PAT
Real Time Release

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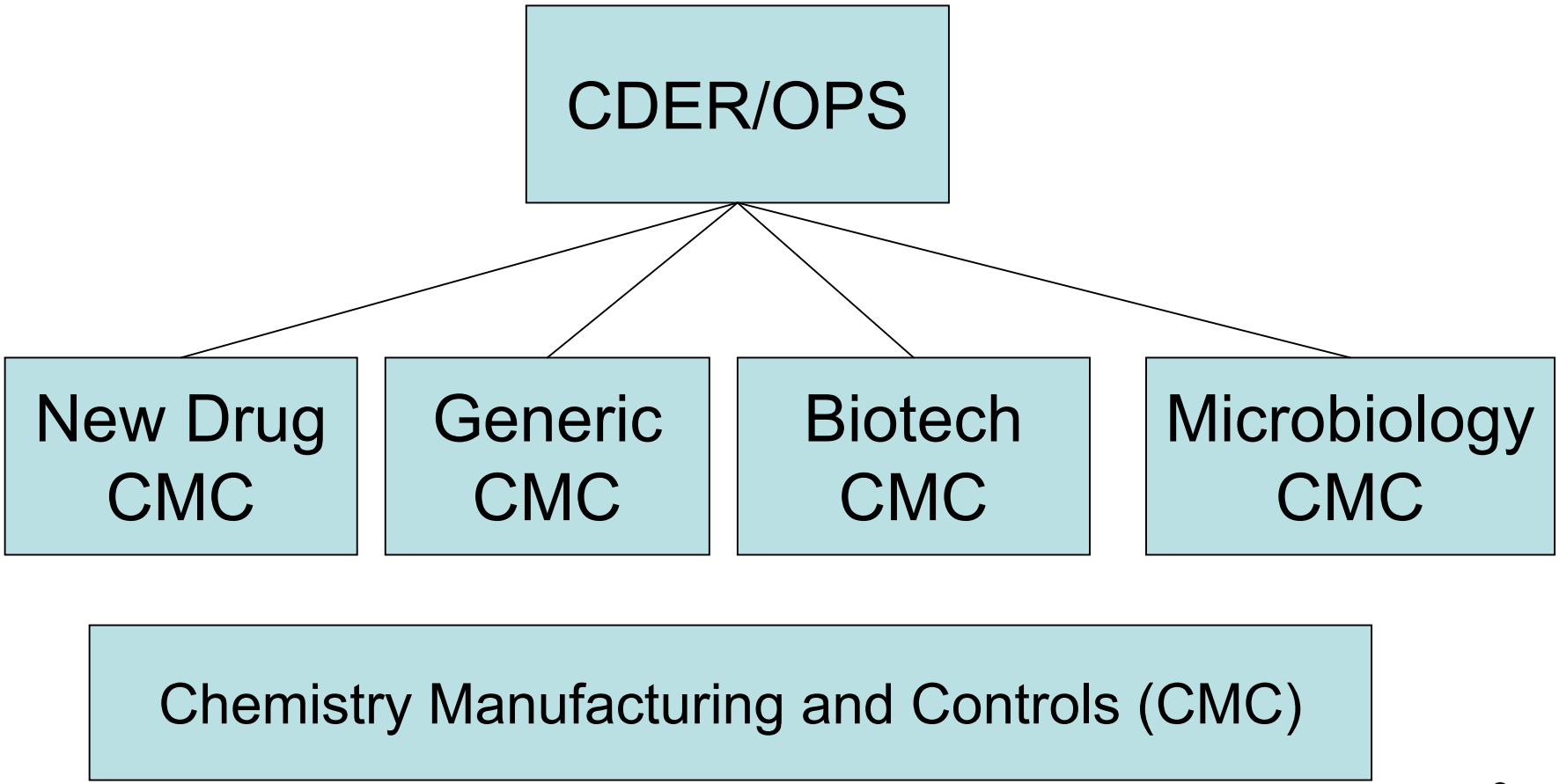


Main Points

- Process Understanding
- Design Space
- Risk Management

Process Understanding

- Term occurs 19 times in PAT guidance
  - 4 more as “process well understood”
- Manufacturing Process
  - Continuous process
  - Batch process
  - Drug Product
  - Drug Substance
  - Packaging
  - Filling
  - Storage

What is Process Understanding?

- "When all critical sources of **variability** are identified and explained"
- **"Variability** is managed by the process; and,"
- "Product quality attributes can be accurately and reliably predicted over the **design space** established for materials used, process parameters, manufacturing, environmental, and other conditions."

What is "Real Time Release?"

- Real Time Release builds on Parametric Release
- In real time release, material attributes as well as process parameters are measured and controlled
- "…the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data"

What is PAT?

- "The Agency considers PAT to be a system for designing, analyzing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality."

How can PAT be done:

- Use of relevant information relating to physical, chemical, and biological attributes that enables process control and optimization:
  - At line
  - On line
  - In line

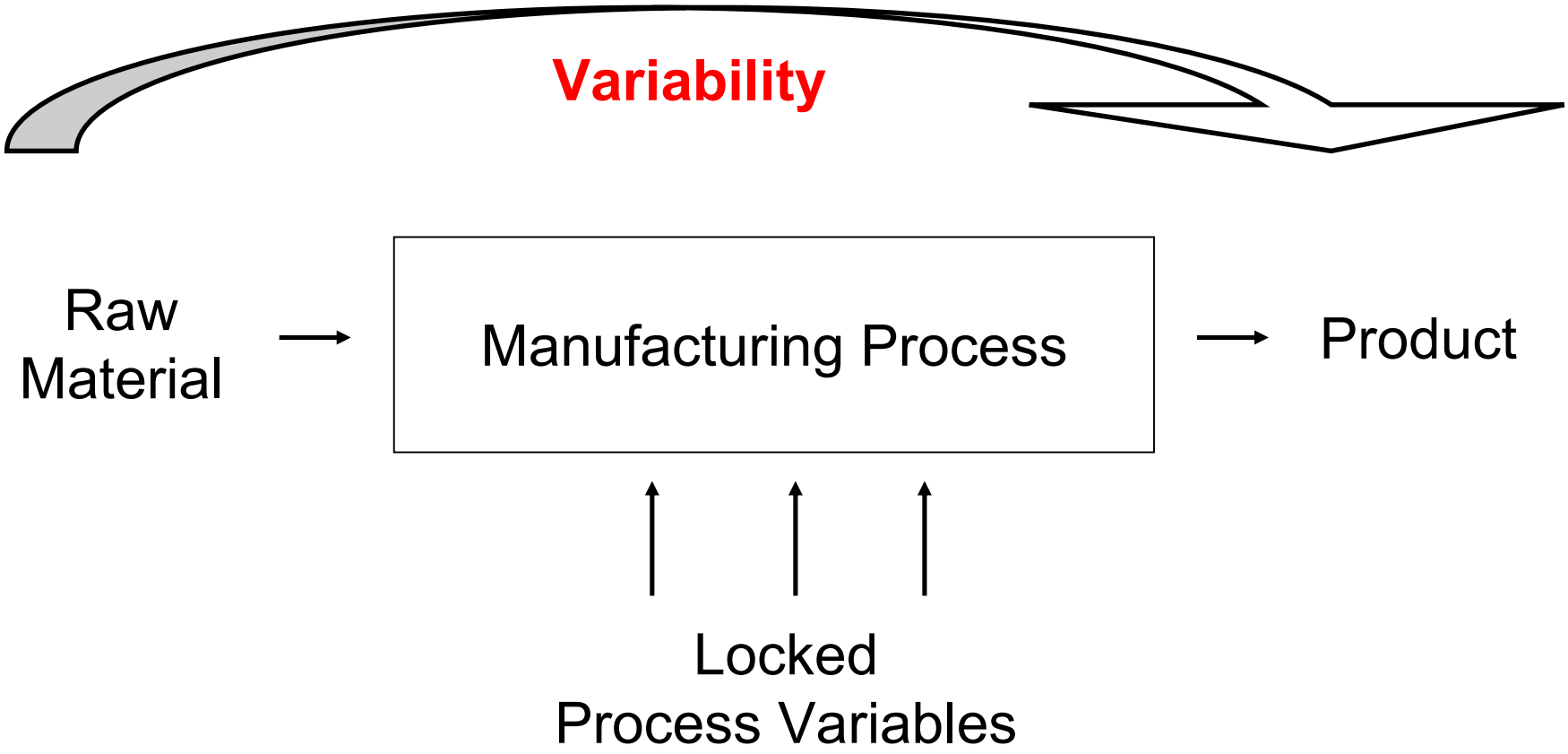
At-line

- Sample is removed from process stream
- Analyzed near by the process stream
- Process is controlled in response to measurement

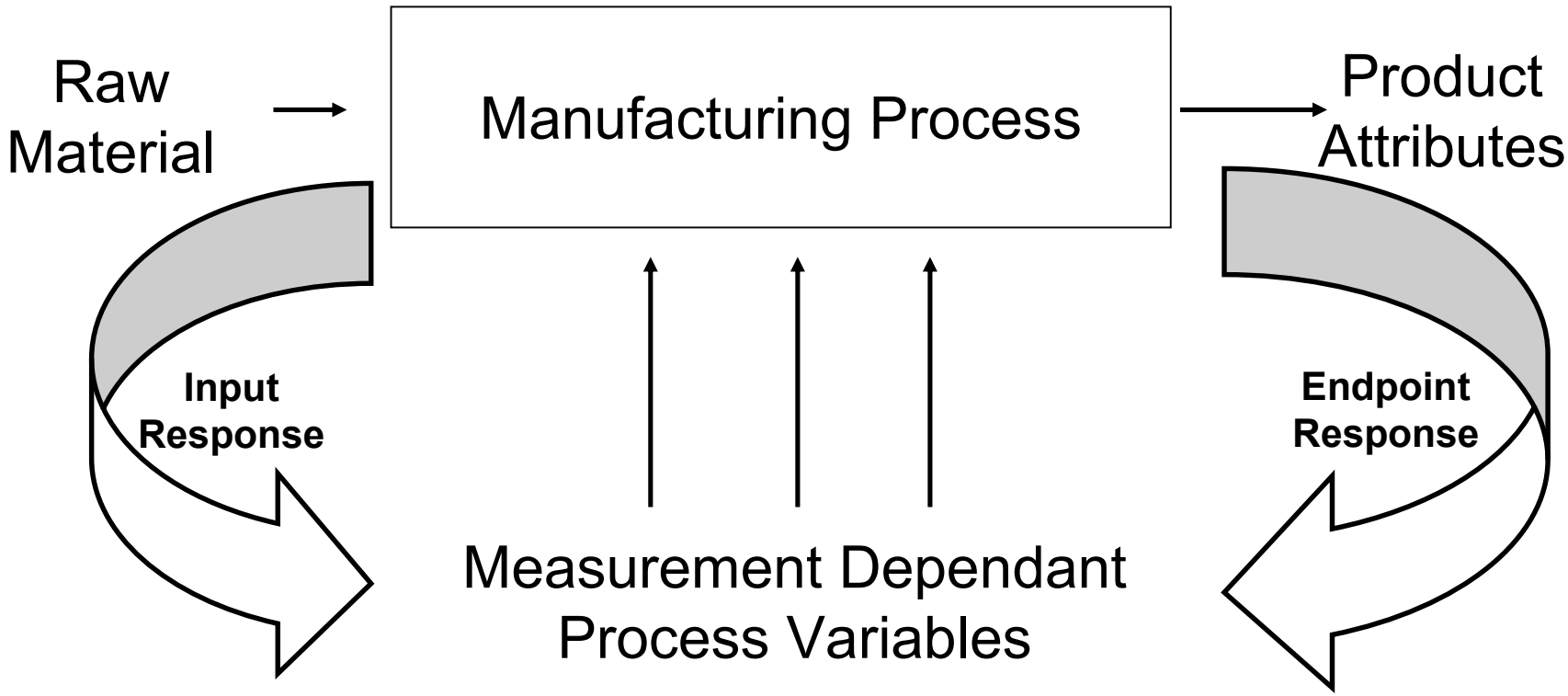
On / In Line

- On-Line
  - Sample is diverted from process
  - Analyzed
  - Process is controlled in response to measurement
  - Sample returned to process
- In-Line
  - Sample not removed from process stream
  - Process is controlled in response to measurement

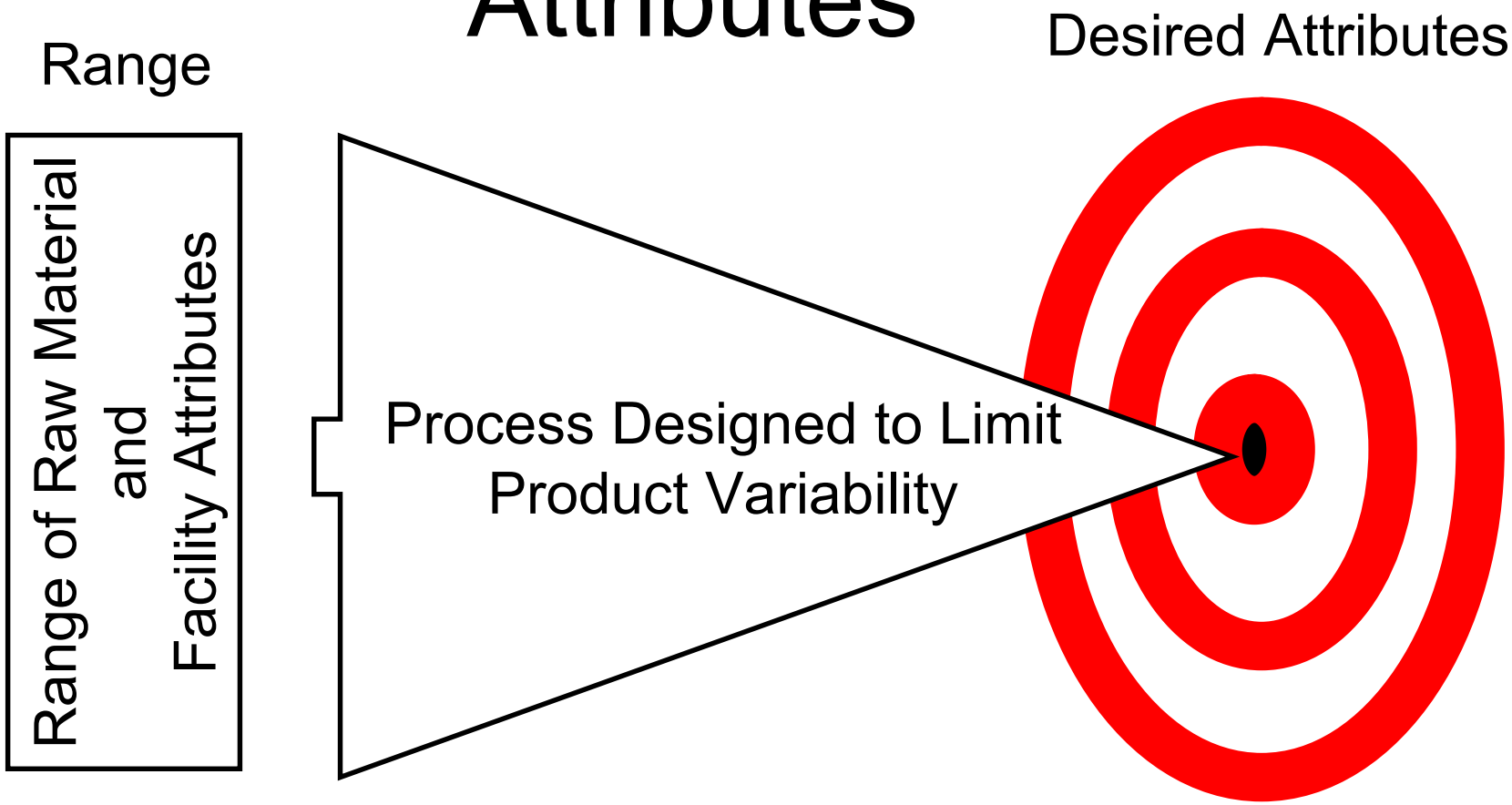
Traditional Paradigm



Dynamic System



Target Desired Product Attributes



PAT Guidance

- **PAT** is FDA Guidance (final)
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf
  - 19 pages (easy reading)

- Much of our progress at FDA began with developing this document

Scenario 1

- Please discuss the situation in Scenario 1
  - See the “note” attached to this slide

Q8(R1); Design Space; QbD

International Conference on Harmonization (ICH)

Consider the Document

- ICH Quality topic 8 (Q8)
- Focus is on Drug Product quality
- Specific to one section of the Common Technical Document (CTD)
  - 3.2.P.2 **Pharmaceutical Development**

Pharmaceutical Development

- "Scientific understanding to support specifications and controls"
- Basis for "risk management"
- "Aspects of drug substances, excipients, and manufacturing processes that are critical and that present a significant risk to product quality, aspects of drug substances, excipients, and manufacturing processes that are critical and that present a significant risk to product quality,"

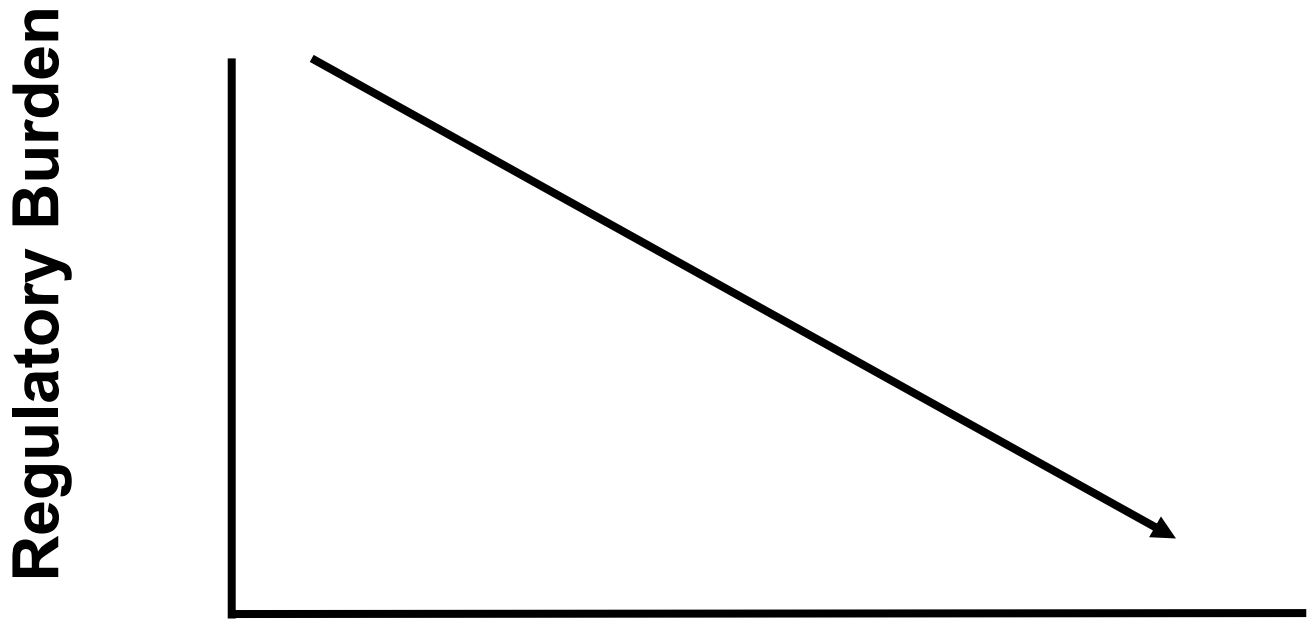
Pharmaceutical Development

- "Risk based regulatory decisions (reviews and inspections)"
- "Manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;"
- ""Real time" quality control, leading to a reduction of end-product release testing"

Knowledge not data

- "It is the recognized that the level of knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science- and risk-based submissions and regulatory evaluations."
- "knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the ***design space***, specifications, and manufacturing controls."

Value of Knowledge



Design Space

- "Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process"

- "Design space is proposed by the applicant and is subject to regulatory assessment and approval."

Systematic Approach and QbD

- Target Product Profile (TPP)
- Critical Quality Attributes (CQA) so that TPP is assured
- Determine quality attributes of components that assure CQA
- Identify a control strategy
- Identify material attributes and process parameters that affect CQA
- Link functional relationships between process parameters, material attributes and CQA
- Manage risk to establish multidimensional Design Space that will deliver CQA
- Continual improvement on sources of variability
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073507.pdf

Aspect	Minimal Approach	Enhanced, quality by design Approach
Overall Pharmaceutical Development	• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, relating mechanistic understanding of input material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilised
Manufacturing Process	• Fixed • Validation primarily based on initial full-scale batches • Focus on optimisation and reproducibility	• Adjustable within design space • Lifecycle approach to validation and, ideally, continuous process verification • Focus on control strategy and robustness • Use of statistical process control methods
Process Controls	• In-process tests primarily for go/no go decisions • Off-line analysis	• PAT tools utilised with appropriate feed forward and feedback controls • Process operations tracked and trended to support continual improvement efforts post-approval
Product Specifications	• Primary means of control • Based on batch data available at time of registration	• Part of the overall quality control strategy • Based on desired product performance with relevant supportive data
Control Strategy	• Drug product quality controlled primarily by intermediate and end product testing.	• Drug product quality ensured by risk-based control strategy for well understood product and process • Quality controls shifted upstream, with the possibility of real-time release or reduced end-product testing
Lifecycle Management	• Reactive (i.e., problem solving and corrective action)	• Preventive action • Continual improvement facilitated

Q8 Pharmaceutical Development

- **Q8** is ICH Guidance (final)
  - http://www.fda.gov/cder/guidance/6746fnl.pdf
- Revision of Q8 is in draft as Q8R1
  - http://www.fda.gov/cder/guidance/8084dft.pdf

Scenario 2

- Please discuss the situation in Scenario 2
  - See the “note” attached to this slide

Measurement Based Control

Measurement of the Material in Process

Sampling for Release Testing

- Applications generally contain specifications that carefully describe the test procedure and result criteria for collection of dosage units, a specimen:
  - 20 tablets for assay
  - 30 tablets for uniformity of content
  - 24 tablets for dissolution
  - 20 units for sterility
- How hard is it for a defective batch to pass?

Consider Sterility

- Remington's Pharmaceutical Sciences
  - 18th Edition (1990)
  - A lot with 1 in every 1000 units contaminated
  - With 10 random samples tested
  - Passes 99 times of 100
  - Need 50 contaminated units to get 40% chance of failure
- Example is dated since USP now recommends 20 random samples
  - … or do they???

USP General Notices, 30th Revision

- "These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of a specimen"
- "These procedures should not be confused with statistical sampling plans"
- "Treatments of data handling are available from organizations such as ISO, IUPAC, and AOAC"

- What does the regulation say?

Regulation on Selection of "Units"

- 21 CFR 211.165(d)
  - "…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"

- How do we provide assurance for the untested units in the batch?

Where do we go for help?

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

Mil-Std-1916, April 1996

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

Mil-Std-1916, April 1996

- "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"

- What does USP say about this practice of doing something **"in lieu of"** sampling and testing?

USP General Notices, 30th Revision

- "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 "

- What else does USP say?

USP General Notices, 30th Revision

- "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"
- "Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs"

- What does ICH Q6a, Specifications, say about this?

Q6a

- “Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or tighter than the release requirement, (e.g., pH (hydrogen-ion concentration) of a solution) may be sufficient to satisfy specification requirements when the test is included in the specification.”

- So, why doesn’t FDA tell us to do it this way?

PAT Guidance, September 2004

- Real Time Release (PAT Guidance)
  - "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"

Draft Process Validation Guidance; US FDA

- "More advanced strategies, such as process analytical technology (PAT), use timely analysis and control loops to adjust the processing conditions so that the output remains constant."
- "Manufacturing systems of this type can provide a higher degree of process control."
- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Holistic Process Validation

- Collection and evaluation of data from design throughout production to establish that a process is capable of consistent quality
  - Stage 1 Process Design
  - Stage 2 Process Qualification
  - Stage 3 Continued Process Verification

Manufacturers Should

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product

Continued Process Verification

- "develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability"

- "anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits."

- "scrutinize intra-batch as well as inter-batch variation as part of a comprehensive *continued process verification* program."

US FDA Requirement

- 21 CFR 211.100(a)
  - Design
- 211.110(a)
  - Monitor output to validate performance
- 211.160(b)(3)
  - Samples represent the batch
- 211.165(a) and (c) and (d)
  - Statical confidence and meets the specification

Sampling for Process Analytical Technologies

- ASTM E55 WK15151
- It is recognized that in-process and end-product specifications should in principle be derived from patient requirements

- As the number of samples increases or decreases the reliability of our ability to meet specifications changes

Demonstrating Capability to Comply

- E 2709 – 09
- Computes probability of passing a lot acceptance procedure
- Uses test results from the lot
- Effectively answers the question:
  - What is the probability of the next sample being within the criteria?

Scenario 3

- Please discuss the situation in Scenario 3
  - See the “note” attached to this slide

Thank You

Say what you do!

Do what you say!