Questions for the FDA/ACPS's PAT-Subcommittee Meeting on 12-13 June 2002

Goals and Objectives of the Initiative:

Using PAT as a model technological opportunity, develop a regulatory framework to facilitate introduction of new manufacturing technologies that enhance process efficiencies and understanding ("win-win")

- Identify and eliminate perceived/real "regulatory hurdles"
- Develop a dynamic, team-based, scientific approach for regulatory assessment (review & inspection) of new technologies
- International harmonization

The proposed "General Guidance" on PAT (referred to as Track #1) is primarily intended to address the first objective, i.e., identify and eliminate perceived/real "regulatory hurdles." We believe the proposed general guidance should provide information and recommendations on:

- General principles and terminology
  - Help to bring the community on the "same page"
- Address issues related to "regulatory uncertainties"
- Clarify the regulatory process
  - Review and inspection process
- Facilitate realization of other tangible benefits to the society
  - Serve as a tool for building consensus
  - Promote research and development activities in the pharmaceutical PAT area

FDA plans to develop other guidance documents to address technical issues. However, these efforts will be initiated after the proposed general guidance document is established. In parallel to Tack #1 efforts, FDA is in the process of hiring staff with expertise in PAT, expanding its research activities, and encouraging companies who have already applied PATs in their foreign or US facilities to consider making regulatory submissions (referred to as Track #2). We expect these efforts to provide technical know-how for development of broad technical guidance documents.

Questions for considerations by the PAT-Subcommittee

A. Definition and Scope of PATs in pharmaceutical manufacturing

Ensuring an appropriate definition of PAT is important for the purposes of developing regulatory policy and procedures. The definition would need to be sufficiently broad to help the public and industry realize benefits of the shared vision of PAT, yet be specific to draw distinction between the PAT concept of *Continuous Quality Control/Assurance* (CQC/A) and the current approach that emphasizes laboratory based testing to document quality.

Question #1: How would the committee articulate its (shared) vision of pharmaceutical manufacturing and CQC/A using PAT?

Question #2: Define CQC/A?

Question #2a: Should CQC/A be distinguished from *parametric release*? If so,

Question #2b: What attributes should be used to draw this distinction?

Question #2c: Should *parametric release* be considered a sub-set of CQC/A?

Note that the term parametric release has only been applied to terminally sterilized solution dosage forms. For this purpose it refers to the following conditions;

> When "***data derived from the manufacturing process sterility assurance validation studies and from in-process controls are judged to provide greater assurance that the lot meets the required low probability of containing a contaminated unit*** (compared to sterility testing results from finished units drawn from the lot), ***any sterility test procedure adopted may be minimal, or dispensed with on a routine basis***." (USP)
>
> The EMEA's *Note for Guidance on Parametric Release* (9/01) defines this term (again for terminally sterilized solutions) as " a system of release that gives assurance that the product is of the intended quality based on the information collected during the manufacturing process and on the compliance with specific GMP requirements related to parametric release." And this note extends this definition of *Parametric Release* to other dosage forms.

Question #3: Does the Sub-committee wish to further refine or modify the working definition of PAT proposed at its fist meeting in (02/02)? If so, how should this be modified?

*Systems for analysis and control of manufacturing processes based on timely measurements during processing, of **critical** quality parameters and performance attributes of raw and in-process materials and processes to assure acceptable end product quality at the completion of the process.*

B. Regulatory Risk/Uncertainty

<u>Question #4</u>: Have we identified the key issues (real/perceived) that can be categorized under the heading of "Regulatory Risk/Uncertainty," and, do you agree with the current thinking on how these risks may be minimized?

Risk #1: Application of PAT's to currently approved products may reveal certain non-random trends or identify issues that could be regarded as "problems" that have always been present but may not apparent under the current testing scheme. Industry concern is that such observations may jeopardize the cGMP compliance status of their products.

There could be several reasons why PAT applications may find trends or "problems" that may have always been present but have not been apparent under the current system. These may include: (1) use of new or different analytical tools, (2) increased sampling/testing frequency, (3) some critical variables may not have been identified, (4) ability to measure certain physical or functional attributes of materials may not have been available in the past, (5) current controls and specifications are often based on limited commercial-scale manufacturing experience, and (6) combination of these and other reasons (e.g., old products/processes).

(a) For marketed "robust" products (good compliance history).

<u>We believe that the current system provides product of good quality that is fit for its intended use</u>. During development of PAT applications on marketed products, the information *collected using experimental PATs* would be considered as *"research data."* Only the approved regulatory tests used for product release and regulatory decisions.

The likely hidden "problems" that may become more prominent or apparent are observation of non-random trends and an increased frequency of finding a small number of **<u>units</u>** outside specifications, a likely result of increased sampling/testing frequency *(see Dr. Woodcock's presentation to the FDA Science Board on 9 April 2002).* We recognize this issue and plan to use a sound statistical approach to evaluate/address such observations. The proposed general guidance may only suggest that such an approach may be considered. Detailed recommendations on statistical methods and analysis will be considered under a separate guidance document.

<u>Question #4a</u>. Are there any other "problem" scenarios that we should consider?

For products in this category, we believe there is a very low probability of discovering, via PAT applications, a "problem" that will raise a safety or efficacy concern. However, if such a "problem" is uncovered a "risk-based" approach will be utilized to define an approach of appropriate resolution of such problems.

<u>Question #4b.</u> What criteria should we consider in developing a "risk-based" approach for resolution of problems uncovered during PAT R&D efforts on products in compliance with cGMP?

<u>Question # 4c.</u> To minimize disagreements or disputes should a priori criteria be developed to assess if a problem uncovered during PAT implementation was present all along during the prior manufacturing history of a product?

(b) For current products that need improvement in manufacturing process

In these cases regulatory acceptance of a PAT application/proposal would be considered on case by case basis.

<u>Question #4d:</u> What other mechanisms do you recommend for consideration.

Risk # 2: Consistency in regulatory assessment and interpretation of (validation) data may become an issue.

A team approach for review and inspection is being considered for regulatory assessment of PAT based manufacturing submissions and validation. This review-inspection team will be trained and certified in the area of PATs. In addition, CDER/OPS is planning to develop a group of experts who will serve as consultants to reviewers and investigators in evaluating PAT-containing applications and also be available to resolve technical disputes in this area.

<u>Question #4e</u>: What are your recommendations for training needs and criteria for certification of the proposed PAT-Team?

Risk #3: NDA/ANDA development and its review by the FDA may be delayed, if a new PAT will be used.

For NDA's there are opportunities for FDA to work with sponsors interested in using PATs, through review of appropriate protocols and data during IND and NDA drug development phases, so that PAT use-related delays in the NDA approval process may not occur. Review of protocols and PAT data will be managed by accepting, reviewing

and commenting on pre-IND submissions, End of Phase 2 packages, and pre-NDA submissions. Separate CMC discussion meetings may be possible with CDER's PAT review and inspection team while developing and implementing new PAT. The guidance will also indicate the general nature and extent of data that should be submitted to the Review and Inspection team prior to Agency's meeting with the sponsor.

For ANDA's a mechanism would need to be developed.

> **Question #4f: What other mechanisms (for both NDA and ANDA) do you recommend for consideration by the Agency, so that a new drug development process may not be delayed due to use of new PATs?**

Risk #4: If PAT is use for one unit operation, or for one product, it will be required for all products manufactured by a company.

In the proposed general guidance we plan to clarify that the use of all **new** PATs will be voluntary, and also, conventional methods of quality control and quality assurance will continue to be used according to current regulatory requirements and CGMPs.

> **Question #4g**: **What other clarification should be included in the general guidance on this subject?**

Risk #5: A company will need to use both PAT-based quality assessment method(s) and conventional methods for regulatory purposes, forever.

When PAT-based systems are developed, justified, and appropriately validated for the intended purpose, then, PAT based systems may be relied upon for in-process control and release testing, as an alternate method or as primary regulatory method. Laboratory based testing may be primarily focused to ensure stability.

> **Question #4h**: **What other approach do you recommend for consideration to address this concern?**

C. Regulatory Assessment and Procedures for PAT Submissions

The proposed guidance is intended to address review and inspection aspects of regulatory applications of PAT in drug substance and drug product manufacturing. It will provide recommendations to address regulations and also provide information on how to request meetings to discuss proposed applications of PAT. **The Sub-committee is requested to identify (at the end of day 1 deliberations) questions to be addressed on the day 2 of this meeting by two working groups namely, Product/Process Development and Process/Analytical Validation.**

> **Question #5: What information should be included in the proposed guidance on product/ process development and process/analytical validation?**