The Process Analytical Technology Initiative: PAT and the Pharmacopeias

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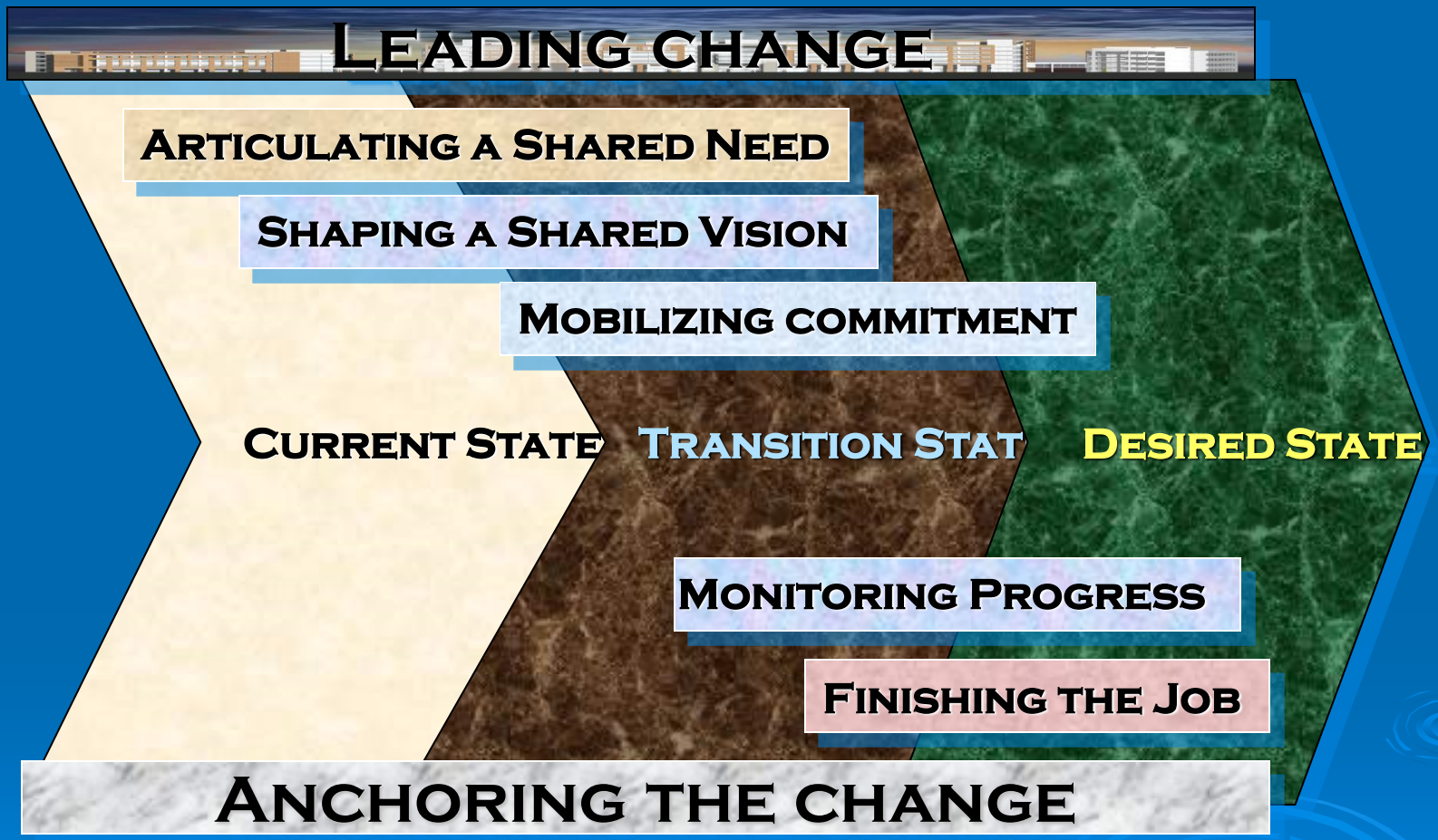
Presentation Outline

- The PAT Initiative
  - A part of the Pharmaceutical Quality for the 21st Century Initiative
- PAT and the USP
  - Opportunities for the USP to support the PAT Framework



Change Model, adapted for the purpose of outlining this presentation, from Quality Progress, April 2004

Articulating a Shared Need

- **US Drug products are of high quality, But..**
  - Increasing trend toward manufacturing-related problems
  - Low manufacturing process efficiency--cost implications
  - Innovation, modernization and adoption of new technologies slowed
  - High burden on FDA resources

Dr. Janet Woodcock, FDA Science Board, 2001 &2002

Articulating a Shared Need

- **Analysis of Industry Factors**
  - **Reluctance to innovate/invest in manufacturing sector - poor stepchild compared to R&D?**
  - **Emphasis on getting product out discourages early work on process and changes after marketing**
  - **Possible role of regulatory oversight--unintended consequences**

Dr. Janet Woodcock, FDA Science Board, 2001 &2002

Articulating a Shared Need

- **Analysis of Regulatory Role**
  - **Thirty years ago--FDA's emphasis was on institution of basic procedures and recordkeeping--evolved to cGMP**
  - **Currently: FDA attempting to drive innovation and investment in manufacturing sector via compliance/enforcement actions**

Dr. Janet Woodcock, FDA Science Board, 2001 &2002

Shaping a Shared Vision

- **Opportunity**
  - Empirical methods are probably approaching their theoretical maximum effectiveness
  - New scientific understanding & new technologies can provide science-based approaches
  - Plan: Use PAT as model

Dr. Janet Woodcock, FDA Science Board, 2001 &2002

Shaping a Shared Vision: Team Approach to CMC Review and CGMP Inspection

PAT Steering Committee

Doug Ellsworth, ORA/FDA
Dennis Bensley, CVM/FDA
Mike Olson, ORA/FDA
Joe Famulare, CDER/FDA
Keith Webber, CDER/FDA
Frank Holcomb, CDER/FDA
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PAT Training Coordinators

John Simmons, Karen Bernard and See Lam

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Erin McCaffery (ORA/NWJ-DO)
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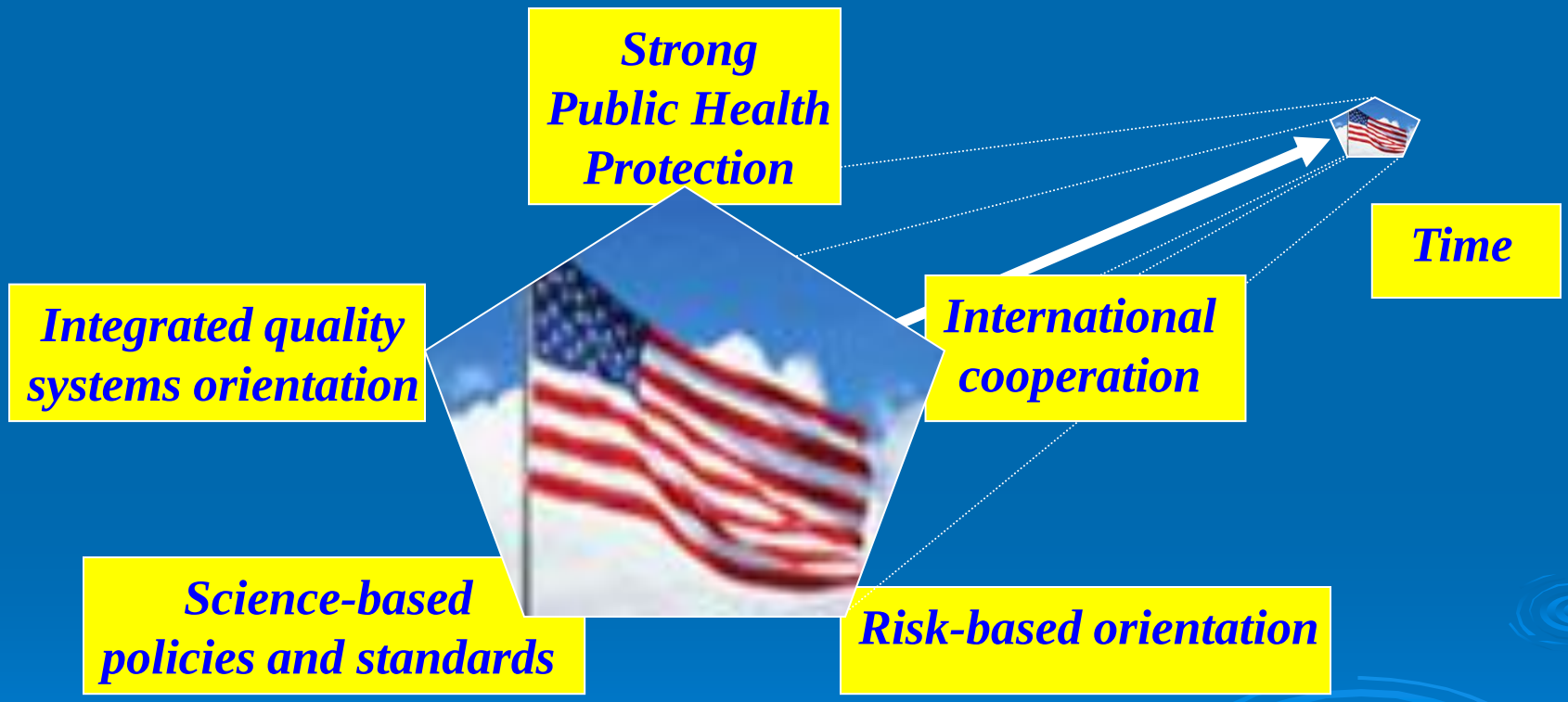
Shaping a Shared Vision: Dimensions of the 21st Century Initiative



FDA Unveils New Initiative To Enhance Pharmaceutical Good Manufacturing Practices
http://www.fda.gov/bbs/topics/NEWS/2002/NEW00829.html (August 21, 2002)

Shaping a Shared Vision: Opportunities

- Scientific
  - Pharmaceutical development and manufacturing is evolving from an art form to one that is now science and engineering based
- Risk mitigation and communication
  - Ability to move from intuitive/subjective approaches to more quantitative approaches
- Quality systems thinking
  - Milestones in quality journey provide a way forward to bring a systems perspective to pharmaceutical quality assessment and assurance

http://www.fda.gov/cder/gmp/21stcenturysummary.htm

Shaping a Shared Vision

- Public meetings, conferences and workshops
  - FDA's Advisory Committee, FDA Science Board, PAT-Sub-committee, Manufacturing Sub-committee
  - Arden House Conferences in US and Europe, Discussions at several ISPE and PDA Conferences in US, Europe and Japan, IFPAC Conferences, PQRI, FIP Workshops,..
  - ICH Meetings in Brussels, Japan, and London

Shaping a Shared Vision: Defining the Desired State

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- Continuous "real time" assurance of quality

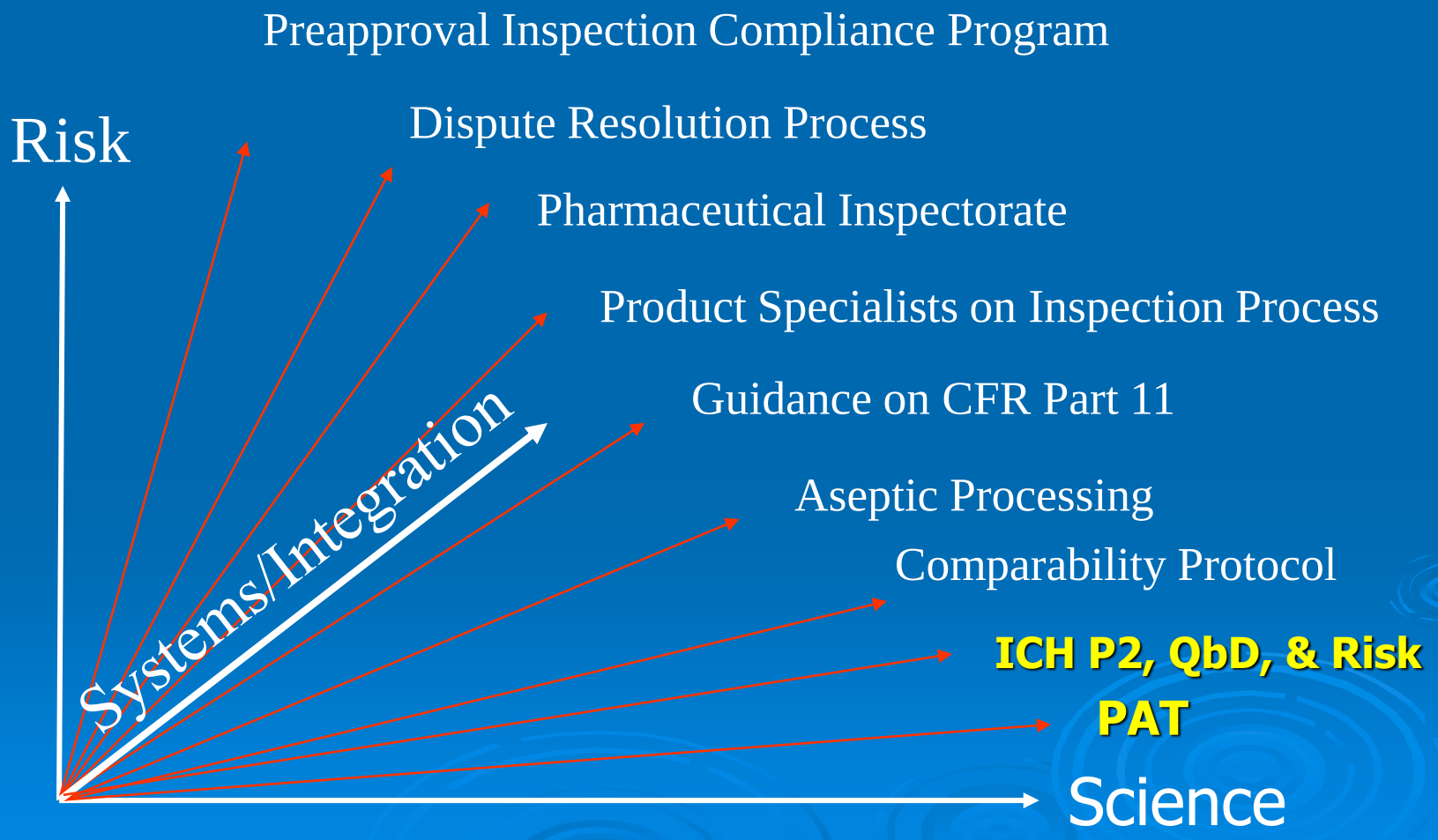
http://www.fda.gov/cder/gmp/21stcenturysummary.htm

Shaping a Shared Vision: Defining the Desired State

- Regulatory policies tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability
- Risk based regulatory scrutiny relate to the:
  - level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance, and
  - the capability of process control strategies to prevent or mitigate risk of producing a poor quality product

http://www.fda.gov/cder/gmp/21stcenturysummary.htm

Mobilizing Commitment



Mobilizing Commitment

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

CDER Human Drugs

Center For Veterinary Medicine

Office of Regulatory Affairs
Compliance, Science, Protection

Draft Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

Mobilizing Commitment: PAT Process

- Commitment to support innovation
  - Framework approach to PAT; not a "how to" guidance, applicable to any new technology
  - Team approach to review and inspection with supportive training, certification, expert consultant and research support
  - A systems approach to provide flexibility in validation of new technology for its indented application, and a very flexible regulatory process by taking advantage of our team approach
  - Address areas of regulatory uncertainty and fear

PAT Framework and Process

PAT is 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:

- chemical, physical, microbiological, mathematical, and risk analysis
- conducted in an integrated manner

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

Process Understanding - Innovation

- Provides a range of options for qualifying and justifying new technologies and to achieve *real time release*
  - less burdensome approaches for validating new technologies for their intended use
    - in absence of process knowledge the *test-to-test* comparison between an on-line process analyzer (e.g., NIR spectroscopy for content uniformity) and a conventional test method (e.g., a wet chemical test) on collected samples may be the only available option

Tools for Process Understanding and Control

- 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

Process Understanding - Justifying "Real Time Release"

- *Real time release* is the ability to evaluate and ensure acceptable quality of in-process and/or final product based on process analytical data

- Process understanding, control strategies, plus on-, in-, or at-line measurement of critical attributes that relate to product quality can provide a scientific risk-based approach to justify how *real time* quality assurance may be equivalent to, or better than, laboratory-based testing on collected samples

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 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

Mobilizing Commitment: PAT Process

- ASTM Committee E55: Pharmaceutical Applications of PAT
  - http://www.astm.org
- Interagency Agreement with NSF
- CRADA with Pfizer on Chemical Imaging as a PAT tool
- Academic and industry champions world wide – to ensure steady progress towards the desired state
- Communication and cooperation with other regulatory agencies

Monitoring Progress

- Several PAT proposals, one approval
  - Expect several application a year from now
- Training of first PAT Team completed
- Under development
  - Quality System for PAT Process
  - Training program for the next PAT team
  - Final PAT Guidance and expansion of its scope to Office of Biotechnology Products
- Increasing
  - ASTM membership and activities
  - Schools (US, Europe and Japan) incorporating PAT in their curriculum
  - Peer-reviewed PAT publications
  - PAT technology and support companies

Anchoring the change

- FDA Strategic Plan
- CFR Part 11
- Warning Letter – Center Review (signifying a Team Approach)
- Work in progress (examples)
  - Final Guidance on PAT, Aseptic processing, Comparability Protocols, Dispute resolution process, etc.,
  - Quality System for CMC Review
  - Dispute resolution process
  - Pharmaceutical Inspectorate
  - Product Specialist on Inspection
  - Other guidance documents planned
  - ICH Q8 and ICH Q9
- Innovation in Medical Technology and the Critical Path Initiatives

Opportunities for the USP to support the PAT Framework

(Note: The author selected to focus on the interrelationship between PAT and the USP and did not wish to generalize the comments to follow to all other Pharmacopeias)

The USP recognizes that assuring quality by design may provide greater assurance than testing to document quality..

- "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." (General Notices, USP 27)

PAT is Consistent with USP Philosophy

- PAT based measurements, controls, and "real time" release based on PAT are expected/likely to be ***"private" or company standards (alternate analytical procedure)***
  - *"Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it." (General Notices, USP 27)*

PAT is Consistent with USP Philosophy

- "However, it is not to be inferred that application of every analytical procedure in the monograph to sample from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution." (General Notices, USP 27)

PAT Framework

- Provides an opportunity to utilize novel/modern process analyzers along with other tools (e.g., multivariate data analysis, feed-back and feed-forward process controls) to:
  - Improve **process understanding** to improve confidence in ***process validation***

PAT Framework

- 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 in physical attributes of Pharmacopieal materials (e.g., API and excipients) that can impact their process-ability**
- Improve manufacturing efficiency and provide a means for "greater assurance" of quality "than analytical data derived from an examination of finished units drawn from that batch" ("text" from General Notices, USP 27)

PAT: USP Compliance Uncertainty?

- Concepts in the PAT Framework are well established (over last ~30 years or longer) and are also recognized in, and supported by, the concepts articulated in the General Notices chapter of the USP
  - However, a perception or view of some in industry is that PAT Framework is not compatible with USP compliance
  - USP can help to remove this misperception!

PAT: USP Compliance Uncertainty?

- PAT Framework provides for higher level of material scrutiny (e.g., possibility of 100% or a large % of in-process and final product evaluated nondestructively)
  - This unfortunately is perceived as increasing the risk that a large number of batches may be judged to be non-compliant with certain USP monograph requirements
    - E.g., Content Uniformity Test

Numbers of tablets found outside range 75-125% among a batch of 1,000,000 tablets for different means, sigma's

	Mean		
Sigma	95%	100%	105%
6%	430	30	430
7%	2150	360	2150
7.8%	5232	1350	5232

Dr. Janet Woodcock, April 9, 2002

PAT: USP Compliance Uncertainty?

- Optimal application of the PAT Framework can assure quality is built into the product and process by design
  - Therefore, companies utilizing this framework will not have to worry about non-conformance to compendial monographs (since such risks would be mitigated by design and the risk level expected to be lower than the corresponding current risk level)
  - However, this aspect is not widely appreciated and some companies seek further clarification on issues with compliance to pharmacopieal monographs for situations with larger sample size for analysis

USP Compliance Uncertainty: How USP Can Support PAT Framework?

- The pharmacopoeias establish marketplace legal standards which help to assure practitioners and patients that products meet their quality requirements
- The marketplace standard must be met regardless of how products are produced (from compounding to PAT based manufacturing process)
- The pharmacopoeias, correctly, do not dictate or define how to achieve the established marketplace standards
  - Any attempt to do so by a pharmacopoeia or a regulatory authority will impede innovation and continuous improvement
- USP can support the PAT Framework by providing clear communication on issues identified as "compendial uncertainty"

Summary

- PAT is defined as a system based on a set of principles and a tool box for process design
  - The FDA draft Guidance is a framework that provides a flexible approach for innovation – it is by design not a "how to" guidance
- PAT Framework is a directional vector in the broader FDA's 21st Century Initiative
- USP can support PAT by:
  - Providing clear communication that PAT based QC/QA is an acceptable alternate approach