A Shared Vision for Pharmaceutical Development and Manufacturing in the 21st Century: Contributions of the PAT Initiative

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21st Century Shared Vision: Who?

- Patients we serve
  - Improved access to high quality affordable and innovative treatment options
- Regulators (US, EU, Japan, others)
  - Higher ability and efficiency to confidently ensure high quality
- Industry (Innovator, Generic, …)
  - Enhanced ability to compete on the basis of innovation, market access, and efficiency
- Academia
  - Improved recognition and resources for training and research

21st Century Shared Vision: What?

- The Desired State (ICH)
  - 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
  - An ability to effect continuous improvement and continuous "real time" assurance of quality

21st Century Shared Vision: How?

- Develop effective CAPA – eliminate “special cause” variability
- Utilize Process capability analysis – reduce/control “common cause” variability

- Identify, understand and acquire ability to predict critical to quality attributes (CQA) (product/process/measurement)
- Focus on the “critical few”

- Establish CQA target values and acceptable variability around the target value
- Utilize a monitoring system that demonstrates “state of control” preferably based on critical material attributes (not just end product testing)

Achieve Total Manufacturing Excellence

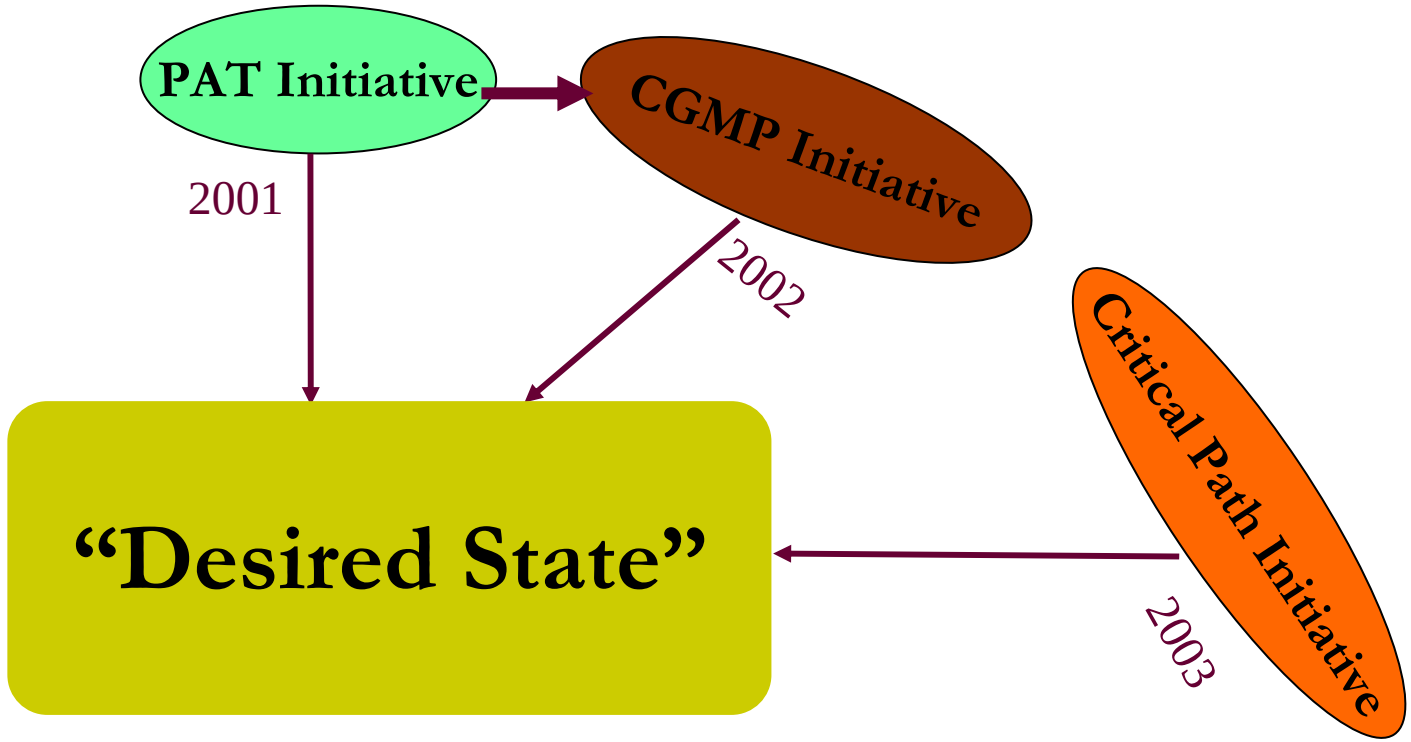
- Improving Efficiency
  - Reduce time to market, production cycle time, eliminate waste,….
- Cutting Costs
  - Improving efficiency and innovation
- Whilst Remaining Compliant
  - Science based design & quality assurance to gain regulatory flexibility for continuous improvement and innovation

Pharmaceutical Manufacturing 2005
Europe's Definitive Pharmaceutical Manufacturing Conference

The “Wrong” Way

- 24 May 2005 - Able suspends manufacturing on QC violations
- 30 May 2005 - Able Labs cuts staff after manufacturing suspension
- 4 July 2005 - Able unable to meet investors
- 12 July 2005 - Able interim CEO walks as FDA sends in 483
- 19 July 2005 - Able Labs files for bankruptcy protection

A Transforming Agenda



Why Transforming Efforts Fail?

- *Not establishing a great enough sense of urgency*
- *Not creating a powerful enough guiding coalition*
- *Lacking a vision*
- *Under communicating the vision by a factor of ten*
- *Not removing obstacles to the new vision*
- *Not systematically planning for and creating short term wins*
- *Declaring victory too soon*
- *Not anchoring changes in the corporation's culture*

The PAT Initiative: Why?

- Problems – CGMP Warning letters and Consent Decree
  - Are improvement efforts focused on the "right" product?
- Pharmaceutical manufacturing and quality assurance lagging other sectors
  - Regulatory uncertainty
- Cost and availability implications
  - Manufacturing costs exceed R&D costs
- Increasing complexity
- Opportunity for product "customization" for a individual patient

“A Paradigm in Crisis”

THE WALL STREET JOURNAL.

WEDNESDAY, SEPTEMBER 3, 2003 - VOL. CCXLII NO. 45 - ★★★★ $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

Main points from this:

- High tech in R & D
- Relatively low tech in Manufacturing
- It matters
  - Big Pharma manufacturing costs are $ 90 Bn
  - Significantly more than R&D

Quality by Design: A Challenge to the Pharma Industry

(CAMP, R. Scherzer. FDA Sci. Board. 4/9/02)

The “best of times”……

- The “block buster” drug model and pre-PDUFA phase may represent the “best of times” for the practitioners of industrial pharmacy
  - Sufficient time for the traditional empirical approaches for product development and testing
  - Relatively simple product designs
  - The documentation burden of “Process validation” and CGMP’s manageable

leading towards “worst of times”?

- Post PDUFA and declining “block buster” market
  - Development “crunch”
  - Increasing complexity
  - Need for flexibility and efficiency
  - High cost of quality and low production efficiency
  - Increasing financial risk and public scrutiny
  - Global competition

The future?

- With increasing complexity the cost of pharmaceuticals is enormous and the risk to public safety daunting
  - And like the leaders of the French Revolution, we look to a future that will bring us everything or nothing, depending on the public trust

The 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 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

The PAT Initiative: What?

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)

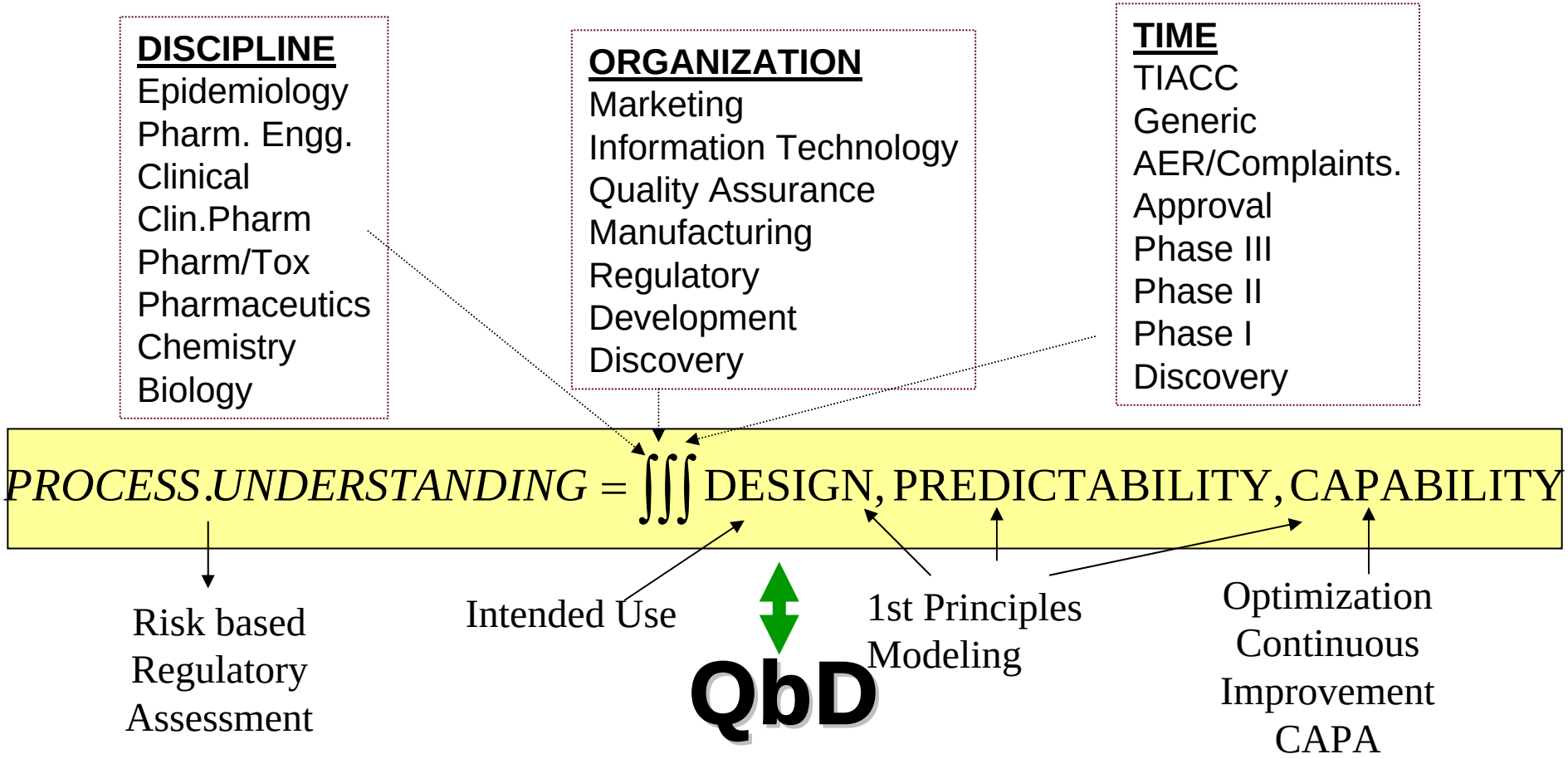
Pharmaceutical CGMPs
September 2004

A Regulatory Strategy Accommodating Process understanding based regulatory flexibility for innovation and continuous improvement

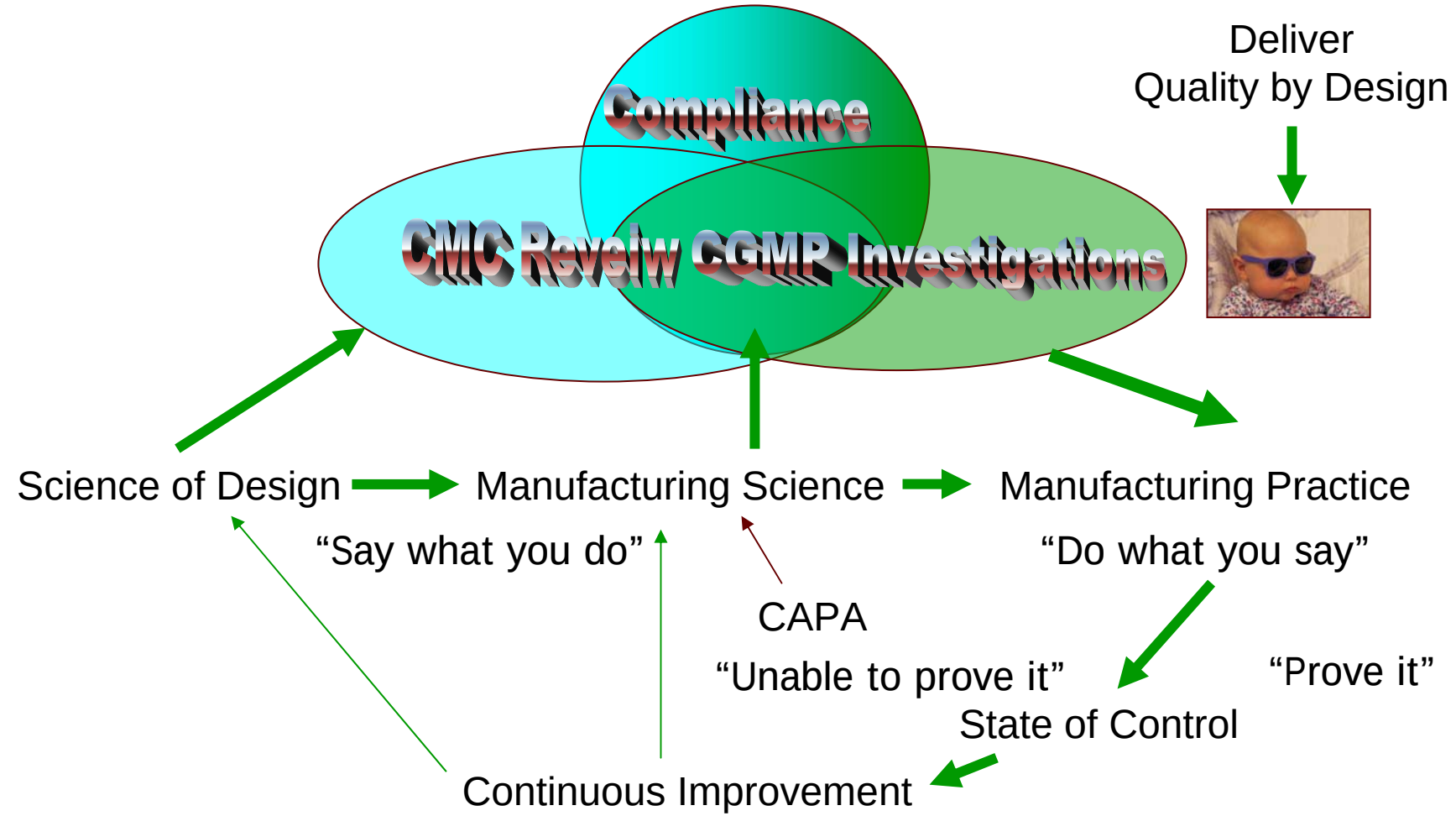
The diverse and determined PAT team has good reason to smile.

Pharmaceutical Manufacturing • www.pharmamanufacturing.com

What? Process Understanding



What? A Collaborative Vocabulary and Focus



Quality can not be tested in...

- A validated manufacturing process has a high level of scientific assurance that it will reliably produce acceptable product
  - http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg490-100.html

Science, engineering, and control technologies….

- "..can provide a high level of process understanding and control capability."
- ".. high assurance of quality by continuously monitoring, evaluating, and adjusting every batch using validated in-process measurements, tests, controls, and process endpoints."
- "..may not be necessary … to manufacture multiple conformance batches prior to initial distribution."

A Process is well understood when…

- all critical sources of variability are identified and explained;
- variability is managed by the process; and,
- product quality attributes can be accurately and reliably predicted over the design space …
  - http://www.fda.gov/cder/guidance/6419fnl.htm

Product and Process Development Life-cycle

- Structured product and process development on a small scale, using experimental design and on- or in-line process analyzers to collect data in real time, can provide increased insight and understanding for process development, optimization, scale-up, technology transfer, and control.
- Process understanding - product quality attributes can be accurately and reliably predicted over the design space when other variables (e.g., environmental and supplier changes) may possibly be encountered.

The Pharmaceutical Development Section

- Opportunity to present the knowledge gained through the application of scientific approaches, and risk management, to the development of a product and its manufacturing process
- provision of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches
- intended to provide a more comprehensive understanding of the product and manufacturing process for reviewers and investigators

Comprehensive understanding for..

- Proactive regulatory decisions
  - Assessing that critical sources of variability are identified and explained and that variability is adequately managed by the process (state of control)
  - Risk based assessment, investigations and knowledge sharing (over a product's life cycle) between reviewers and investigators
  - Basis for flexible regulatory approaches

Regulatory Flexibility: What?

- "..may not be necessary … to manufacture multiple conformance batches prior to initial distribution."
- Risk based assessment and investigations and knowledge sharing (over a product's life cycle)
  - Risk-based specifications, controls, pre-and post approval inspections, CAPA, ..
  - Continuous improvement under the facilities quality system,….
  - Process understanding "can reduce the burden for validating systems by providing more options for justifying and qualifying systems intended to monitor and control biological, physical, and/or chemical attributes of materials and processes."

Regulatory Flexibility: How?

- Quality by design
  - Structured product and process development
  - Process understanding and control capability
  - Design space
- Integration of prior knowledge and pharmaceutical development into C, M, C submission and review
  - Present the knowledge gained to provide a more comprehensive understanding of the product and manufacturing process for reviewers and inspectors
  - Risk based assessment and investigations and knowledge sharing (over a product's life cycle)

Regulatory Flexibility: Why?

- Facilitate continuous improvement and innovation to improve quality, efficiency, knowledge, and availability
- High level of process understanding and control capability can further improve our ability to ensure quality on every batch
  - compared to a validated process with insufficient understanding and for which “state of control” is based primarily on compendial testing

The Beginning of the End of the FDA's PAT Initiative (2005)

- The 2nd and final PAT team
  - Focus on Biotech & Biological
- Introduction of PAT to the Pharmaceutical Inspectorate
- The ONDC's Quality Assessment System
- The OGD's Question based Review program
- PAT in OBP
- PAT concepts throughout FDA's CMC and CGMP process
- ASTM E55 Standards

Question-Based Review for CMC Evaluations of ANDAs

- The QbR will transform the CMC review into a modern, science and risk-based pharmaceutical quality assessment that incorporates and implements the concepts and principles of the FDA's *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach* and *Process Analytical Technology* initiatives.
- The main objectives of this enhanced review system are to:
  - assure product quality through design and performance-based specifications,
  - facilitate continuous improvement and reduce CMC supplements through risk assessment,
  - enhance the quality of reviews through standardized review questions,
  - reduce CMC review time when sponsors submit a quality overall summary that addresses the QbR.

http://www.fda.gov/cder/ogd/QbR.htm

The End of FDA's PAT Initiative

- Means PAT is being "anchored in the corporation's culture"!

Hesitating to act because the whole vision might not be achieved, or because other do not yet share it, is an attitude that only hinders progress.

- M. K. Gandhi

The PAT Initiative: Summary

- A framework and a positive collaborative vocabulary to move pharmaceutical development and manufacturing to the 21st Century
  - Serves as a bridge to the quality revolution that occurred in other industrial sectors (TQM, Lean, Six Sigma, …)
- Focused on science in the interest of public health
  - Looking beyond "current" regulatory "blind" compliance
- Let the innovative industry leaders leave their competition behind
  - Efficiency gains and regulatory flexibility
- Reduced regulatory uncertainty through team approach & training
- Developed a shared vision for the future
  - The 21st Century "desired state"
- Is now anchored in the organization's culture!!