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

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TABLE OF CONTENTS

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I. INTRODUCTION

This guidance is intended to describe a regulatory framework (Process Analytical Technology, PAT) that will encourage the voluntary development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance. Working with existing regulations, the Agency has developed an innovative approach for helping the pharmaceutical industry address anticipated technical and regulatory issues and questions.

This guidance is written for a broad industry audience in different organizational units and scientific disciplines. To a large extent, the guidance discusses principles with the goal of highlighting opportunities and developing regulatory processes that encourage innovation. In this regard, it is not a typical Agency guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance was prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) under the direction of Food and Drug Administration's Process Analytical Technology (PAT) Steering Committee with membership from CDER, Center for Veterinary Medicine (CVM), and Office of Regulatory Affairs (ORA).

II. SCOPE

The scientific, risk-based framework outlined in this guidance, *Process Analytical Technology* or PAT, is intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance. The framework is founded on process understanding to facilitate innovation and risk-based regulatory decisions by industry and the Agency. The framework has two components: (1) a set of scientific principles and tools supporting innovation and (2) a strategy for regulatory implementation that will accommodate innovation. The regulatory implementation strategy includes creation of a PAT Team approach to chemistry manufacturing and control (CMC) review and current good manufacturing practice (CGMP) inspections as well as joint training and certification of PAT review and inspection staff. Together with the recommendations in this guidance, our new strategy is intended to alleviate concern among manufacturers that innovation in manufacturing and quality assurance will result in regulatory impasse. The Agency is encouraging manufacturers to use the PAT framework described here to develop and implement effective and efficient innovative approaches in pharmaceutical development, manufacturing and quality assurance.

This guidance addresses new and abbreviated new (human and veterinary) drug application products and specified biologics regulated by CDER and CVM as well as nonapplication drug products. Within this scope, the guidance is applicable to all manufacturers of drug substances, drug products, and specified biologics (including intermediate and drug product components) over the life cycle of the products (references to 21 CFR part 211 are merely examples of related regulation). Within the context of this guidance, the term *manufacturers* includes human drug, veterinary drug, and specified biologic sponsors and applicants (21 CFR 99.3(f)).

We would like to emphasize that any decision on the part of a manufacturer to work with the Agency to develop and implement PAT is a voluntary one. In addition, developing and implementing an innovative PAT system for a particular product does not mean that a similar system must be developed and implemented for other products.

III. BACKGROUND

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality. This conventional approach has been successful in providing quality pharmaceuticals to the public. However, today significant opportunities exist for improving pharmaceutical development, manufacturing, and quality assurance through innovation in product and process development, process analysis, and process control.

Unfortunately, the pharmaceutical industry generally has been hesitant to introduce innovative systems into the manufacturing sector for a number of reasons. One reason often cited is regulatory uncertainty, which may result from the perception that our existing regulatory system is rigid and unfavorable to the introduction of innovative systems. For example, many manufacturing procedures are treated as being frozen and many process changes are managed through regulatory submissions. In addition, other scientific and technical issues have been

raised as possible reasons for this hesitancy. Nonetheless, industry's hesitancy to broadly embrace innovation in pharmaceutical manufacturing is undesirable from a public health perspective. Efficient pharmaceutical manufacturing is a critical part of an effective U.S. health care system. The health of our citizens (and animals in their care) depends on the availability of safe, effective, and affordable medicines.

Pharmaceuticals continue to have an increasingly prominent role in health care. Therefore pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, along with the best principles of quality management to respond to the challenges of new discoveries (e.g., novel drugs and nanotechnology) and ways of doing business (e.g., individualized therapy, genetically tailored treatment). Regulatory policies must also rise to the challenge.

In August 2002, recognizing the need to eliminate the hesitancy to innovate, the Food and Drug Administration (FDA) launched a new initiative entitled "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach." This initiative has several important goals, which ultimately will help improve the American public's access to quality health care services. The goals are intended to ensure that:

- The most up-to-date concepts of risk management and quality systems approaches are incorporated into the manufacture of pharmaceuticals while maintaining product quality
- Manufacturers are encouraged to use the latest scientific advances in pharmaceutical manufacturing and technology
- The Agency's submission review and inspection programs operate in a coordinated and synergistic manner
- Regulations and manufacturing standards are applied consistently by the Agency and the manufacturer
- Management of the Agency's Risk-Based Approach encourages innovation in the pharmaceutical manufacturing sector
- Agency resources are used effectively and efficiently to address the most significant health risks

Pharmaceutical manufacturing continues to evolve with increased emphasis on science and engineering principles. Effective use of the most current pharmaceutical science and engineering principles and knowledge — throughout the life cycle of a product — can improve the efficiencies of both the manufacturing and regulatory processes. This FDA initiative is designed to do just that by using an integrated systems approach to regulating pharmaceutical product quality. The approach is based on science and engineering principles for assessing and mitigating risks related to poor product and process quality. In this regard, the desired state of pharmaceutical manufacturing and regulation may be characterized as follows:

- Product quality and performance are ensured through the design of effective and efficient manufacturing processes
- Product and process specifications are based on a mechanistic understanding of how formulation and process factors affect product performance
- Continuous *real time* quality assurance

- Relevant regulatory policies and procedures are tailored to accommodate the most current level of scientific knowledge
- Risk-based regulatory approaches recognize

  – the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance

  – the capability of process control strategies to prevent or mitigate the risk of producing a poor quality product

This guidance, which is consistent with the Agency's August 2002 initiative, is intended to facilitate progress to this desired state.

This guidance was developed through a collaborative effort involving CDER, the Center for Veterinary Medicine (CVM), and the Office of Regulatory Affairs (ORA).[2] Collaborative activities included public discussions, PAT team building activities, joint training and certification, and research. An integral part of this process was the extensive public discussions at the FDA Science Board, the Advisory Committee for Pharmaceutical Science (ACPS), the PAT-Subcommittee of ACPS, and several scientific workshops. Discussions covered a wide range of topics including opportunities for improving pharmaceutical manufacturing, existing barriers to innovation, possible approaches for removing both real and perceived barriers, and many of the principles described in this guidance.

IV. PAT FRAMEWORK

The Agency considers PAT to be 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. It is important to note that the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. The goal of PAT is to enhance understanding 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*. Consequently, the tools and principles described in this guidance should be used for gaining process understanding and can also be used to meet the regulatory requirements for validating and controlling the manufacturing process.

Quality is built into pharmaceutical products through a comprehensive understanding of:

- The intended therapeutic objectives; patient population; route of administration; and pharmacological, toxicological, and pharmacokinetic characteristics of a drug
- The chemical, physical, and biopharmaceutic characteristics of a drug

[2] For products regulated by the Center for Biologics Evaluation and Research (CBER), manufacturers should contact CBER to discuss applicability of Process Analytical Technology.

- Design of a product and selection of product components and packaging based on drug attributes listed above
- The design of manufacturing processes using principles of engineering, material science, and quality assurance to ensure acceptable and reproducible product quality and performance throughout a product's shelf life

Using this approach of *building quality into products,* this guidance highlights the necessity for process understanding and opportunities for improving manufacturing efficiencies through innovation and enhanced scientific communication between manufacturers and the Agency. Increased emphasis on *building quality into products* allows more focus to be placed on relevant multi-factorial relationships among material, manufacturing process, environmental variables, and their effects on quality. This enhanced focus provides a basis for identifying and understanding relationships among various critical formulation and process factors and for developing effective risk mitigation strategies (e.g., product specifications, process controls, training). The data and information to help understand these relationships can be leveraged through preformulation programs, development and scale-up studies, as well as from improved analysis of manufacturing data collected over the life of a product.

Effective innovation in development, manufacturing and quality assurance would be expected to better answer questions such as the following:

- What are the mechanisms of degradation, drug release, and absorption?
- What are the effects of product components on quality?
- What sources of variability are critical?
- How does the process manage variability?

A desired goal of the PAT framework is to design and develop well understood processes that will consistently ensure a predefined quality at the end of the manufacturing process. Such procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency. Gains in quality, safety and/or efficiency will vary depending on the process and the product, and are likely to come from:

- Reducing production cycle times by using on-, in-, and/or at-line measurements and controls
- Preventing rejects, scrap, and re-processing
- Real time release
- Increasing automation to improve operator safety and reduce human errors
- Improving energy and material use and increasing capacity
- Facilitating continuous processing to improve efficiency and manage variability
  - For example, use of dedicated small-scale equipment (to eliminate certain scale-up issues)

This guidance facilitates innovation in development, manufacturing and quality assurance by focusing on process understanding. These concepts are applicable to all manufacturing situations.

A. Process Understanding

A process is generally considered well understood when (1) all critical sources of variability are identified and explained; (2) variability is managed by the process; and, (3) product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions. The ability to predict reflects a high degree of process understanding. Although retrospective process capability data are indicative of a state of control, these alone may be insufficient to gauge or communicate process understanding.

A focus on 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. In the absence of process knowledge, when proposing a new process analyzer, the test-to-test comparison between an on-line process analyzer and a conventional test method on collected samples may be the only available validation option. In some cases, this approach may be too burdensome and may discourage the use of some new technologies.

Transfer of laboratory methods to on-, in-, or at-line methods may not necessarily be PAT. Existing regulatory guidance documents and compendial approaches on analytical method validation should be considered.

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 then continues in the production phase when other variables (e.g., environmental and supplier changes) may possibly be encountered. Therefore, continuous learning over the life cycle of a product is important.

B. Principles and Tools

Pharmaceutical manufacturing processes often consist of a series of unit operations, each intended to modulate certain properties of the materials being processed. To ensure acceptable and reproducible modulation, consideration should be given to the quality attributes of incoming materials and their process-ability for each unit operation. During the last 3 decades, significant progress has been made in developing analytical methods for chemical attributes (e.g., identity and purity). However, certain physical and mechanical attributes of pharmaceutical ingredients are not necessarily well understood. Consequently, the inherent, undetected variability of raw materials may be manifested in the final product. Establishing effective processes for managing physical attributes of raw and in-process materials requires a fundamental understanding of attributes that are critical to product quality. Such attributes (e.g., particle size and shape variations within a sample) of raw and in-process materials may pose a significant challenge

because of their complexities and difficulties related to collecting representative samples. For example, it is well known that powder sampling procedures can be erroneous.

Formulation design strategies exist that provide robust processes that are not adversely affected by minor differences in physical attributes of raw materials. Because these strategies are not generalized and are often based on the experience of a particular formulator, the quality of these formulations can be evaluated only by testing samples of in-process materials and end products. Currently, these tests are performed off line after preparing collected samples for analysis. Different tests, each for a particular quality attribute, are needed because such tests only address one attribute of the active ingredient following sample preparation (e.g., chemical separation to isolate it from other components). During sample preparation, other valuable information pertaining to the formulation matrix is often lost. Several new technologies are now available that can acquire information on multiple attributes with minimal or no sample preparation. These technologies provide an opportunity to assess multiple attributes, often nondestructively.

Currently, most pharmaceutical processes are based on time-defined end points (e.g., blend for 10 minutes). However, in some cases, these time-defined end points do not consider the effects of physical differences in raw materials. Processing difficulties can arise that result in the failure of a product to meet specifications, even if certain raw materials conform to established pharmacopeial specifications, which generally address only chemical identity and purity.

Appropriate use of PAT tools and principles, described below can provide relevant information relating to physical, chemical, and biological attributes. The process understanding gained from this information will enable process control and optimization, address the limitation of the time-defined end points discussed above, and improve efficiency.

1. PAT Tools

There are many tools available that enable process understanding for scientific, risk-managed pharmaceutical development, manufacture, and quality assurance. These tools, when used within a system, can provide effective and efficient means for acquiring information to facilitate process understanding, continuous improvement, and development of risk-mitigation strategies. In the PAT framework, these tools can be categorized according to the following:

- Multivariate tools for design, data acquisition and analysis
- Process analyzers
- Process control tools
- Continuous improvement and knowledge management tools

An appropriate combination of some, or all, of these tools may be applicable to a single-unit operation, or to an entire manufacturing process and its quality assurance.

a. Multivariate Tools for Design, Data Acquisition and Analysis

From a physical, chemical, or biological perspective, pharmaceutical products and processes are complex multi-factorial systems. There are many development strategies that can be used to identify optimal formulations and processes. The knowledge acquired in these development programs is the foundation for product and process design.

This knowledge base can help to support and justify flexible regulatory paths for innovation in manufacturing and postapproval changes. A knowledge base can be of most benefit when it consists of scientific understanding of the relevant multi-factorial relationships (e.g., between formulation, process, and quality attributes), as well as a means to evaluate the applicability of this knowledge in different scenarios (i.e., generalization). This benefit can be achieved through the use of multivariate mathematical approaches, such as statistical design of experiments, response surface methodologies, process simulation, and pattern recognition tools, ***in conjunction*** with knowledge management systems. The applicability and reliability of knowledge in the form of mathematical relationships and models can be assessed by statistical evaluation of model predictions.

Methodological experiments based on statistical principles of orthogonality, reference distribution, and randomization, provide effective means for identifying and studying the effect and interaction of product and process variables. Traditional one-factor-at-a-time experiments do not address interactions among product and process variables.

Experiments conducted during product and process development can serve as building blocks of knowledge that grow to accommodate a higher degree of complexity throughout the life of a product. Information from such structured experiments supports development of a knowledge system for a particular product and its processes. This information, along with information from other development projects, can then become part of an overall institutional knowledge base. As this institutional knowledge base grows in coverage (range of variables and scenarios) and data density, it can be mined to determine useful patterns for future development projects. These experimental databases can also support the development of process simulation models, which can contribute to continuous learning and help to reduce overall development time.

When used appropriately, these tools enable the identification and evaluation of product and process variables that may be critical to product quality and performance. The tools may also identify potential failure modes and mechanisms and quantify their effects on product quality.

b. Process Analyzers

Process analysis has advanced significantly during the past several decades, due to an increasing appreciation for the value of collecting process data. Industrial drivers of productivity, quality, and environmental impact have supported major advancements in this area. Available tools have evolved from those that predominantly take univariate process measurements, such as pH, temperature, and pressure, to those that measure biological, chemical, and physical attributes. Indeed some process analyzers provide

nondestructive measurements that contain information related to biological, physical, and chemical attributes of the materials being processed. These measurements can be:

- at-line: Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.
- on-line: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.
- in-line: Measurement where the sample is not removed from the process stream and can be invasive or noninvasive

Process analyzers typically generate large volumes of data. Certain data are likely to be relevant for routine quality assurance and regulatory decisions. In a PAT environment, batch records should include scientific and procedural information indicative of high process quality and product conformance. For example, batch records could include a series of charts depicting acceptance ranges, confidence intervals, and distribution plots (inter- and intrabatch) showing measurement results. Ease of secure access to these data is important for real time manufacturing control and quality assurance. Installed information technology systems should accommodate such functions.

Measurements collected from these process analyzers need not be absolute values of the attribute of interest. The ability to measure relative differences in materials before (e.g., within a lot, lot-to-lot, different suppliers) and during processing will provide useful information for process control. A flexible process may be designed to manage variability of the materials being processed. Such an approach can be established and justified when differences in quality attributes and other process information are used to control (e.g., feed-forward and/or feed-back) the process.

Advances in process analyzers make real time control and quality assurance during manufacturing feasible. However, multivariate methodologies are often necessary to extract critical process knowledge for real time control and quality assurance.

Comprehensive statistical and risk analyses of the process are generally necessary to assess the reliability of predictive mathematical relationships. Based on the estimated risk, a simple correlation function may need further support or justification, such as a mechanistic explanation of causal links among the process, material measurements, and target quality specifications. For certain applications, sensor-based measurements can provide a useful *process signature* that may be related to the underlying process steps or transformations. Based on the level of process understanding, these signatures may also be useful for process monitoring, control, and end point determination when these patterns or signatures relate to product and process quality.

Design and construction of the process equipment, the analyzer, and their interfaces are critical to ensure that collected data are relevant and representative of process and product attributes. Robust design, reliability, and ease of operation are important considerations.

Installation of process analyzers on existing process equipment in production should be done after risk analysis to ensure this installation does not adversely affect process or product quality.

A review of current standard practices (e.g., ASTM International) for process analyzers can provide useful information and facilitate discussions with the Agency. A few examples of such standards are listed in the bibliography section. Additionally, standards forthcoming from the ASTM Technical Committee E55 may provide complimentary information for implementing the PAT Framework. We recommend that manufacturers developing a PAT process consider a scientific, risk-based approach relevant to the intended use of an analyzer for a specific process and its utility for understanding and controlling the process.

c. Process Control Tools

It is important to emphasize that a strong link between product design and process development is essential to ensure effective control of all critical quality attributes. Process monitoring and control strategies are intended to monitor the state of a process and actively manipulate it to maintain a desired state. Strategies should accommodate the attributes of input materials, the ability and reliability of process analyzers to measure critical attributes, and the achievement of process end points to ensure consistent quality of the output materials and the final product.

Design and optimization of drug formulations and manufacturing processes within the PAT framework can include the following steps (the sequence of steps can vary):

- Identify and measure critical material and process attributes relating to product quality
- Design a process measurement system to allow real time or near real time (e.g., on-, in-, or at-line) monitoring of all critical attributes
- Design process controls that provide adjustments to ensure control of all critical attributes
- Develop mathematical relationships between product quality attributes and measurements of critical material and process attributes

Within the PAT framework, a process end point is not a fixed time; rather it is the achievement of the desired material attribute. This, however, does not mean that process time is not considered. A range of acceptable process times (process window) is likely to be achieved during the manufacturing phase and should be evaluated, and considerations for addressing significant deviations from acceptable process times should be developed.

Where PAT spans the entire manufacturing process, the fraction of in-process materials and final product evaluated during production could be substantially greater than what is currently achieved using laboratory testing. Thus, an opportunity to use more rigorous statistical principles for a quality decision is provided. Rigorous statistical principles should be used for defining acceptance criteria for end point attributes that consider

measurement and sampling strategies. Multivariate Statistical Process Control can be feasible and valuable to realizing the full benefit of real time measurements. Quality decisions should be based on process understanding and the prediction and control of relevant process/product attributes. This is one way to be consistent with relevant CGMP requirements, as such control procedures that validate the performance of the manufacturing process (21 CFR 211.110(a)).

Systems that promote greater product and process understanding can provide a high assurance of quality on every batch and provide alternative, effective mechanisms to demonstrate validation (per 21 CFR 211.100(a), i.e., production and process controls are designed to ensure quality). In a PAT framework, validation can be demonstrated through continuous quality assurance where a process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls, and process end points.

Risk-based approaches are suggested for validating PAT software systems. The recommendations provided by other FDA guidances, such as *General Principles of Software Validation*[3] should be considered. Other useful information can be obtained from consensus standards, such as ASTM.

d. Continuous Improvement and Knowledge Management

Continuous learning through data collection and analysis over the life cycle of a product is important. These data can contribute to justifying proposals for postapproval changes. Approaches and information technology systems that support knowledge acquisition from such databases are valuable for the manufacturers and can also facilitate scientific communication with the Agency.

Opportunities need to be identified to improve the usefulness of available relevant product and process knowledge during regulatory decision making. A knowledge base can be of most benefit when it consists of scientific understanding of the relevant multi-factorial relationships (e.g., between formulation, process, and quality attributes) as well as a means to evaluate the applicability of this knowledge in different scenarios (i.e., generalization). Today's information technology infrastructure makes the development and maintenance of this knowledge base practical.

2. Risk-Based Approach

Within an established quality system and for a particular manufacturing process, one would expect an inverse relationship between the level of process understanding and the risk of producing a poor quality product. For processes that are well understood, opportunities exist to develop less restrictive regulatory approaches to manage change (e.g., no need for a regulatory submission). Thus, a focus on process understanding can facilitate risk-based regulatory decisions and innovation. Note that risk analysis and management is broader than what is discussed within the PAT framework and may form a system of its own.

[3] See guidance for industry and FDA staff, *General Principles of Software Validation*.

3. Integrated Systems Approach

The fast pace of innovation in today's information age necessitates integrated systems thinking for evaluating and timely application of efficient tools and systems that satisfy the needs of patients and the industry. Many of the advances that have occurred, and are anticipated to occur, are bringing the development, manufacturing, quality assurance, and information/knowledge management functions so closely together that these four areas should be coordinated in an integrated manner. Therefore, upper management support for these initiatives is critical for successful implementation.

The Agency recognizes the importance of having an integrated systems approach to the regulation of PAT. Therefore, the Agency developed a new regulatory strategy that includes a PAT team approach to joint training, certification, CMC review, and CGMP inspections.

4. Real Time Release

Real time release is the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data. Typically, the PAT component of *real time release* includes a valid combination of assessed material attributes and process controls. Material attributes can be assessed using direct and/or indirect process analytical methods. The combined process measurements and other test data gathered during the manufacturing process can serve as the basis for real time release of the final product and would demonstrate that each batch conforms to established regulatory quality attributes. We consider real time release to be comparable to *alternative analytical procedures* for final product release.

Real time release as defined in this guidance builds on *parametric release* for heat terminally sterilized drug products, a practice in the United States since 1985. In real time release, material attributes as well as process parameters are measured and controlled.

The Agency's approval should be obtained prior to implementing real time release for products that are the subject of market applications or licenses. Process understanding, control strategies, plus on-, in-, or at-line measurement of critical attributes that relate to product quality provides a scientific risk-based approach to justify how real time quality assurance is at least equivalent to, or better than, laboratory-based testing on collected samples. Real time release as defined in this guidance meets the requirements of testing and release for distribution (21 CFR 211.165).

With real time quality assurance, the desired quality attributes are ensured through continuous assessment during manufacture. Data from production batches can serve to validate the process and reflect the total system design concept, essentially supporting validation with each manufacturing batch.

C. Strategy for Implementation

The Agency understands that to enable successful implementation of PAT, flexibility, coordination, and communication with manufacturers is critical. The Agency believes that

current regulations are sufficiently broad to accommodate these strategies. Regulations can effectively support innovation when clear, effective, and meaningful communication exists between the Agency and industry, for example, in the form of meetings or informal communications.

The first component of the PAT framework described above addresses many of the uncertainties with respect to innovation and outlines broad principles for addressing anticipated scientific and technical issues. This framework should assist a manufacturer in proposing and adopting innovative manufacturing and quality assurance. The Agency encourages such proposals and has developed a regulatory strategy to consider such proposals. The Agency's regulatory strategy includes the following:

- A PAT team approach for CMC review and CGMP inspections
- Joint training and certification of PAT review, inspection and compliance staff
- Scientific and technical support for the PAT review, inspection and compliance staff
- The recommendations provided in this guidance

Ideally, PAT principles and tools should be introduced during the development phase. The advantage of using these principles and tools during development is to create opportunities to improve the mechanistic basis for establishing regulatory specifications. Manufacturers are encouraged to use the PAT framework to develop and discuss approaches for establishing mechanistic-based regulatory specifications for their products. The recommendations provided in this guidance are intended to alleviate concerns with approval or inspection when adopting the PAT framework.

In the course of implementing the PAT framework, manufacturers may want to evaluate the suitability of a PAT tool on experimental and/or production equipment and processes. For example, when evaluating experimental on- or in-line process analyzers during production, it is recommended that risk analysis of the impact on product quality be conducted before 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 research is conducted in a production facility, it should be under the facility's own quality system.

When using new measurement tools, such as on- or in-line process analyzers, certain data trends, intrinsic to a currently acceptable process, may be observed. Manufacturers should scientifically evaluate these data to determine how or if such trends affect quality and implementation of PAT tools. FDA does not intend to inspect research data collected on an existing product for the purpose of evaluating the suitability of an experimental process analyzer or other PAT tool. FDA's routine inspection of a firm's manufacturing process that incorporates a PAT tool for research purposes will be based on current regulatory standards (e.g., test results from currently approved or acceptable regulatory methods). Any FDA decision to inspect research data would be based on exceptional situations similar to those outlined in Compliance Policy Guide Sec.

130.300.[4] Those data used to support validation or regulatory submissions will be subject to inspection in the usual manner.

V. PAT REGULATORY APPROACH

One goal of this guidance is to tailor the Agency's usual regulatory scrutiny to meet the needs of PAT-based innovations that (1) improve the scientific basis for establishing regulatory specifications, (2) promote continuous improvement, and (3) improve manufacturing while maintaining or improving the current level of product quality. To be able to do this, manufacturers should communicate relevant scientific knowledge to the Agency and resolve related technical issues in a timely manner. Our goal is to facilitate a consistent scientific regulatory assessment involving multiple Agency offices with varied responsibilities.

This guidance provides a broad perspective on our proposed PAT regulatory approach. Close communication between the manufacturer and the Agency's PAT review and inspection staff will be a key component in this approach. We anticipate that communication between manufacturers and the Agency may continue over the life cycle of a product and that communication will be in the form of meetings, telephone conferences, and written correspondence.

We have posted much of the information you will need on our PAT Web page located at ***http://www.fda.gov/cder/OPS/PAT.htm***. Please refer to the Web page to keep abreast of important information. We recommend general correspondence related to PAT be directed to the FDA PAT Team. Manufacturers can contact the PAT Team regarding any PAT questions at: ***PAT@cder.fda.gov***. Address any written correspondence to the address provided on the PAT Web page. All written correspondence should be identified clearly as **PROCESS ANALYTICAL TECHNOLOGY** or **PAT.**

All marketing applications, amendments, or supplements to an application should be submitted to the appropriate CDER or CVM division in the usual manner. When consulting with the Agency, manufacturers may want to discuss not only specific PAT plans, but also thoughts on a possible regulatory path. Information generated from research on an existing process, along with other process knowledge, can be used to formulate and communicate implementation plans to Agency staff.

In general, PAT implementation plans should be risk based. We are proposing the following possible implementation plans, where appropriate:

- PAT can be implemented under the facility's own quality system. CGMP inspections by the PAT Team or PAT certified Investigator can precede or follow PAT implementation.

[4] FDA/ORA Compliance Policy Guide, Sec. 130.300, FDA Access to Results of Quality Assurance Program Audits and Inspections (CPG 7151.02).

- A supplement (CBE, CBE-30 or PAS) can be submitted to the Agency prior to implementation, and, if necessary, an inspection can be performed by a PAT Team or PAT certified Investigator before implementation.
- A *comparability protocol*[5] can be submitted to the Agency outlining PAT research, validation and implementation strategies, and time lines. 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 preoperational review of a PAT manufacturing facility and process by the PAT Team (see ORA Field Management Directive No.135)[6] by contacting the FDA Process Analytical Technology Team at the address given above.

It should be noted that when certain PAT implementation plans neither affect the current process nor require a change in specifications, several options can be considered. Manufacturers should evaluate and discuss with the Agency the most appropriate option for their situation.

[5] FDA guidance for industry, Comparability Protocols – Chemistry, Manufacturing, and Controls Information, issued February 2003. Once finalized, it will represent the Agency's current thinking on this topic.

[6] FDA Field Management Directive 135. http://www.fda.gov/ora/inspect_ref/fmd/fmd135a.html.

BIBLIOGRAPHY

A. Useful Standards

1. ASTM Standards

E2363-04: Standard Terminology related to PAT

D 3764 - 01: Standard Practice for Validation of Process Stream Analyzer Systems.

D 4855 - 97: Standard Practice for Comparing Test Methods.

D 6299 - 02: Standard Practice for Applying Statistical Quality Assurance Techniques to Evaluate Analytical Measurement System Performance.

E 456-02: Standard Terminology Relating to Quality and Statistics

E1325-02: Standard Terminology Relating to Design of Experiments.

2. Parenteral Drug Association

PDA. May/June 2000. Technical Report No. 33: Evaluation, Validation and Implementation of New Microbiological Testing Methods. PDA Journal of Pharmaceutical Science and Technology 54(3) Supplement TR33

B. Literature

For additional information, refer to FDA's PAT Web page at http://www.fda.gov/cder/OPS/PAT.htm.