BIBLIOGRAPHY

A. Useful Standards

1. ASTM Standards

E2363-04: Standard Terminology related to PAT

D 3764 - 01: Standard Practice for Validation of Process Stream Analyzer Systems.

D 4855 - 97: Standard Practice for Comparing Test Methods.

D 6299 - 02: Standard Practice for Applying Statistical Quality Assurance Techniques to Evaluate Analytical Measurement System Performance.

E 456-02: Standard Terminology Relating to Quality and Statistics

E1325-02: Standard Terminology Relating to Design of Experiments.

2. Parenteral Drug Association

PDA. May/June 2000. Technical Report No. 33: Evaluation, Validation and Implementation of New Microbiological Testing Methods. PDA Journal of Pharmaceutical Science and Technology 54(3) Supplement TR33

B. Literature

For additional information, refer to FDA's PAT Web page at http://www.fda.gov/cder/OPS/PAT.htm.

PAT – A Frame work for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance

Dr. Cris Watts, FDA/CDER

クリス・ワッツ博士（FDA/CDER）

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

PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

D. Christopher Watts, Ph.D.
Office of Pharmaceutical Science, CDER, FDA

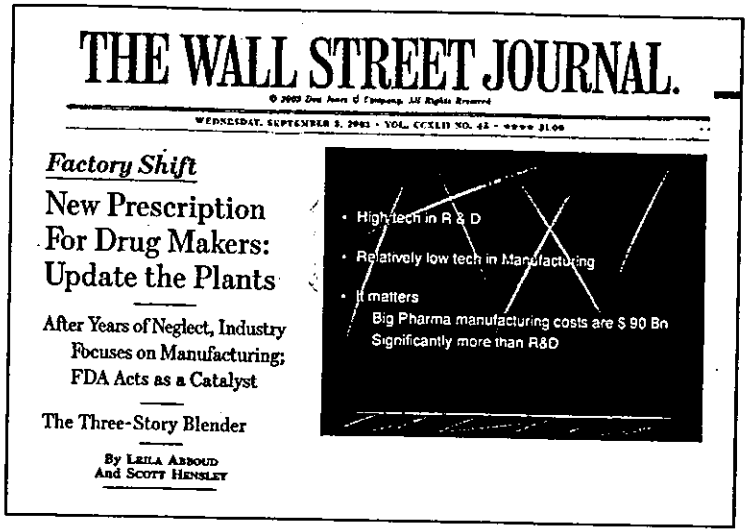
FDA/ISPE Guidance Workshop
December 8, 2004

Guidance Workshops

- Co-sponsored Public Workshops on PAT Guidance
  - ISPE, RPS
- London, UK
  - December 14, 2004
- Brussels, Belgium
  - February 22, 2005
- Mumbai, India
  - February 25, 2005

The Course

- History of PAT
- Guidance Overview
  - What is PAT?
  - Principles and Tools
  - Strategy for Implementation
- Regulatory Approach
  - Who is involved?
- Where are we going with PAT?



THE WALL STREET JOURNAL.

WEDNESDAY, SEPTEMBER 3, 2003 · VOL. CCXLII NO. 43 · ****¢ $1.00

Factory Shift

New Prescription For Drug Makers: Update the Plants

After Years of Neglect, Industry Focuses on Manufacturing; FDA Acts as a Catalyst

The Three-Story Blender

By Leila Abboud And Scott Hensley

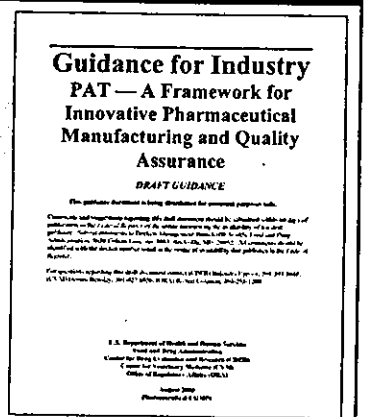
The Genesis of PAT: A Proactive Initiative

- Began at ACPS Discussions in July, 2001
- FDA Science Board Meetings (11/01, 4/02)
  - Current state of Pharmaceutical Manufacturing
    - Industrial Practice
    - FDA Regulation
  - Science Board support for FDA's proposal to facilitate innovation

http://www.fda.gov/cder/OPS/PAT.htm#scienceboard

Draft PAT Guidance

- Released September 3, 2003
- Public Comment through November 4, 2003 (http://www.fda.gov/ohrms/dockets)
- Involve FDA PAT Team
  - Review comments
  - CDER, ORA, CVM
  - Team Approach
  - Certification



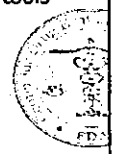
Guidance for Industry

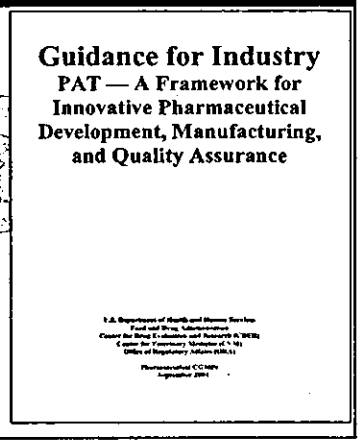
PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

DRAFT GUIDANCE

PAT Guidance

- Released September 29, 2004
- Scientific principles and tools supporting innovation
  - Process Understanding
  - PAT Tools
  - Risk-Based Approach
  - Integrated Approach
- Regulatory Strategy accommodating *innovation*
  - PAT Team approach to Review *and* Inspection
  - Joint training and certification of staff





Guidance Scope

- Framework founded on process understanding
  - facilitate innovation and risk-based regulatory decisions
- Two components:
  - Scientific principles and tools supporting innovation
  - Regulatory strategy to accommodate innovation
    - Team approach to review and inspection
    - Joint training and certification of PAT review and inspection staff

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

Guidance Scope

- Alleviate concern that innovation will result in regulatory impasse
- New and abbreviated new (human and veterinary) drug application products and specified biologics regulated by CDER and CVM, as well as nonapplication drug products
- Voluntary
- PAT system implementation for particular products, no need to extended to other products

PAT Framework

- The goal of PAT is to enhance understanding and control of the manufacturing process
- *quality cannot be tested into products; it should be built-in or should be by design.*
- allows more focus to be placed on relevant multi-factorial relationships
  - provides a basis for identifying and understanding relationships among various critical formulation and process factors and for developing effective risk mitigation strategies (e.g., product specifications, process controls, training)

PAT Framework: Process Understanding

- A focus on process understanding can reduce validation burden
  - providing more options for justifying and qualifying systems intended to monitor and control biological, physical, and/or chemical attributes of materials and processes
- Transfer of laboratory methods to on-, in-, or at-line methods may not necessarily be PAT
  - Existing regulatory guidance documents and compendial approaches on analytical method validation should be considered

PAT Framework: PAT = Process Understanding

- A process is well understood when:
  - all critical sources of variability are identified and explained
  - variability is managed by the process
  - product quality attributes can be accurately and reliably predicted
- Accurate and Reliable predictions reflect process understanding
- Process Understanding inversely proportional to risk

Principles and Tools

- PAT Tools
- Risk Based Approach
- Integrated Systems Approach
- Real Time Release

PAT Tools

- Multivariate tools for design, data acquisition and analysis
- Process analyzers
- Process control tools
- Continuous improvement and knowledge management tools
- An appropriate combination of some, or all, of these tools may be applicable to a single-unit operation, or to an entire manufacturing process and its quality assurance

PAT Tools: Process Analyzers

- Evolution of Process Analyzers
  - univariate process measurements (pH, T, P) to
  - nondestructive measurement of biological, chemical, and physical attributes of material
- Need not be absolute values of attributes
- Flexible process to manage material variability
  - justified when differences in quality attributes used to control (e.g.,feed-forward and/or feed-back) the process

PAT Tools: Multivariate Tools

- Products and processes are complex multi-factorial systems
  - physical, chemical, biological
- statistical design of experiments
  - one-factor-at-a-time experiments do not address interactions of product and process
  - ID critical product and process variables
- mathematical relationships
  - applicability and reliability of model predictions can be assessed by statistical evaluation

PAT Tools: Process Analyzers

- Comprehensive statistical and risk analyses of the process generally necessary
  - Assess the reliability of predictive mathematical relationships
  - Based on risk, a simple correlation function may need further support or justification (mechanistic explanation of causal links)
  - Installation on existing production equipment
- *Process signature* may be used for process control
  - when related to product and process quality

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
  - ahievement of process end points to ensure consistent quality
- End points = achievement of the desired material attribute (not process "t")
  - range of acceptable times likely to develop

PAT Tools: Process Control Tools

- 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
- Software validation via risk-based approach
  - recommendations provided by other guidances
  - information from consensus standards (ASTM)

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: Continuous Improvement and Knowledge Management

- Continuous learning through data collection and analysis over the life cycle of a product
  - contribute to justifying proposals for postapproval changes
- Within products and processes
- Across products and processes

PAT: Risk-Managed Approach to Regulatory Scrutiny

- Expect an inverse relationship between the level of process understanding and the risk of producing a poor quality product
- Well understood process → less restrictive regulatory approaches to manage change
- Focus on process understanding can facilitate risk-managed regulatory decisions and innovation

Real Time Release

- *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.

Integrated Systems Approach

- Necessary for evaluation and timely application of systems
- Across disciplines and organizations
  - upper management support critical

Research Data

- Suitability of PAT tool production equipment
  - risk analysis determine impact on product quality (prior to implementation)
  - within the facility's quality system without prior notification to the Agency
- Data collected using an experimental tool should be considered research data
  - intrinsic data trends may be observed
  - scientifically evaluate to determine affect on quality and implementation of PAT

Research Data

- FDA does not intend to inspect research data collected on an existing product for the purpose of evaluating the suitability of an experimental process analyzer or other PAT tool

Regulatory Implementation Strategy

- Flexibility, coordination, and communication critical to enable successful implementation of PAT
- Agency's regulatory strategy
  - 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 recommendations provided in this guidance

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PAT Regulatory Approach

- Tailor the regulatory scrutiny to meet the needs of PAT-based innovations that
  - improve the scientific basis for establishing regulatory specifications
  - promote continuous improvement
  - improve manufacturing efficiency while maintaining or improving the current level of product quality
- Goal is to facilitate a consistent scientific regulatory assessment involving multiple Agency offices with varied responsibilities

PAT Regulatory Approach

- Any questions contact PAT Team at PAT@cder.fda.gov
- All written correspondence clearly identified as PROCESS ANALYTICAL TECHNOLOGY or PAT.
- All marketing applications, amendments, or supplements to an application should be submitted to the appropriate CDER or CVM division in the usual manner

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Implementation Options

- Under the facility's own quality system
  - Inspections by the PAT Team or PAT certified Investigator can precede or follow PAT implementation.
- A supplement (PAS, CBE, etc) can be submitted prior to implementation
  - if necessary, an inspection can be performed by a PAT Team or PAT certified Investigator before implementation.
- A comparability protocol can be submitted
  - Following approval of this comparability protocol by the Agency, one or a combination of the above regulatory pathways can be adopted for implementation
- To facilitate adoption or approval, a preoperational review of a PAT manufacturing facility and process may be requested

The FDA PAT Team (ORA, CDER, CVM)

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Dennis Bensley, CVM/FDA
Patricia Lefler, ORA/FDA
Joe Famulare, CDER/FDA
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PAT Approach: Quality by Design

Focus on Process Understanding

- What parameters are critical to Product Quality?
  - Experimental Design
- How do we analyze these parameters?
  - K.I.S.
- How do we control these parameters throughout the process?
  - Feed-back/-forward

Questions to Consider

- Is this a PAT submission?
- PAT principles and tools:
  - Are the systems for design, measurement, control, continuous improvement and knowledge management acceptable?
  - Is the approach to risk management acceptable?
  - Is the strategy for integrating systems acceptable?
  - Is the strategy for real time release acceptable?
- Is the proposed regulatory process acceptable?

PAT and CGMP Initiative

- FDA CGMP Initiative
  - Risk-based regulation
  - "Non-impeding" regulation
  - Consistent regulation
- Success based on Broad Cooperation
  - Industry
  - Academia
  - FDA

http://www.fda.gov/bbs/topics/NEWS/2002/NEW00829.html

ASTM Technical Committee E55

- Technical Committee E55: The Pharmaceutical Application of Process Analytical Technology
  - Consensus Standards
  - Industry, Academia, FDA
  - Balanced
- ASTM International
  - Global
  - ANSI accredited
  - > 100 years experience
- Committee Organization
  - E55.01: PAT System Management
  - E55.02: PAT System Implementation and Practice
  - E55,90: Executive Committee
  - E55.91: Terminology
- NTTAA

Summary

- Not just analyzers
  - System for design, analysis, and control
  - Focus on Process Understanding
- Voluntary
- Several Options for Implementation
  - Existing Products and Processes
    - Research Data
  - New Products and Processes
  - Proposed by firm
- Team Approach to Regulation
  - Joint Training and Certification
  - Continued Training of FDA Staff

PAT – A Frame work for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance

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FDA

ISPE
THE SOCIETY FOR LIFE SCIENCE PROFESSIONALS

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

PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance

Ali Afnan, Ph.D.
Office of Pharmaceutical Science, CDER, FDA
FDA/ISPE Guidance Workshop
8th December 2004
Tokyo, Japan

What is PAT?

An Enabling Framework

- **For innovation in development, manufacturing and quality assurance by**
  - **removing "regulatory fear/uncertainty"**
  - **utilizing science & risk-based approach to regulatory requirements and oversight**
  - **providing a flexible and less burdensome regulatory approach for well understood processes**
  - **creating an environment that facilitates rationale science, risk, and business decisions**

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

The goal of PAT is to <u>understand</u> and <u>control</u> the manufacturing process

What is PAT?

Scientific principles and tools supporting innovation

- PAT Principles
  - Process Understanding
  - Risk-Based Approaches
  - Regulatory Strategy to accommodate innovation
  - Real Time Release
- PAT Tools
  - Multivariate data acquisition and analysis tools
  - Modern process analyzers or process analytical chemistry tools
  - Process and endpoint monitoring and control tools
  - Continuous improvement and knowledge management tools

What is PAT?

- Integrated Approach
  - PAT Team approach to Review *and* Inspection
  - Joint training and certification of staff

PAT

- Ensure appropriate control of all relevant critical attributes of in-process materials (e.g., using process endpoints) to allow the process to manage the inherent variability of <u>material attributes</u> that can impact the quality of the output

PAT Framework

PAT goals are achieved through

- Dynamic Processes that manage variability
- Using validated controls

Process Understanding?

- A process is well understood when:
  - all critical sources of variability are identified and explained
  - variability is managed by the process
  - product quality attributes can be accurately and reliably predicted.
- Accurate and Reliable predictions reflect process understanding
- Process Understanding inversely proportional to risk

What is a PAT application?

- Is this a PAT submission?
- PAT principles and tools:
  - Are the systems for design, measurement, control, continuous improvement and knowledge management acceptable?
  - Is the approach to risk management (assessment and mitigation) acceptable?
  - Is the strategy for integrating systems acceptable?
  - Is the strategy for real time release acceptable?
- Is the proposed regulatory process acceptable?

Process Understanding - Validation

- Can provide a high assurance of quality on every batch and provide alternative, effective mechanisms to achieve validation
  - process validation can be enhanced
    - possibly continuous quality assurance where a process is continually monitored, evaluated, and adjusted
    - using validated in-process measurements, tests, controls, and process endpoints
  - A process is controlled using validated controls

FDA PAT guidance and Qualification

A focus on process understanding can reduce the burden for validating systems, providing more options for qualifying and justifying systems intended to measure and control biological, physical, and/or chemical attributes of materials.

FDA PAT guidance and Qualification

Risk-based approaches are suggested for validation of PAT software systems. The recommendations provided by other FDA guidances such as *General Principles of Software Validation* should be considered. Other useful information can be obtained from consensus standards, such as ASTM.

PAT: Risk-Managed Approach to Regulatory Scrutiny

- Expect an inverse relationship between the level of process understanding and the risk of producing a poor quality product
- Well understood process → less restrictive regulatory approaches to manage change
- Focus on process understanding can facilitate risk-managed regulatory decisions and innovation

Real Time Release (RTR)

- Process understanding, control strategies, plus on-, in-, or at-line measurement of critical attributes
  - that relate to product quality
- provide a scientific risk-based approach to real time quality assurance

Real Time Release (RTR)

- 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
  - supporting validation with each manufacturing batch.

Real Time Release (RTR)

- Is the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data.

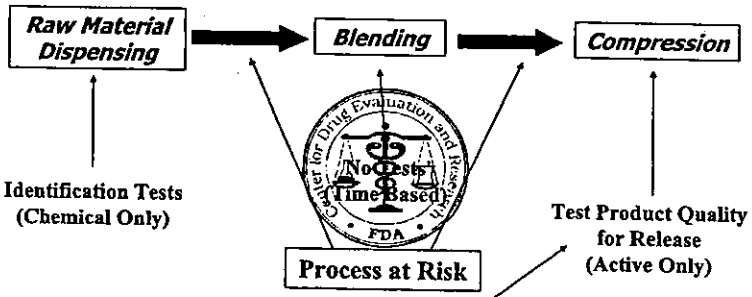
Real Time Release

- Typically, a valid combination of
  - material attributes
    - assessed using direct and/or indirect process measurements.
  - process controls
- serve as the basis for real-time release of the final product
- demonstrating each batch conforms to established regulatory quality attributes.

PAT Regulatory Process

- A flexible process
  - generally starts with a scientific proposal by a sponsor followed by discussions with PAT team
  - to ensure clear understating of scientific principles and the type of information and knowledge necessary to support the proposed application
- This discussion may lead to a regulatory submission (e.g., a supplement or a comparability protocol)
  - the guidance provides for other flexible options
- Evaluation/assessment of the submission and a team approach for ensuring all aspects are addressed and followed by a team based inspection

How can PAT help?
Example: Current Tablet Production



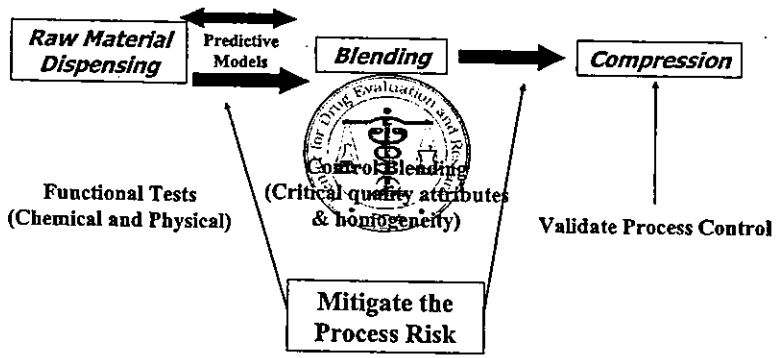
Current Tablet Production: Testing to Document Quality

- What is the Product Test?
  - Typically 30 Tablets/batch (1,000,000)
- What process Information does this provide?
  - None. Testing is Product-focused.
- Will we see "failures"?
  - Expect number of "failing" tablets/batch, even though 30 tablets/batch "pass"
  - 4% of batches may fail, even though not different from a "passing" batch
- Does this facilitate process understanding and control?
  - No

"Novel Technology" Approach: Still Testing to Document Quality

- What is the Product Test?
  - Test every tablet (all 1,000,000)
- What process Information does this provide?
  - None. Testing is still Product focused.
  - Better estimate of variability in Final Product
- Why the variability?
  - ?
  - Change acceptance criteria?
    - Allow some outside 75%-125%
- Facilitate process understanding and control?
  - No

PAT Approach Example: Tablet Production



Process Focused

PAT Approach: Quality by Design

Focus on Process Understanding

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  - Experimental Design
- How do we measure/ monitor these parameters?
  - Appropriate Instrumentation
- How do we control these parameters throughout the process?

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The goal of PAT is to <u>understand</u> and <u>control</u> the manufacturing process

Forthcoming Guidance Workshops

London, UK
December 14, 2004

Brussels, Belgium
February 22, 2005

Mumbai, India
February 25, 2005

www.ispe.org

Perspective on PAT and related challenges with Quality Regulations under Revised Pharmaceutical Affair Law

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Outline of Presentation

- Overview of quality regulations under the revised pharmaceutical affair law
- Product/process understanding and regulatory process
- Technical issues and challenges

ABOUT Process Analytical Technology

- Perhaps, PAT started in industry, especially manufacturing area in late 80's or earlier
- Health science (kouseikagaku) study on PAT:
  Kojima, Hiyama,Terashita, Yanagihara PHARMA TECH JAPAN 19、1471−1489, 2003
  -Implementation of ICH Q6A in Japan/Presentations by two US/EU companies/GMP quality assurance system
  -Significant benefits: Quality built in ("QbD")
  -Concerns: Real time release by Not So Robust NIR technique
- PAT seminar at Chiba University, July 2003
- Various PAT development activities in industry and in academic societies (ISPE, Seikiken & PDA)

Current Thinking: Regulatory Framework Process Analytical Technology

- As a Means of Process Control-No concern
- For real time release (skip/eliminate QC test): "combination of good process control and monitoring" is probably minimum. Key procedures must be reviewed/assessed (by reviewers and inspectors)
- Further technology development is needed; NIR could be better. Imaging technique to study heterogeneous materials.
- Visit to manufacturing plants in Germany by invitation of EFPIA (July 2003) and high activities in industry Anticipate PAT based product application any time soon

Paradigm Shift

Large Variability in Validation Practices

Paradigm 2 (Today)
- Process design
- Indirect process control
- Assurance with Validation and QC tests

Paradigm 3 (Future)
- Product and process understanding
- Direct and continuous monitoring
- Real time release ?
- Pharmacopeia standards still requirement Testing may not be

Paradigm 1

Quality control by QC test results ; JP test is NOT sensitive enough for process control

- JP content uniformity N=10

  $/M-X/ + 2.2 \times \sigma < 15\%$

e.g assay range 93.0%~105.0% batch size =500,000

When assay is 95.0%, σ has to be less than 4.5%

In a lot (500,000 tablets) with true σ of 4.5%, the number of tablets less than 75% label (Xi< 75% 4.4σ) is 1-2.

In a lot with true σ of 6.7%(90%), the number of tablets less than 75% of label is 673.

When assay is 100.0%、 σ has to be less than 6.8%

In a lot with true σ of 6.8%, the number f tablets less than 75% label is 53.

In a lot with true σ of 9.9% would have 11,000 tablets less than 75% of the label. Xi<75% 2σ