Release (PAT Guidance)

- n is the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data
- n The combined process measurements and other test data gathered during the manufacturing process can serve as the basis for real time release of the final product and would demonstrate that each batch conforms to established regulatory quality attributes

What is a specification?

- n “A list of tests” ...
 - n Can these be process control measurements?
- n “references to analytical procedures” ...
 - n Can this describe process control measurement?
- n “appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described”
 - n This too?