U.S. Department of Health and Human Services
Food and Drug Administration

FDA Perspective On A PAT Driven Future

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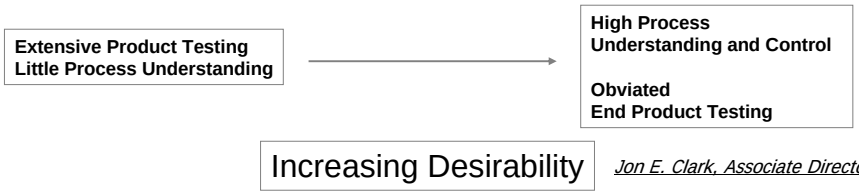
What are the objectives?

Discussion Topics

- Integrating Process Control
- Validation
- Real-Time Release
- Evolution of “Specifications”
- Future Challenges and Opportunities

FDA "Desired State"



Increasing Desirability

Jon E. Clark, Associate Director, OPS

Processes controlled

- well, and with high capability
- lot acceptance via sampling and inspection of the product is redundant and unnecessary

"Design Space"

- Allow Continuous Improvement
- Founded on Material Attributes
- Clinical Relevance
  - BA/BE
- Not parametric in focus

What is PAT?

A system for:

- designing, analyzing, and controlling manufacturing
- timely measurements (i.e., during processing)
- critical quality and performance attributes
- raw and in-process materials
- processes

"Analytical" includes:

- integrated chemical, physical, microbiological, mathematical, and risk analysis

Focus of PAT is Understanding and Controlling the manufacturing Process

PAT Tools

- Multivariate tools for design, data acquisition and analysis
- Process analyzers
- Process control tools
- Continuous improvement and knowledge management tools

- Combination of some, or all
  - single-unit operation, or to an entire manufacturing process and its quality assurance

PAT Tools: Process Control Tools

- Monitor the state of a process and actively manipulate it to maintain a desired state
- Strategies accommodate
  - attributes of input materials
  - the ability and reliability of process analyzers to measure critical attributes
  - achievement of process end points to ensure consistent quality
- End points = achievement of the desired material attribute (not process “t”)

PAT Tools: Process Control Tools

- Multivariate Statistical Process Control
  - can be feasible and valuable to realizing the full benefit of real time measurements
- Decisions based on process understanding
  - prediction and control of relevant (critical) process/product attributes
  - consistent with CGMP requirements, as such control procedures validate the performance of the manufacturing process - 21 CFR 211.110(a)

PAT Tools: Process Control & Validation

- Alternative, effective mechanisms to demonstrate validation
  - high assurance of quality on every batch (designed to ensure quality)
  - validation demonstrated through continuous quality assurance
    - process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls, and process end points

Validation

- Process
  - Evaluation and Control of Critical Quality Attributes
  - Continuously validate process in control

Systems that promote greater product and process understanding can provide a high assurance of quality on every batch and provide alternative, effective mechanisms to demonstrate validation (per 21 CFR 211.100(a), i.e., production and process controls are designed to ensure quality). In a PAT framework, validation can be demonstrated through continuous quality assurance where a process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls, and process end points.

Real Time Release – PAT Guidance

- *Real time release* is the ability to evaluate and ensure the acceptable quality of in-process material and/or final product based on process data.
- Typically, the PAT component of *real time release* includes a valid combination of assessed material attributes and process controls.
- 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?

- ICH Q6a
  - A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described.
  - What is to be tested?
    - Most of the time we rely on a sample of the finished product
    - Is this the best approach?

Consider Batch Specification

- Applications generally contain specification 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
- Does this characterize the batch?
- Where can we find help with this?

MIL-STD-1916 (April 1996)

3. DoD procurement practices encourage industry innovation and provide flexibility to achieve the benefits of continuous improvement.

4. There is an evolving industrial product quality philosophy that recognizes the need for quality policy changes that will provide defense contractors with opportunities and incentives toward improvement of product quality and cooperative relationships between the contractor and the Government.

5. Process controls and statistical control methods are the preferable means of preventing nonconformances, controlling quality, and generating information for improvement. An effective process control system may also be used to provide information to assess the quality of deliverables submitted for acceptance. 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.

6. Sampling inspection by itself is an inefficient industrial practice for demonstrating conformance to the requirements of a contract and its technical data package. The application of sampling plans for acceptance involves both consumer and producer risks; and increased sampling is one way of reducing these risks, but it also increases costs. Suppliers can reduce risks by employing efficient processes with appropriate process controls. To the extent that such practices are employed and are effective, risk is controlled and, consequently, inspection and testing can be reduced.

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"
- Is there anything about batch variability?

Regulation on In-Process Specifications and Variability

- 21 CFR 211.110(b)
  - 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
- What does USP say?

USP General Notices, 29th 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 this say about USP used for batch release?

USP General Notices, 29th 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
- What does this say about how not to characterize a batch?

USP General Notices, 29th 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 is a specification?

- "A list of tests"...
  - Can these be process control measurements?
- "references to analytical procedures"...
  - Can this describe process control measurement?
- "appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described"
  - This too?
- Is this what we mean by "Life Cycle"?

Evolution of Processing

- Continuous Processes
  - How do we define a batch?
    - t-based?
    - Mass?
    - Mass balance/flow
- Scaled-down processes
  - continuous
- …

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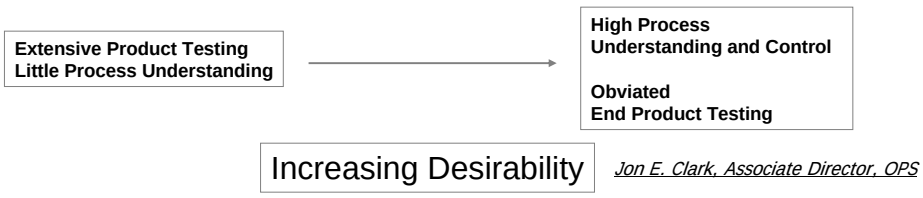

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How may this evolve?

- Innovations in *Critical Path* research
  - advanced techniques for the predictability of safety and efficacy
  - mechanisms for the direct evaluation and control of clinical performance
  - integrated into process control strategies
- Associated “specifications”
  - formal means to convey implications of product and process changes
  - minimal uncertainty
  - minimal risk to the patient

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What will happen?

Summary

- Agency support
- RTR
- Evolution of “specifications”

- Other issues...

Acknowledgement
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