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

Royal Pharmaceutical Society of Great Britain

PAT Guidance: Going from the Current Negative Vocabulary to an Manufacturing Science Enabling Vocabulary

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FDA PROCESS ANALYTICAL TECHNOLOGY FORUM
in association with the **New Technologies Forum of RPS**
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Best Wishes to Professor Tony Moffat

- On his retirement from the Royal Pharmaceutical Society on Friday 17th December 2004
- Without Tony's leadership and contributions it is very likely the PAT revolution would not have occurred at the beginning of the 21st Century
- I have learned tremendously from my interactions with him – Thank you Tony

Preface

- **The thoughts outlined in this presentation are based on**
  - My personal learning through the opportunity (provided by Ms. Winkle and Dr. Woodcock) to lead the FDA's PAT Initiative and its subsequent evolution into the CGMP's for the 21st Century and the Critical Path Initiative
    - FDA Advisory Committee Meetings and numerous scientific workshops and learning from my FDA co-workers
    - Opportunity to study and discuss the development and evolution of PAT programs at several companies
  - FDA's White Paper – "Innovation and Continuous Improvement in Pharmaceutical Manufacturing"
    - http://www.fda.gov/cder/gmp/gmp2004/manufSciWP.pdf
  - Dr. Woodcock's paper "The Concept of Pharmaceutical Quality", American Pharmaceutical Review, Nov/Dec. 2004
  - The pioneering work of quality leaders such as Shewart, Deming, Juran, Taguchi, and others

FDA's PAT Guidance

- A framework for innovation and continuous improvement in pharmaceutical industry
  - Product Development
  - Manufacturing
  - Quality Assurance
- Outlines principles for improving process understanding to facilitate
  - Achieving and communicating (documenting) Quality by Design (QbD) and risk-reduction

FDA's PAT Guidance

- A communication tool that changes the current "negative" pharmaceutical quality vocabulary to a "positive", enabling, and collaborative vocabulary
  - Scientific disciplines (e.g., chemistry-pharmacy-engineering)
  - Organizations (R&D – Manufac. – QA – Reg…)
  - Pharmaceutical Industry and regulators
  - Pharmaceutical and other industries
  - Industry and public

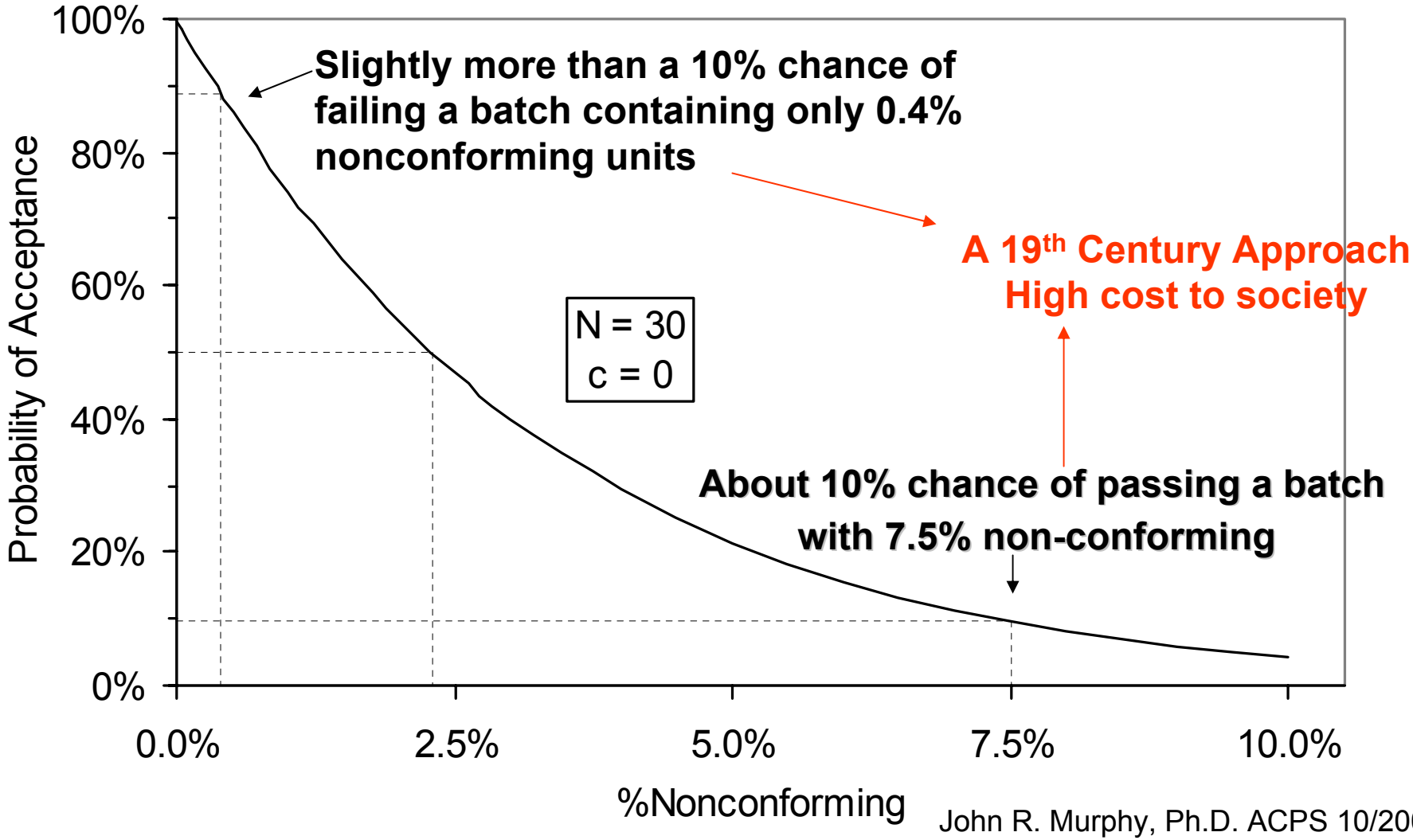
Current "Negative Vocabulary": Examples

- "Testing to Document Quality"
  - In-process and final product tests and acceptance criteria based on "pass/fail" or attribute criteria
    - Generally based on an Pharmacopeial methods that are designed to serve as "market standards"
    - Utility of these to control/release a batch is essentially a 19th Century approach to quality assurance, inhibits process understanding and continuous improvement, and often penalizes scientific efforts in manufacturing and QA
    - Provides the lowest acceptable documented level of quality and can contribute to the high and often non-value added costs to society

".. lowest documented level of quality and… high and non-value added costs to society"

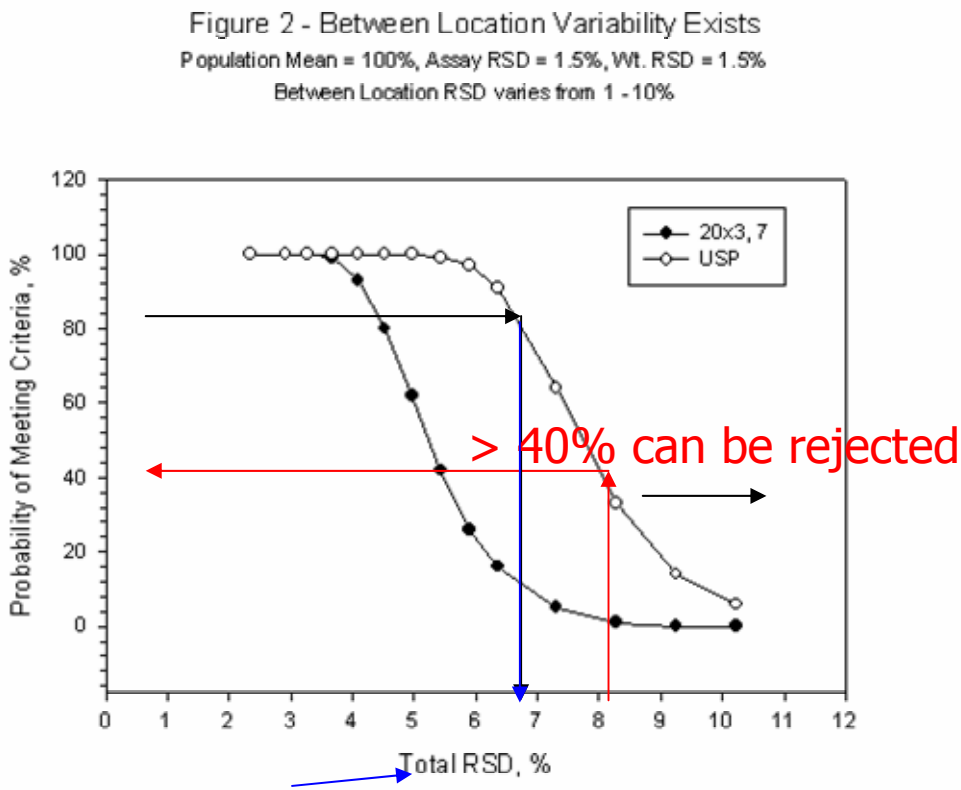
- To be very clear – Pharmacopeial standards are important and serve a useful function. But are -
  - Minimal standards
  - Not well suited for "mass production", i.e., in-process and final product testing and batch release
- Modern in-process controls and quality assurance approaches can provide an enhanced "win (patient)-win (company)-win (society)" approach

Testing to Document Quality: "Pass/Fail" or Attribute Criteria



John R. Murphy, Ph.D. ACPS 10/2003

Testing to Document Quality: "Pass/Fail" or Attribute Criteria



n=10/30, how robust are %RSD estimates?

Testing to Document Quality: Dissolution Test Method

- Do we currently have the ability to document lower variability in dissolution rate than that of the USP Dissolution Calibrator Tablets?
  - $\sigma^2_{Total} = \sigma^2_{Product} + \sigma^2_{Measurement} + \sigma^2_{Random}$
  - $\sigma^2_{Measurement} = \sigma^2_{Repeatability} + \sigma^2_{Reprodicibility}$
- $\sigma^2_{(Total\ for\ Calib.)}$
  - $= \sigma^2_{(Calib.)} + \sigma^2_{C*Measurement} + \sigma^2_{C*Random}$

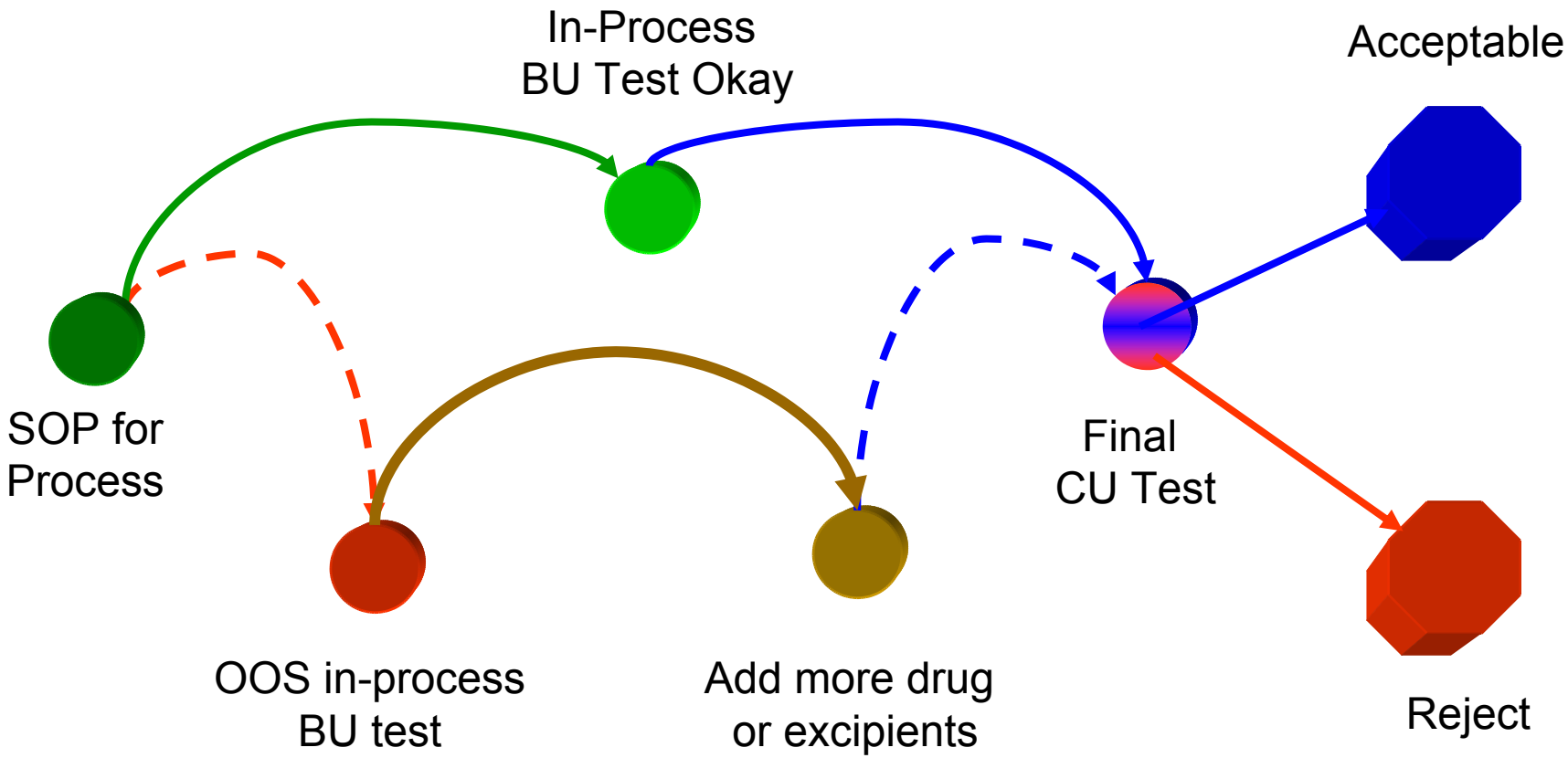
Dissolution Test

Testing to Document Quality using Attribute Criteria

- What is observed in the sample can not provide a high degree of certainty regarding the untested units
- Zero accept criteria inhibits process understanding, removes flexibility and leads to minimalistic strategies
  - Example: Risk of a “stability failure” increases as the number of tests are performed (even for cases where the characteristic does not actually change over time)
  - Contributes towards pushing validation to be a “well rehearsed demonstration that three consecutive batches can be manufactured to be in conformance” and de-values its scientific underpinning and making it little more than a “roll of the dice”

Negative vocabulary “Testing in to Compliance”

"Testing to Document Quality" is not "Quality by Design"



Negative vocabulary –recognition/penalty system - can contribute to "fear" that can increase risk to patient

PRODUCTION SYSTEM

4. Deviations from approved drug formulations are performed when in-process specifications are not met. The deviations consist of adding varying quantities of active ingredient or diluting the batch. There are no validation studies to assure that there is no adverse product impact throughout shelf life. Investigations do not always determine the cause of the abnormal assay result or corrective/preventive action. For example:

a. In-process assay of [redacted] revealed low potency results ranging from [redacted] (specifications are [redacted]. An additional quantity of [redacted] of the active ingredient was added to the batch. There is no determination into the cause of the low assay or preventative actions from recurrence.

Negative Vocabulary: Other Examples

- Out of Specification Investigations – “Root Cause Unknown” or blame the poor analyst
  - If a company finds the “root cause” will the regulators say – “your process is not validated”?
- “Process validation” is a “well rehearsed demonstration that three consecutive batches can be manufactured to be in conformance” – does not provide a means to assess process “stability” and “state of control” has to be documented via conformance to SOP’s - fixed process conditions (contrary to 2nd Law of Thermodynamics?) and end product testing

Negative Vocabulary: Other Examples

- "Change is bad"
  - "Don't rock the boat"
  - Uncertainty with respect to the potential impact of any change on manufacturability, quality, and performance
    - revalidation and prior approval process requirements
- Process improvement efforts to reduce variability
  - Often it is suspected that the primary reason for reducing variability by an innovator company is to block generic competition
  - "Your tolerance or acceptance criteria are too wide" (Regulators)

Scientific principles supporting innovation

- PAT is a system ...
  - enhance understanding and control the manufacturing process
  - used to meet the regulatory requirements for validating and controlling the manufacturing process
    - all critical sources of variability are identified and explained
    - variability is managed by the process
    - product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions
    - The ability to predict reflects a high degree of process understanding.

Going from a Negative to an Enabling Vocabulary

- Not a typical Agency guidance
  - Written for a broad industry audience in different organizational units and scientific disciplines.
  - Discusses principles with the goal of highlighting opportunities and developing regulatory processes that encourage innovation
  - Encourage the voluntary development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance approaches

Going from a Negative to an Enabling Vocabulary

- A focus on process understanding can facilitate risk-based regulatory decisions and innovation
- Continuous learning through data collection and analysis over the life cycle of a product is important
- With real time quality assurance, the desired quality attributes are ensured through continuous assessment during manufacture
  - Data from production batches can serve to validate the process and reflect the total system design concept, essentially supporting validation with each manufacturing batch.

Going from a Negative to an Enabling Vocabulary

- Data collected using an experimental tools should be considered research data
  - FDA's routine inspection ….. based on current regulatory standards
  - Data used to support validation or regulatory submissions will be subject to inspection

Going from a Negative to an Enabling Vocabulary

- 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
- 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

Going from a Negative to an Enabling Vocabulary

- When certain PAT implementation plans neither affect the current process nor require a change in specifications, several options can be considered
- The ASTM Technical Committee E55 - complimentary information for implementing the PAT Framework
  - Focus on control theory and not “testing to document quality”

Going from a Negative to an Enabling Vocabulary

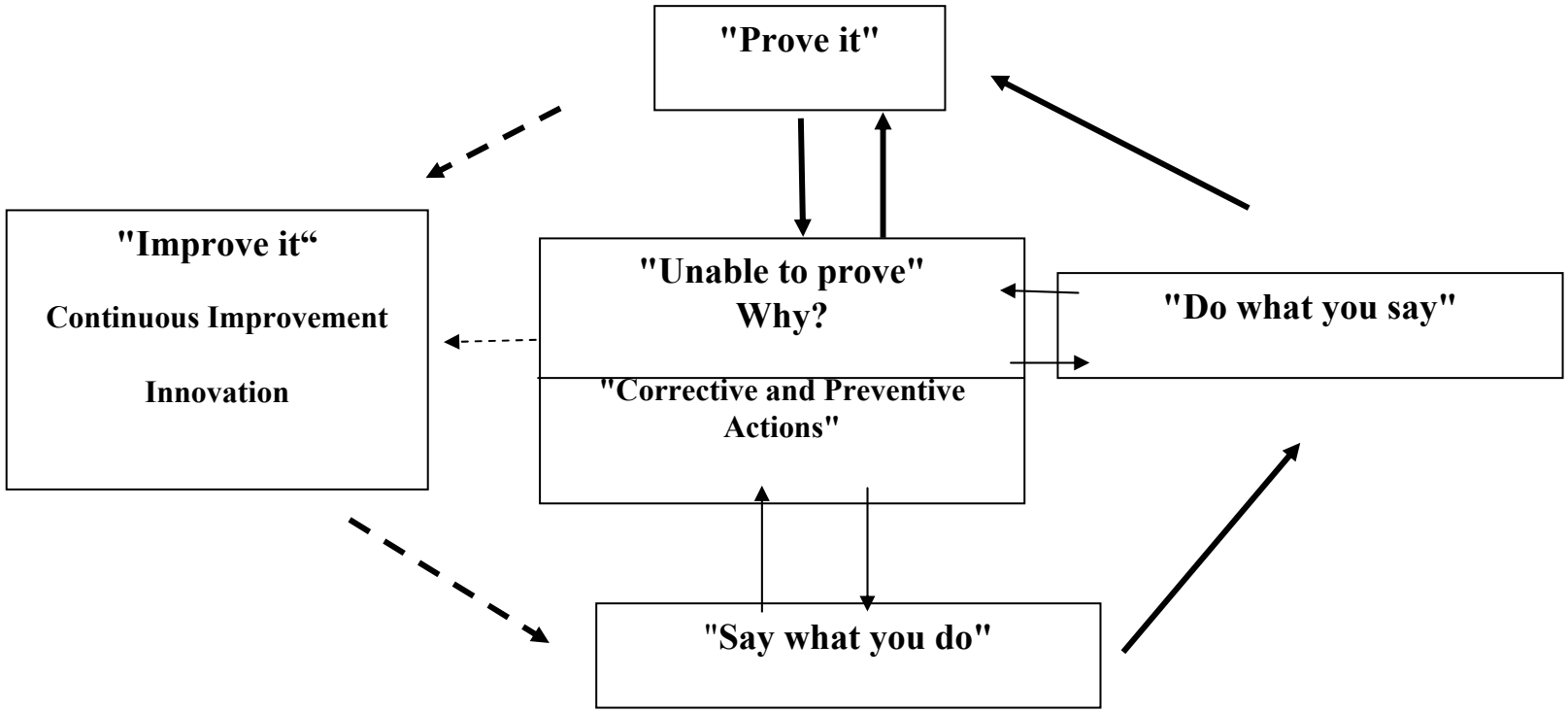
- The PAT Guidance is supported by
  - A PAT team approach for CMC review and CGMP inspections
  - Joint training and certification of PAT review, inspection and compliance staff
  - Scientific and technical support for the PAT review, inspection and compliance staff
  - The ASTM Technical Committee E55

PAT Provides the Pharmaceutical Context to many Productivity Improvement Tools

- TQM, Lean manufacturing, Six Sigma, Lean Six Sigma, and other trends in industry
  - "Lurching from Fad to Fad" or searching for an ideal system?
- Without the PAT Framework
  - Limited productivity and quality improvements are currently possible in pharmaceutical industry
  - Improving the quality of the "paper product"
  - Is it feasible or prudent to improve the efficiency of processes that are not well understood?

Modern Quality System

http://www.fda.gov/cder/gmp/index.htm



http://www.fda.gov/cder/gmp/gmp2004/manufSciWP.pdf

The CGMP Initiative & ICH

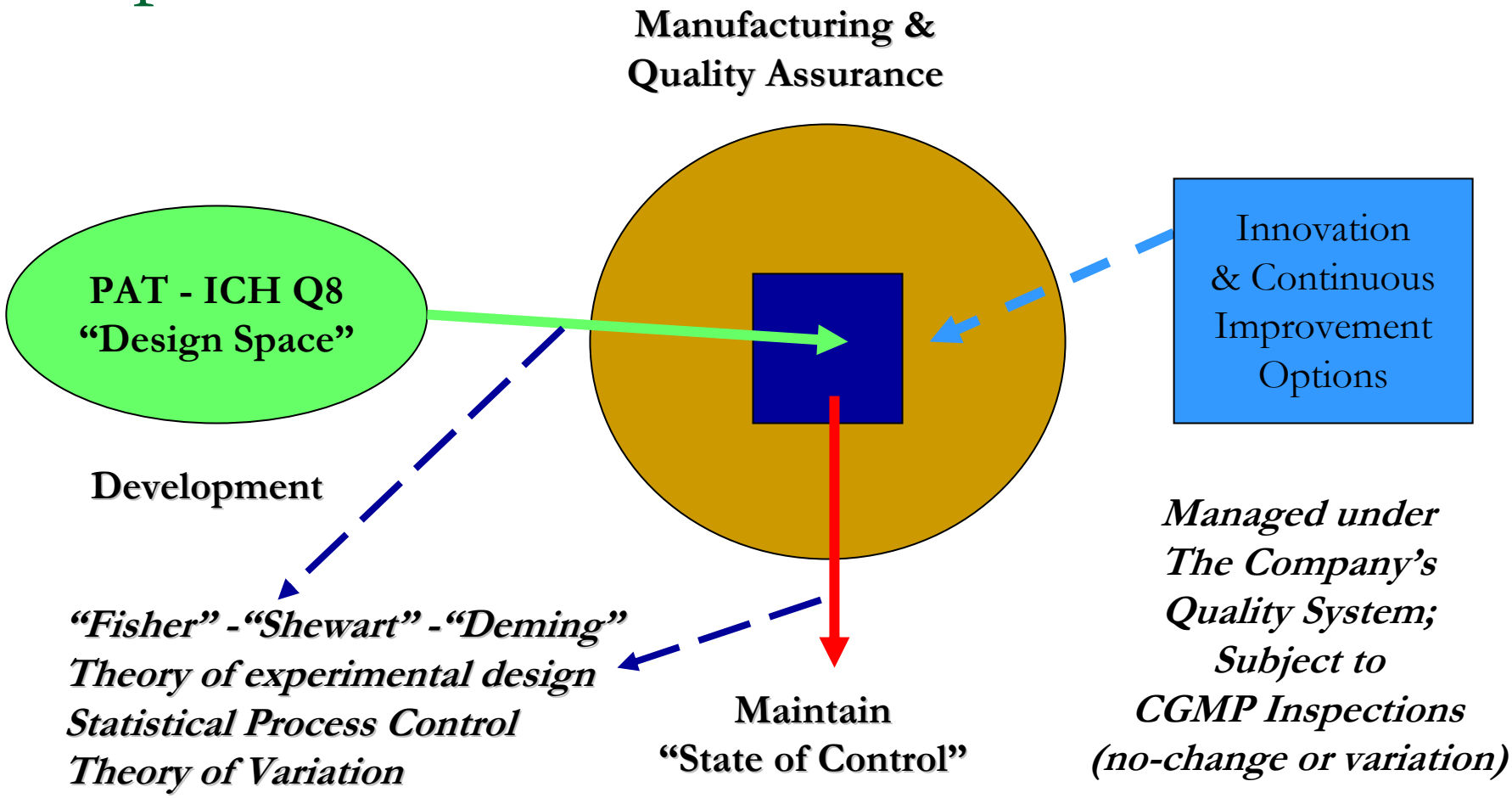
USA

- PAT Guidance
- CPG 7132c.08
- Comparability Protocol
- Quality Systems Approach to Pharmaceutical CGMP's
- A Vision for the future – the "desired state"

International

- ICH Q8 (Step 2)
  - A Vision for the future – the "desired state"
  - PAT definition and principles of QbD
  - Design Space
- ICH Q9
  - Risk tools and risk communication
- Proposed Q10
  - "Change control"

PAT: "Change Control" to "Continuous Improvement"



The "Desired State": A Shared Vision for the Future (ICH Q8 EWG)

1. Product quality and performance achieved and assured by design of effective and efficient manufacturing processes

2. Product specifications based on mechanistic understanding of how formulation and process factors impact product performance

3. An ability to effect Continuous Improvement and Continuous "real time" assurance of quality