



Regulatory Perspective on PAT Implementation: From Development through Product Lifecycle

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Outline

➤ PAT Initiative

- History and Regulatory Milestones

➤ PAT Framework

- What is PAT and its Scope
- PAT Approach
- What is Not PAT
- Implementation Strategy
- Regulatory Options

➤ PAT Continuum...

➤ Closing Remarks

Opinions expressed in and during this presentation are author's opinions and may not necessarily represent the final views or policies of the USFDA [*21CFR 10.85(k)]

PAT Initiative: History

- Began at Advisory Committee for Pharmaceutical Science (ACPS) Meeting in July 2001
- FDA Science Board Meetings (Nov 01, April 02)*
 - Current state of Pharmaceutical Manufacturing
 - ◆ Industry Practice & FDA Regulations
 - ◆ Pharmaceutical Manufacturing and associated regulatory practices **did not adequately support** or facilitate innovation and continuous improvement
 - ◆ An innovative regulatory process was necessary to transform pharmaceutical manufacturing to meet the current and future needs of the US public
 - Science Board support for FDA's proposal to facilitate innovation
- ACPS - PAT Subcommittee Meetings
 - February, July, October 2002

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

Why **PAT** Initiative? **Industry Perspective**

Current Paradigm:

- Utilization levels - 30% or less
- Scrap and rework - plan for 5-10%
- Time to effectiveness - takes years
 - Many supplements in first few years
- Costs of Quality – in excess of 20%
- Hesitant to Innovate
 - Incentive?
 - “Don’t ask/Don’t tell”
- Manufacturing Costs: \$90 Billion*
 - *Significantly more than R & D*

Doug Dean, PriceWaterHouseCoopers, FDA Science Board, Nov 16, 2001

**Ray Scherzer, GSK, CAMP, FDA Science Board, Apr 2, 2002*

Why PAT Initiative?

Product Quality & Process σ

	Sigma	ppm Defects	Yield	Cost of Quality
Pharma →	2 σ	308,537	69.2%	25-35%
	3 σ	66,807	93.3%	20-25%
	4 σ	6,210	99.4%	12-18%
Semicon →	5 σ	233	99.98%	4-8%
	6 σ	3.4	99.99966%	1-3%

- Doug Dean & Frances Bruttin, PwC Consulting,
FDA Science Board Meeting, Nov 16, 2001

Why **PAT** Initiative?

Public Health Perspective

US Drug products are of high quality, **BUT:**

- **Increasing trend** toward manufacturing-related problems
- **Recalls** - 176 in 1998 rising to 354 in 2002
- Loss of availability of essential drugs
- Disruption of manufacturing operations
- Negative impact on new drug approvals
- **Efficient pharmaceutical development and manufacturing** are vital components of the “**Critical Path**” leading to an effective U.S. health care system

- Dr. Janet Woodcock, FDA Science Board Meeting, Nov 16, 2001

Why PAT Initiative?

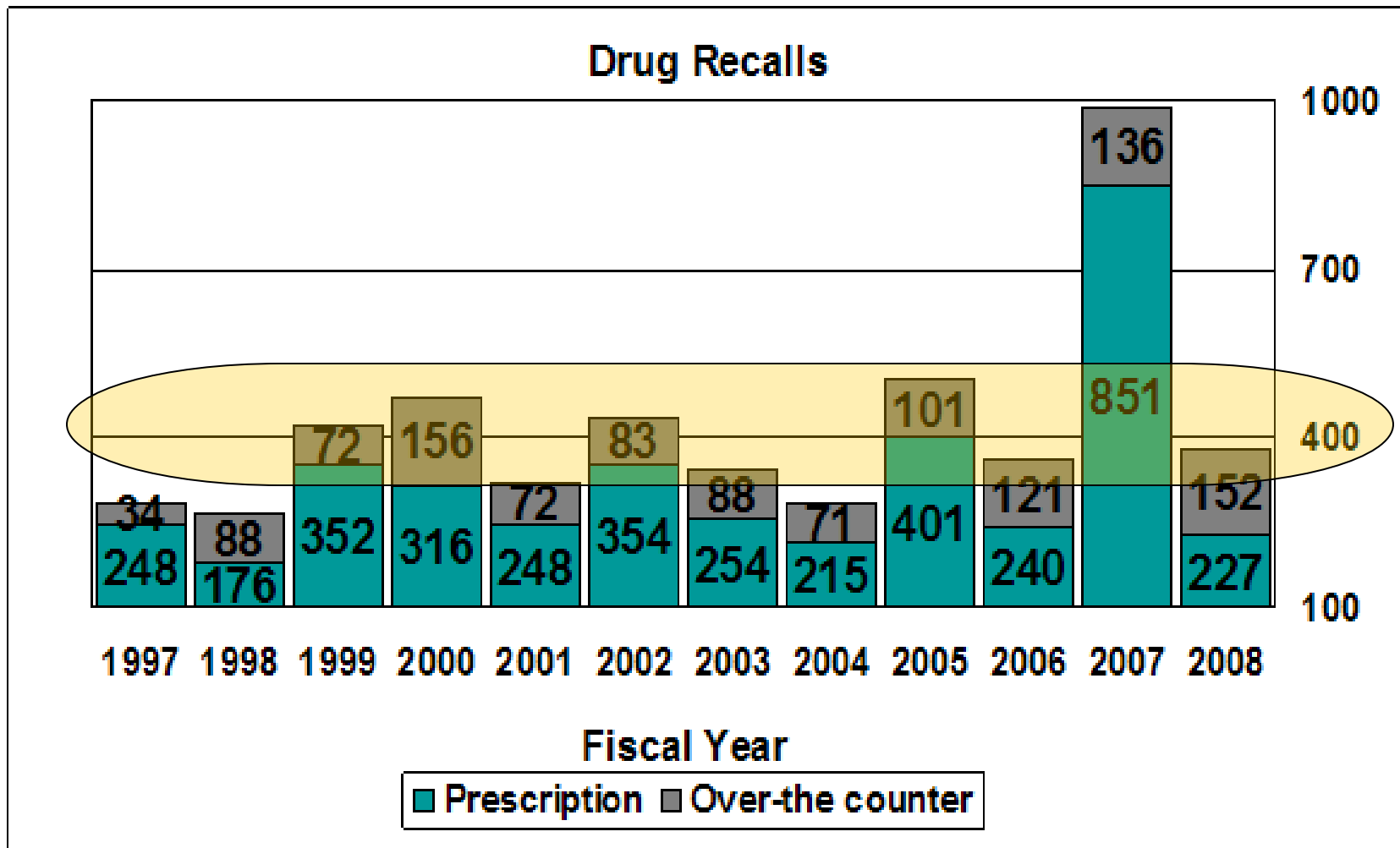
FDA Perspective

- An increasing **burden** on FDA resources:
 - ~ 4,000 manufacturing supplements annually
 - Unable to meet **statutory** biennial GMP inspection requirement
 - Lower scrutiny of non-domestic industry
- Cost implications for the industry from:
 - Low manufacturing and QA efficiency

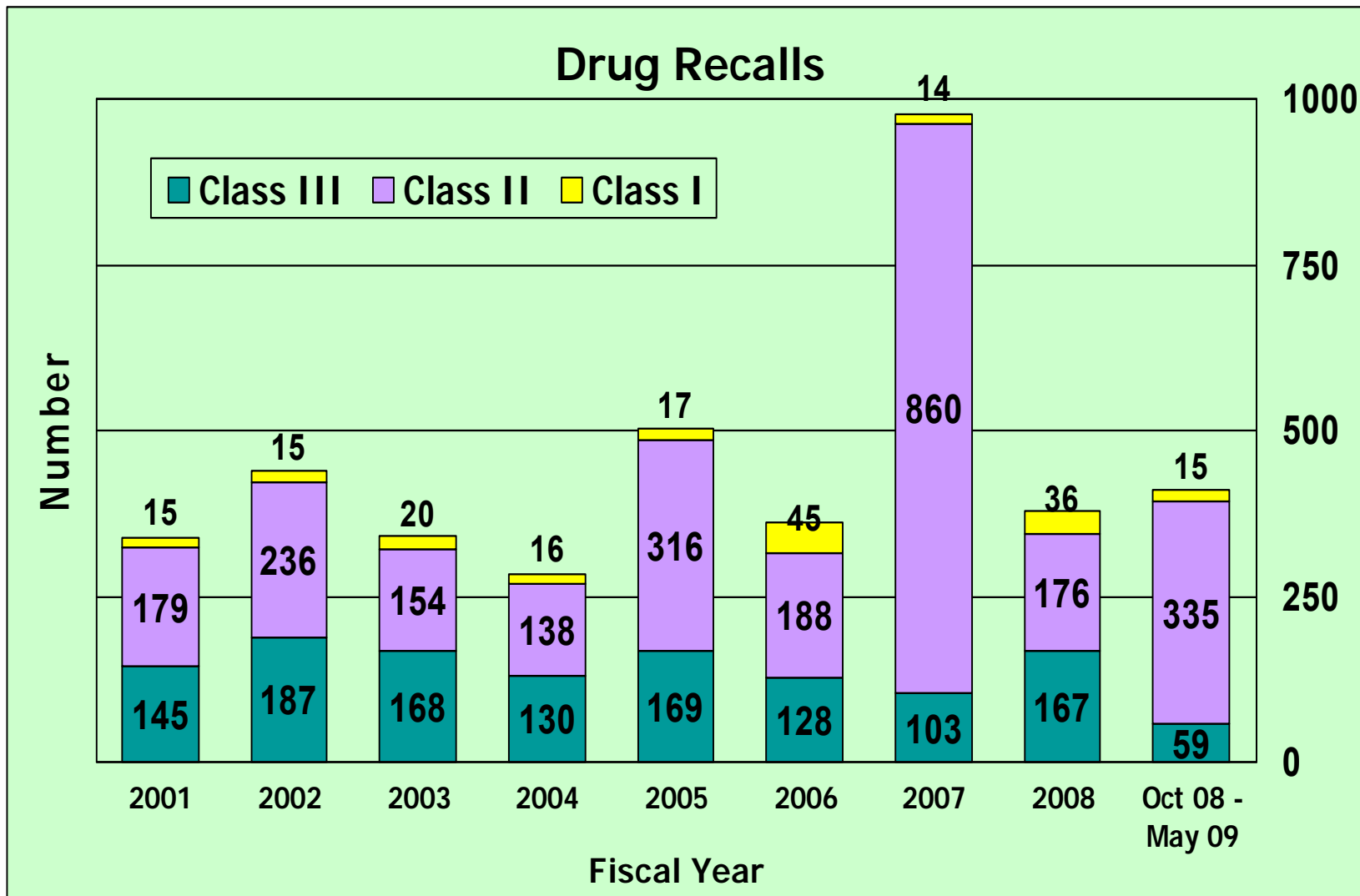
- Dr. Janet Woodcock, FDA Science Board Meeting, Nov 16, 2001

Human Drug Recalls Through FY 2008

Prescription vs. OTC



Human Drug Recalls Through May 2009 By Hazard Class



Human Drug Recalls Through FY 2008

➤ *Top reasons for recalls - FY2008*

● **CGMP Deviations**

- Impurities/Degradation Products
- Failed USP dissolution test requirements
- Presence of Foreign Substance(s)
- Marketed without an approved NDA/ANDA
- Defective Container
- Illegible Labeling
- Labeling: Incorrect or Missing Package Insert
- **Super potent** (Single Ingredient Drug)
 - Miscalibrated and/or Defective Delivery System
- **Sub potent** (Multiple Ingredient Drug)
- **Super potent** (Multiple Ingredient Drug)

FDA Resources

Challenging Task

- **Domestic US inspections:**
 - ~2,200 drug facilities (not medical gas)
 - ~1,000 inspections per year

- **Worldwide inspections:**
 - ~400 inspections per year in over 20 countries; ~3,500 facilities
 - ~60% are inspections of APIs

PAT Initiative: Why? - Summary

- Problems – CGMP Warning letters and Consent Decree
 - Are improvement efforts focused on the “right” issues?
- Pharmaceutical manufacturing and quality assurance lagging other sectors
 - Semiconductor (5 - 6 σ) vs. Pharma (2.5 σ)
 - Regulatory uncertainty
- Cost and availability implications
 - Manufacturing costs up to \$90 Billion
 - Exceeding R & D costs
- Increasing complexity of Drug Products
- **Recognition of opportunity for “Improvement”**

PAT Initiative: How?

- Focus on science in the interest of public health
 - Looking beyond “current” regulatory “blind” compliance
- A framework approach
 - Not a **regulatory** requirement or a “prescriptive” guideline
 - **Reduce** regulatory uncertainty and regulatory risk through team approach & training
- A **shared** vision for the future
 - The 21st Century “**desired state**”
- Let the **innovative** industry leaders leave their competition behind
 - Efficiency gains and regulatory flexibility
 - **PAT - the bridge to pharmaceutical Lean & Six Sigma type of programs**

“Desired State”

A **Mutual** goal of Industry, Society, and Regulators:

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

Janet Woodcock, M.D.
October 5, 2005

PAT Guidance

- Draft Guidance in Sept 2003
- Final guidance in Sept 2004
- An **Enabling** Framework approach
 - For innovation in development, manufacturing and quality assurance
- Not a **“how to”** guidance, but emphasis on
 - **Team approach** to review and inspection with joint training, certification, expert consultant and research support
 - **Systems approach** to provide flexibility to manufacturing and regulation
 - **To address** areas of regulatory uncertainty and fear
- Expanded to Biotech products

Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

Pharmaceutical CGMPs
September 2004

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf>



Office of Pharmaceutical Science (OPS) Process Analytical Technology (PAT) Initiative

- [Introduction](#)
- [FDA PAT Team Members](#) (ORA, CDER, CVM)
- [Steering Committee Members](#) (12/14/2005)
- [Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance](#) [[HTML](#)] or [[PDF](#)]
- [Presentations](#)
 - [Presentations and Meeting Information for the Process Analytical Technology Subcommittee of the Advisory Committee for Pharmaceutical Science](#)
 - [Advisory Committee for Pharmaceutical Science](#)
 - [FDA Science Board](#)
 - [Other Presentations](#)
- [Educational Activities](#),
- [Additional Information on Process Analytical Technology](#)
- [Other Resources](#)
- [Contact Us](#)

Introduction

The goal of PAT is to understand and control the manufacturing process, which is consistent with our current drug quality system: *quality cannot be tested into products; it should be built-in or should be by design.*

Outline

➤ PAT Initiative

- History and Regulatory Milestones

➤ PAT Framework

- What is PAT and its Scope
- PAT Approach
- What is Not PAT
- Implementation Strategy
- Regulatory Options

➤ PAT Continuum

➤ Closing Remarks

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PAT Guidance Scope

- Human and veterinary Drug Products
 - New and Abbreviated Drug Applications (NDA/ANDA) regulated by CDER
 - Specified biologics regulated by CDER and CVM
 - Non-application drug products
- PAT system implementation for a particular product does not imply extension to others
- **Voluntary** implementation
- **Team Concept** to product quality assessment
 - to Alleviate concern that innovation will result in regulatory impasse

PAT Framework...

The **scientific**, and **risk-managed** framework ..., *Process Analytical Technology* or PAT, is intended to support **innovation** and **efficiency** in pharmaceutical development, manufacturing, and quality assurance

PAT Framework...

- Founded on **process understanding** to facilitate
 - **innovation** and **risk-managed regulatory decisions** both by the industry and the Agency

- The framework has two components:
 - a set of **scientific principles and tools** supporting innovation and
 - a **strategy** for **implementation** that will accommodate innovation

What is PAT ?

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

- ICH, ASTM, and PAT

The term, *Analytical* in Process Analytical Technology is viewed broadly to include *chemical*, *physical*, *microbiological*, *mathematical*, and *risk analysis* in an **integrated** manner.

What is PAT ?

Instruments

Manufacturing Execution
SystemsProcess
ModelsData
Communications
Infrastructure

“PAT is considered to be a
system

SOPs

Raw
Materials
DataPredicted
CQAs

for designing, analysing, and
controlling manufacturing
through timely measurements of
critical quality attributes and
performance attributes... with
the goal of ensuring final product
quality”

Regulatory
ApprovalControl
ModelsReal-Time
Data
ManagementAnalysis
toolsProcess Equipment
DevelopmentMechanistic
ModelsProcess
Control
Systems

What is PAT ?

“PAT is considered to be a *system* for
designing

analysing, and controlling manufacturing
through timely measurements of critical
quality attributes and performance
attributes... with the goal of ensuring final
product quality”

The Manufacturing Process

Adapted from Gawayne Mahboubian-Jones, © 2006 Optimal Industrial Automation

What is PAT ?

“PAT is considered to be a *system* for designing
analysing

and controlling manufacturing through timely measurements of critical quality attributes and performance attributes... with the goal of ensuring final product quality”

**The Condition of the Process material
And...**

**Measuring the Critical Quality Attributes
during the Process**

What is PAT ?

“PAT is considered to be a *system* for designing, analysing and

controlling

manufacturing through timely measurements of critical quality attributes and performance attributes... with the goal of ensuring final product quality”

The Trajectory of the Manufacturing Process

To ensure that one can and does achieve the desired final Critical Quality Attributes

What is **PAT** ?

“**PAT** is considered to be a system for **designing**, **analysing**, and **controlling** **manufacturing** through timely measurements of critical quality attributes and performance attributes... with the goal of ensuring final product quality”

So to implement **PAT**
one must do **all THREE**

How and Why to Apply **PAT** ?

“PAT is considered to be a system for designing, analysing, and controlling manufacturing through timely measurements of critical quality attributes and performance attributes... with the goal of ensuring final product quality”

Definitions of Some Key Terms

➤ Critical Quality Attribute (CQA)

- A quality attribute that must be controlled within predefined limits to ensure acceptable product quality

➤ Attribute

- A characteristic or inherent property or feature

CQAs are measures of the product (in-process and final)

ASTM E55 Terminology

Definitions of Some Key Terms

➤ Parameter

- A measurable or quantifiable characteristic of a system or process

Parameters are measures of the process

- Equipment, environment, systems and processes

ASTM E55 Terminology

Definitions of Some Key Terms

➤ Control

The **action** or **ability** to *direct*, *measure*, and *improve* performance and output of a process or system

The feedback loop of a process through which actual performance is measured.

- American Society for Quality (ASQ)

CONTROL systems are NOT paper records

PAT Framework: Principles & Tools

1. PAT Tools supporting innovation

- a) Multivariate tools for design, data acquisition and analysis
- b) Process analyzers
- c) Process control tools
- d) Continuous improvement and knowledge management tools

2. Scientific Principles

- a) Risk-Based Approach
- b) Integrated Systems Approach
- c) Real Time Release

An appropriate **combination** of *some*, or *all*, of these tools can be applied to...

- **single**-unit operation,
- **more than one** Unit Operation or
- an **entire** manufacturing process and its quality assurance



PAT Approach

PAT Approach

- Product quality and performance
 - Ensured through **design** of effective and efficient (well understood) manufacturing processes
- Product and process **specifications**
 - Based on a *mechanistic* understanding
 - How formulation and process factors affect product performance
 - Process knowledge becomes the basis for specifications
- Continuous *real time* control of manufacturing, quality assurance and opportunity for *real time release* under the oversight of *Quality Unit*
 - Output validates the performance of the process
 - Each batch is an opportunity for optimization

PAT Approach..

- Goal is to move away from uncertainty-based (current) state to a risk-managed (desired) state to
 - Support relevant regulatory policies and procedures
 - Establish relevant and effective Standards

- For Any Process...
 - **Minimize** (or Reduce) Uncertainty
 - **Quantify** Risk (to product quality)
 - **Manage** Variability (feed forward and feed back control)
 - Capture, retain and utilize **knowledge**

A large, faint, circular seal of the Center for Drug Evaluation and Research (CDER) is visible in the background. The seal features a central figure holding a scale of justice, with a caduceus (a staff with two snakes) behind it. The text 'Center for Drug Evaluation and Research' is written around the top inner edge, and 'FDA' is at the bottom. Two small dots separate the top and bottom text.

Process Understanding, Controls and Risk

Process Understanding..

Can be realized When:

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

Assessment of Process Understanding...

- The ability to predict product CQAs **reflects** a high degree of process understanding
 - Retrospective process capability data indicative of a state of control, but may be insufficient to gauge or communicate process understanding.
- Continual learning over the life cycle of a product is important and vital for continuous quality assurance

Process Understanding and Real Time Control

- The desired quality attributes
 - ensured through **continuous assessment** and **control** during manufacture
- Data from production batches validates the process
 - reflecting the **total system** design concept
- Supports validation with each manufacturing batch

Process Understanding and Risk

- Process understanding and controls **reduce** the **risk** of producing a poor quality product
 - i.e., Process understanding with validated controls is **inversely** proportional to risk (to product)
- Well understood and controlled process
 - less restrictive regulatory oversight to operate and manage change
- Focus on process understanding, controls and the facility's Quality System
 - Can facilitate risk-managed innovation and regulatory decisions

Real Time Release (RTR)*

- The **ability** to evaluate and ensure the acceptable quality of in-process and/or final product based on process data and ...
 - Valid combination of
 - ◆ Assessed material attributes using direct and/or indirect **timely** measurements
 - ◆ process controls
- Conceptually, this can serve as the basis for real time release of the final product
 - By demonstrating each batch conforms to established regulatory quality attributes.

*meets the requirement of CGMP 21 CFR 211.165

Process Understanding - Validation

Focus on Process Understanding

- Can provide alternative, effective mechanisms to achieve validation with a **high degree** of quality assurance of quality on **every** batch
 - Process validation can be enhanced and possibly consist of 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
- Thus, it can **surpass** the expected benefits of 'Conventional' Process Validation, Qualification and Change Control and may reduce regulatory oversight

Process Understanding – How?

How does one “begin to understand” the process?

- Choose relevant “quality attributes” to understand
 - ◆ Conduct appropriate Design of Experiments
- Design, define and establish the “Design Space”
- Implement and validate “control”

Process Understanding – How?

Focus on:

- What parameters are **critical** to **Product Quality**?
 - Design of Experiment (DoE)
- How to **analyze** these **parameters**?
 - K.I.S.S (Keep It Simple Scotty!)
- How to **control** these **parameters** throughout the process?
 - Feed-back/ feed-forward loops as applicable

Process Understanding – How?

Design of Experiment:

➤ Elucidates

- Relationship & significance of inputs and outputs
- Relationship between variables, and their action on one another; as well as the output (i.e. dependencies)

➤ Can **facilitates** harvesting knowledge in the design space

- Institutional knowledge becomes a key tool

➤ Can **define** the design space

➤ Can **validate** control design and control limits


Process Control Strategy – How?

- **Identify and measure CQAs** (process and product)
 - Measure limits of acceptable variability
 - Ascertain sources of variability
 - Define critical process steps
- **Design a process measurement system**
 - Real time or near real time monitoring of CQAs
 - Develop mathematical relationship between product CQAs and measurement of critical material and process attributes
- **Define and design the Controls** (strategy, limits, methods, etc.)
 - Implement the controls
 - Qualify controls
- **Verify and optimize process specifications**
 - Throughout the manufacturing life cycle

What is *NOT* PAT?

(In *Absence* of Process Understanding)

- Use of process analyzers on-line = alternate analytical method (not = PAT)
- Real time monitoring (on-line or at-line measurement) **alone** will NOT qualify as PAT
- Increase of in-process sample size or automated end product testing are NOT PAT
- Transfer of laboratory methods to on-, in-, or at-line methods may not necessarily be PAT
- Automation or Robotics is not PAT
- Absence of understanding, and no plans for learning or controlling the mfg process

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PAT System Implementation Strategy and Regulatory Process

PAT Implementation Feasibility Studies

- To evaluate **suitability** of a PAT tool either on experimental or in production equipment (e.g., on- or in-line process analyzer), it is **recommended** that
 - **risk analysis** be conducted to determine **impact** on product quality (prior to installation)
 - This can be accomplished within the facility's Quality System without prior notification to the Agency
- Data collected using an *experimental* tool should be considered **research** data
- If feasibility studies are conducted in a production facility, it should be under the facility's Quality System

PAT Implementation Feasibility Research Data

- Certain data trends intrinsic to a currently acceptable process if observed,
 - should be evaluated scientifically to determine their effect on quality and implementation of PAT tools
- FDA does **not** intend to inspect research data while
 - collected on existing product for the purpose of evaluating feasibility of such tools
- Any FDA decision to inspect research data would be based on
 - exceptional situations similar to those outlined in Compliance Guide Sec. 130.300.
- Those data used to support validation or regulatory submission will be subject to inspection in the usual manner.

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 (CBE, CBE-30, PAS, 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 (CP) 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 of a PAT process, manufacturers may request a **pre-operational review** of a PAT manufacturing facility and process

PAT: Regulatory Process

- **Flexible** approach - initiated by the applicant
- Communicate with the Agency's PAT Team or the CMC Team from respective Office
- Discuss an appropriate route to submit information to the Agency
- Request a Pre-Operational Review (POR) of the mfg site by PAT Review-Inspection-Compliance Team (PATRIC)
- Implement within the Quality System framework – under Continuous Improvement

PAT Initiative: Regulatory Milestones

- PAT Guidance publication – September 2004
- PAT Team Certification, September 2004
- 1st PAT submission:
 - 1st Comparability Protocol (CP) for PAT systems implementation for an approved DP, Oct 2004
 - ◆ CP approved, December 2004
 - ◆ Pre-Operational Review of mfg facilities and **Team model** for CP assessment
- CMC Pilot Program Announcement, July 2005
 - 1st NDA including CP for PAT systems implementation, 2006
 - ◆ NDA and the CP were approved in 2008
- OBP Pilot Program Announcement, June 24, 2008
 - Request for participation by Sept 2009

The FDA PAT Team: ORA, CDER, CVM

Current

PAT Review – Inspection Team

Investigators (ORA):

Rebeca Rodriguez (ORA)
Erin McCaffery (ORA)
George Pyramides (ORA)
Dennis Guilfoyle (ORA)

Compliance Officers:

Albinus D'Sa (CDER)
Mike Gavini (CDER)
Brenda Uratani (CDER)
Vibhakar Shah (CDER)
William Bargo (CVM)

Reviewers:

Norman Schmuff (CDER)
Lorenzo Rocca (CDER)
Rosario D'Costa (CDER)
Bryan Riley (CDER)
Raafat Fahmy (CVM)

Steering Committee

Patricia Alcock (ORA)
Dennis Bensley (CVM)
Joe Famulare (CDER)
Keith Webber (CDER)
Frank Holcomb (CDER)
Moheb Nasr (CDER)

Helen Winkle, Chair (CDER)

PAT Policy Development Team:

Chris Watts, (CDER)
Ali Afnan, (CDER)

PAT Training Coordinators:

See Lam (CDER)

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PAT Continuum

Where are we now?

➤ PAT Training Program Update

- 2nd PAT Team Training – Sept 2007
 - ◆ 35 Participants
 - Product Specialists (CDER, CBER, CVM)
 - Field Investigators (ORA)
- 3rd PAT Team Training – Sept 2009
 - ◆ 36 participants
 - Product Specialists (CDER)
 - Field Investigators (ORA)
 - International Regulators (EMEA, TGA)

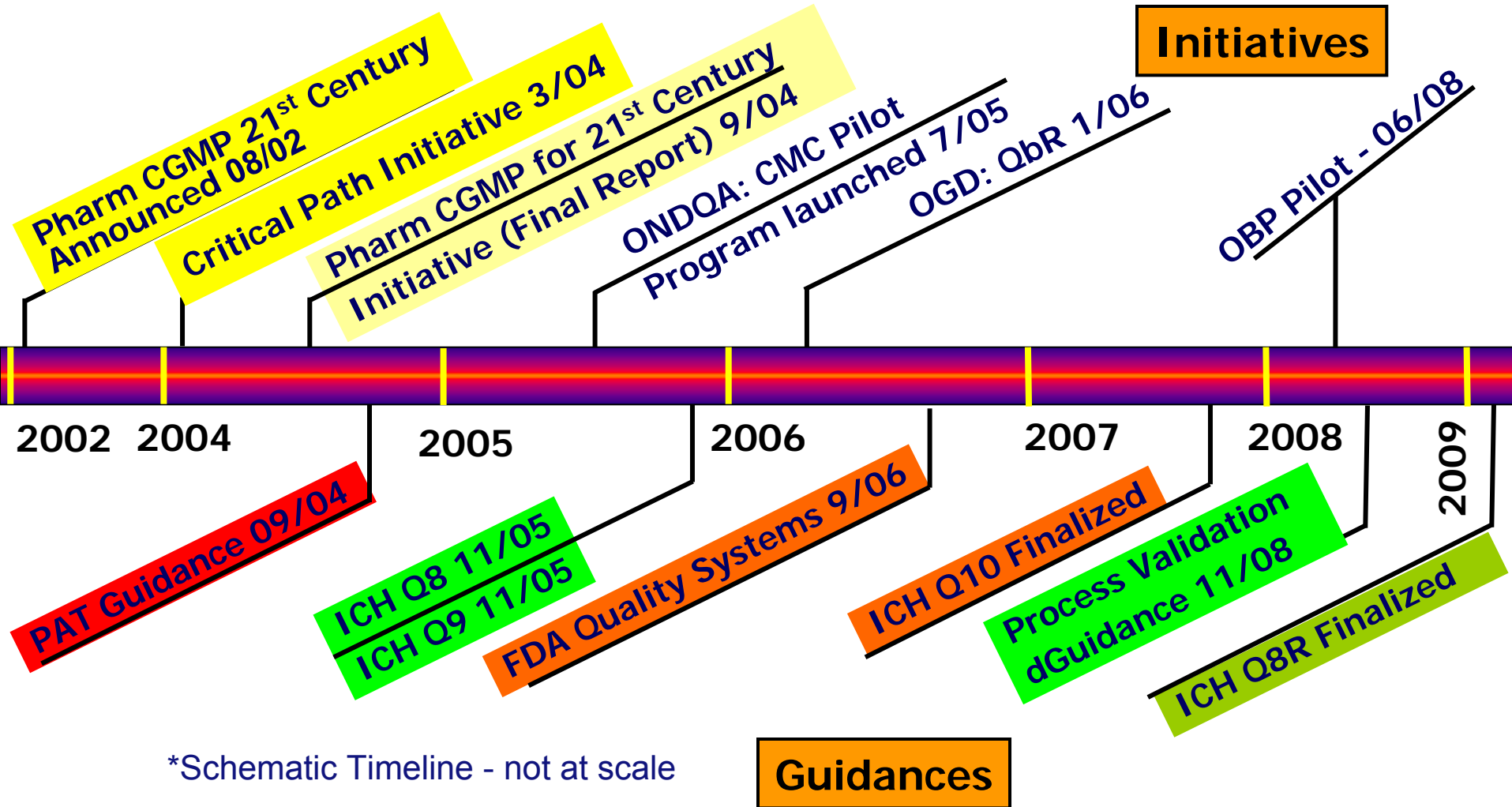
➤ FDA Quality Initiatives - Continuum

- Pharmaceutical CGMPS for 21st Century to Now
 - ◆ PAT, QbD, Quality Systems...
 - ◆ ICH Quality Vision



FDA Quality Initiatives – Continuum*

“Pharm. CGMPS for 21st Century” to Now



*Schematic Timeline - not at scale

Guidances

PAT and QbD - demystified

“....if you truly understand FDA’s new paradigm, you’d understand that **PAT** is really the **underpinning** of the entire concept of **Quality by Design**, that is understanding process.”

Helen Winkle
Director
OPS, CDER, FDA

PAT and QbD

If **QbD** is the **vision** for 21st Century
Pharmaceuticals....

PAT Framework

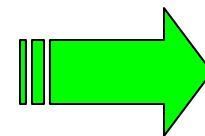
(as explained in the Guidance)

can be considered as
an enabling, **flexible regulatory**

Roadmap

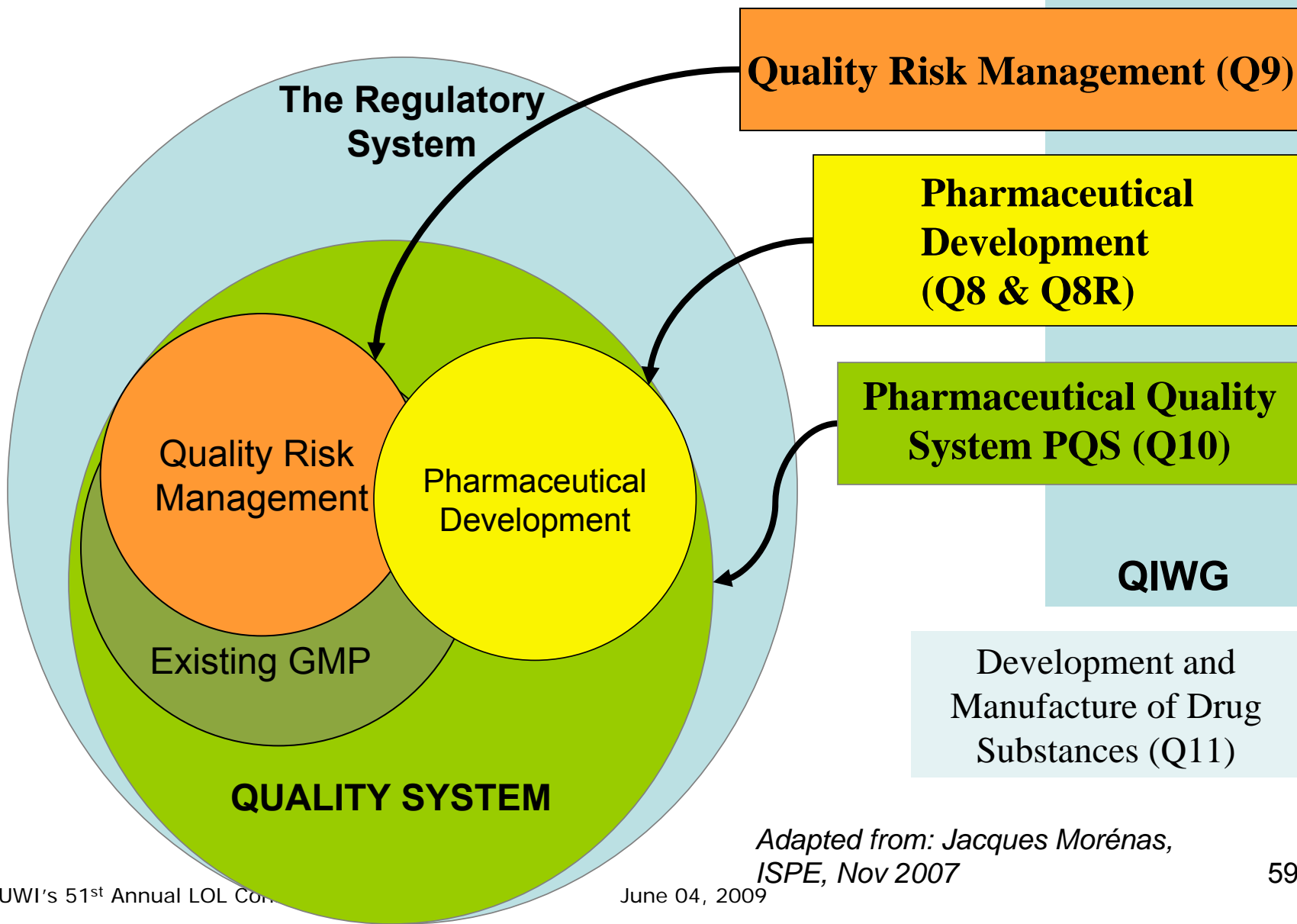
to achieve this vision
from beginning of development
through

Product Life Cycle



ICH Vision for Pharmaceutical Quality

“Pharm. CGMPs for 21st Century” to Now



Adapted from: Jacques Moréas,
ISPE, Nov 2007

June 04, 2009

CDER Offices: Quality Initiatives

“Pharm. CGMPS for 21st Century” to Now

➤ Office of Pharmaceutical Science

- Office of New Drug Quality Assessment (ONDQA)
- Office of Biotechnology Products (OBP)
- Office of Generic Drugs (OGD)

➤ Office of Compliance

- Division of Manufacturing and Product Quality (DMPQ)

Office Of Compliance/DMPQ

“Pharm. CGMPS for 21st Century” to Now

- Implementing Manufacturing Modernization in the 21st Century
 - Pharmaceutical cGMPS for the 21st Century: A risk-based Approach
 - ◆ <http://www.fda.gov/Cder/gmp/> , Aug 2002, Sept 2004
 - Process Analytical Technology Guidance
 - ◆ <http://www.fda.gov/cder/guidance/6419fnl.pdf>, Sept 2005
 - Quality Systems Approach to pharmaceutical CGMP Regulations
 - ◆ <http://www.fda.gov/cder/guidance/7260fnl.pdf> Sept 2006

Office Of Compliance/DMPQ

"Pharm. CGMPS for 21st Century" to Now

- Implementing Manufacturing Modernization in the 21st Century
 - ICH Q9 Quality Risk management
 - ◆ <http://www.fda.gov/cder/guidance/7153fnl.pdf>, June 2006
 - ICH Q10 Pharmaceutical Quality Systems (PQS)
 - ◆ <http://www.fda.gov/cder/guidance/7891dft.pdf>, July 2007
 - **Process validation:** General principles and Practices, Draft Guidance issued, Nov 27, 2008
<http://www.fda.gov/cder/guidance/8019dft.pdf>
- Enhancing Center-Field synergy to facilitate changes under a firm's PQS
 - Knowledge Transfer Initiative

Process Validation - Life Cycle Approach

- **Process Validation - a cGMP requirement**
- **Process Validation is not**
 - a one time event dependent on X number of batches
 - based on non statistical and non representative samples
- **Process validation lifecycle**
 - **Process Design**
 - ◆ Lab, pilot, small scale and commercial scale studies to establish process
 - **Process Qualification**
 - ◆ Facility, utilities and equipment
 - ◆ Performance Qualification
 - **Commercialization:**
 - ◆ Monitor, collect information, assess
 - ◆ Maintenance, continuous verification, process improvement.
- **Requires Statistical Quality Control criteria for**
 - Appropriate acceptance or rejection levels

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

Knowledge Transfer Initiative

Center-Field Synergy

- Formal process to **share** product specific knowledge from the application review under Prior Approval Inspection (PAI) compliance program (7346.832)
 - Between CDER and Office of Regulatory Affairs (ORA)
 - Creates “handshake” from Center to ORA
 - Similar to technology transfer from R&D to commercial scale-up and manufacture

- DMPQ/OC recommends product specific areas of coverage for the PAI
 - Where data integrity may be questionable
 - Where proposed manufacturing controls are either in question or need additional technical input and collaboration for a more integrated approach for review, inspection and compliance evaluation of the manufacturing site

ONDQA: QbD Initiative

- **FR Notice of CMC Pilot Program:**
 - Submission of CMC Information in a New Drug Application under the New Pharmaceutical Quality Assessment System; [Docket No. 2005N-0262], announced on July 7, 2005
 - ◆ http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4187B1_01_10-FR-7-14-05.pdf
 - Program Participation Request:
 - ◆ Deadline to request for participation: March 31, 2006
 - ◆ Deadline to submit NDA or supplement: March 31, 2007
 - **Goal:** 12 original NDAs and supplements
 - **Status:**
 - ◆ 9 original and 3 supplemental NDAs accepted
 - ◆ 11 submitted to date: 8 approved, 3 under review (as of Jan 1, 2008)

- Christine Moore, Deputy Director, ONDQA, IFPAC-2009

OBP: QbD Initiative

➤ FR Notice of Pilot Program:

- Submission of Quality Information for Biotechnology Products in the Office of Biotechnology Products [Docket No. FDA-2008-N-0355], June 24, 2008
- Program Participation Request:
 - ◆ Written and electronic
 - ◆ September 30, 2009

<http://edocket.access.gpo.gov/2008/E8-14999.htm>

OGD: Question based Review (QbR)

A New Quality Assessment System for Generic Drugs

**FDA's Pharmaceutical cGMP
for the 21st Century
QbD Initiative**

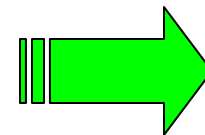
**Generic Sponsor:
Implementing
QbD in development
and manufacturing**

**FDA Office of
Generic Drugs:
Developed a Question-
based Review System
that assesses sponsor's
QbD ANDAs**

- Lawrence Yu, Director for Science, OGD, IFPAC-2009

Closing Remarks

- Agency's PAT guidance is an **enabling, science-driven**, and a **risk-managed flexible** regulatory framework to **facilitate innovation** and **efficiency** in drug development, manufacture, quality assurance and continual improvement through product life cycle.
- Agency **encourages** Industry to employ PAT/QbD principles routinely in their drug development, manufacture, quality assurance and management of product life cycle.
- Agency is **willing** and **available** to discuss and **facilitate** the regulatory approach you choose for the implementation of PAT System in the manufacture of your drug product.



PAT Contact Details

Please send questions or comments regarding **PAT Implementation** to:

- pat@cder.fda.gov

OR

- **Process Analytical Technology Team**
Center for Drug Evaluation & Research
U S. Food & Drug Administration
Building 51, Room 4334
10903 New Hampshire Ave
Silver Spring MD 20993-0002

Desired State

A **Mutual** goal of Industry, Society, and Regulators:

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

Janet Woodcock, M.D.
October 5, 2005

Thank you

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