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The Process Analytical Technology (PAT) Initiative: Progress Report and Next Steps

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Motivation

- Significant potential and need exists for improving the efficiencies of pharmaceutical manufacturing and associated regulatory processes
- Technological opportunities (e.g., PAT) available for realizing this potential
  - Industry reluctant to take advantage of such opportunities due to "regulatory uncertainties," prefers to adopt a "Don't Use" or "Don't Tell" approach
    - An undesirable situation for both industry and public health

Why PAT?

- PAT provides an opportunity to move from the current "testing to document quality" paradigm to a "Continuous Quality Assurance" paradigm that can improve our ability to ensure quality was "built-in" or was "by design" - ultimate realization of the true spirit of cGMP!
  - At/On/In-line measurement of "performance" attributes
  - Real-time or rapid feedback controls (focus on prevention)
  - Greater insight and understating of processes
  - Potential for significant reduction in production (and development) cycle time
  - Reduce (regulatory) concerns and potential for remote inspection strategies

Goals and Objectives

- Using PAT as a model technological opportunity, develop a regulatory framework to facilitate introduction of new manufacturing technologies that enhance process efficiencies and understanding
  - Identify and eliminate perceived/real "regulatory hurdles"
  - Develop a dynamic, team-based, scientific approach for regulatory assessment (review & inspection) of new technologies
  - International harmonization

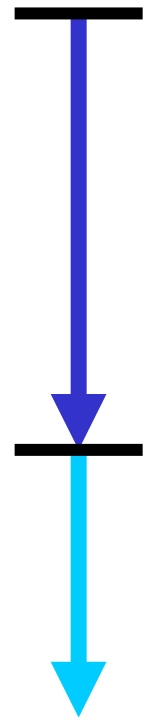
Strategy

- A “win-win” approach with input from the ACPS and the FDA Science Board
  - Internal Collaboration: CDER & ORA
    - FDA PAT Steering Committee
  - External Collaboration: Industry & Academia
    - FDA/ACPS Subcommittee on PAT
    - PQRI
- Two parallel tracks
  - Guidance for industry on PAT
    - Step 1: General principles (not focused on any one technology)
  - Encourage submission
    - Team approach for review & inspection during development phase

Progress Report: Timeline

- 19 July 2001: Advisory Committee for Pharmaceutical Science

- **16 November 2001: FDA Science Board Meeting**
  - 28 November 2001: Advisory Committee for Pharmaceutical Science
  - 24-25 February 2002: FDA/ACPS PAT-Subcommittee Meeting
- **9 April 2002: FDA Science Board Meeting**
  - *8 May 2002: Advisory Committee for Pharmaceutical Science*
  - *12-13 June 2002: FDA/ACPS PAT-Subcommittee Meeting*



Collaboration: Internal

- FDA's PAT Steering Committee
  - Doug Ellsworth (NJDO, ORA)
  - Mike Olson (DFS, ORA)
  - Diane Obrien (DFS, ORA)
  - Joseph Famulare (OC, CDER)
  - Moheb Nasr (OTR/OPS, CDER)
  - Frank Holcomb (OGD/OPS, CDER)
  - Yuan-yuan Chiu (ONDC/OPS, CDER)
  - Ajaz Hussain (OPS, CDER) [Chair]
- Consensus building and awareness
  - CDER Science Rounds, Seminars, Visiting Lecture Series,….

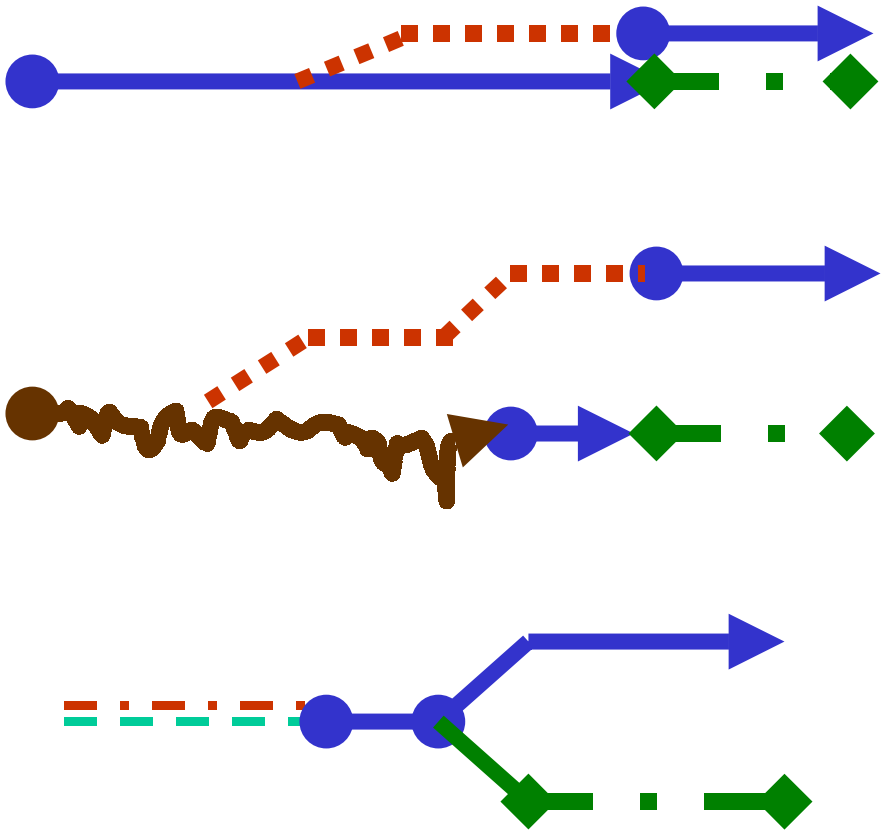
Collaboration: External

- FDA/ACPS Subcommittee on PAT
  - Federal Register Notice (10/25/01) requesting nominations from industry, academia, ...
- Product Quality Research Institute (PQRI)
  - Research program (Blending/NIR)
- Academia (Pharmacy, Chemistry and Engineering)
  - Currently three NSF “Process” Centers
    - Development of training and certification program
    - Continuing education program

General (principles) Guidance on PAT

- Proposed Goals and Objectives
  - General principles and terminology
    - Bring the community on the "same page"
  - Address issues related to "regulatory uncertainties"
  - Clarify the regulatory process
    - Review and inspection
  - Other tangible benefits
    - Serve as a tool for building within-company consensus
    - Promote research and development activities in the pharmaceutical PAT area

Options for Introducing PAT



A. Currently marketed "robust" products. PAT to improve efficiency (minimal improvement in quality assurance)*

B. Currently marketed products that need improvement. Step wise PAT approach - first improve quality and then improve the efficiency

C. New products. PAT utilized throughout development and scale-up. Lab based tests to ensure shelf-life and/or for establishing "public standards."

*Note that a step-by-step approach, one unit operation at a time similar to option B, is also an option

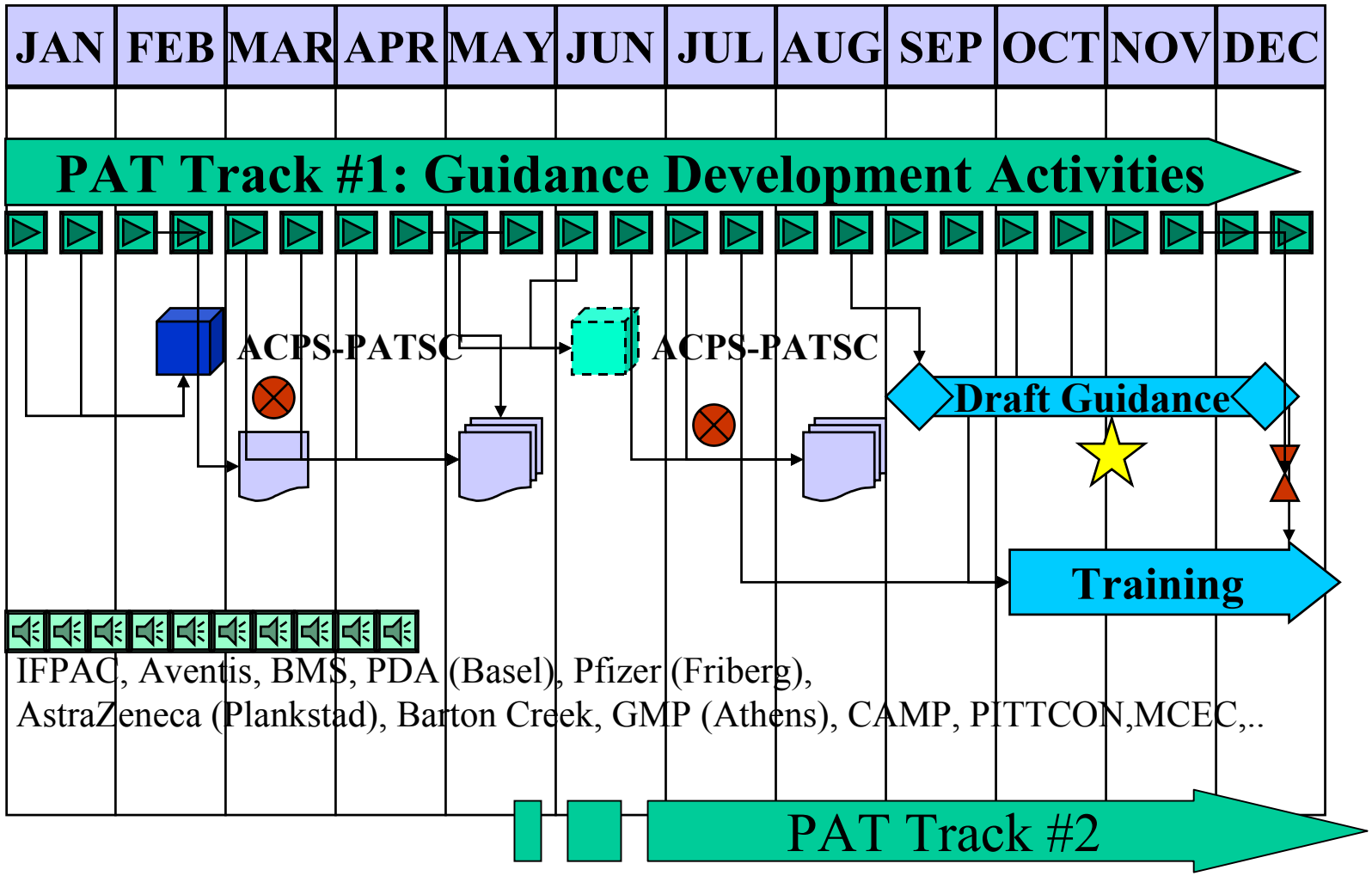
Track #2: Encourage Submissions (now)

- Companies can propose PAT submissions
  - Contact the OPS/CDER/FDA to discuss their proposed PAT applications or submissions
  - Review-Inspection teams for these submissions
    - Concurrent development -review/inspection
  - **To date we have received two formal requests (major US companies) for a meeting to discuss proposed submissions**

Track #2a: Encourage Established PAT Technologies

- Encourage application of selected on/in/at line measurement tools for unit operations and/or as alternate tests
  - Unit operations: blending, drying
  - Technologies: NIR, Raman, Chemical imaging
- Incorporate regulatory recommendations within current projects (e.g., draft Blend Uniformity Guidance document)

PAT Initiative:Timeline (2002)



Next Steps

- Establish a CDER-ORA PAT team for joint review/inspection of PAT based submissions.
  - Team review-inspection process and procedures
  - Select four reviewers and four inspectors to be part of this first team
  - Recruit expert consultants: Process/Chemical Engineer (PD-drafted), Process Analytical Chemist, Chemometrician, Industrial Pharmacist.

Next Steps

- Develop a training (and certification) program PAT Review-Inspection Team
  - Proposal (curriculum) to be discussed at the 06/02 meeting of the PAT-Subcommittee
- Expand FDA research efforts to understand issues related to PAT based applications
  - NIR, Chemical imaging, Prediction of product performance (dissolution)
- Publish the proposed general guidance (draft)

Next Steps

- Public workshops on PAT
  - Program developed for the Arden House Conference (AAPS PT Section)
    - USA 01/03; UK 03/03 (AAPS-RPS; FDA-MCA)
  - FDA/AAPS PAT Workshop under development (target 04/03)
- Formalize efforts towards International Harmonization
  - Currently informal communications with a few European regulators