Guidance for Industry

PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

DRAFT GUIDANCE

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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)

August 2003
CMC

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PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

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PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to describe a regulatory framework that will encourage the voluntary development and implementation of innovative pharmaceutical manufacturing and quality assurance technologies. Working with existing regulations, the Agency has developed a new innovative approach for helping the pharmaceutical industry address the technical and regulatory issues and questions anticipated during the introduction of such technologies.

The scientific, risk-based framework outlined in this guidance, *Process Analytical Technology* or PAT, should help manufacturers develop and implement new efficient tools for use during the pharmaceutical development, manufacturing, and quality assurance while maintaining or improving the current level of product quality assurance. The framework we have developed has two components: (1) a set of scientific principles and tools supporting innovation and (2) a strategy for regulatory implementation that will accommodate innovation. Among other things, the regulatory implementation strategy includes creation of a PAT team approach to CMC review and CGMP inspections and joint training and certification of PAT review and inspection staff. Together with the recommendations in this guidance, our new strategy is intended to alleviate the fear among manufacturers that introducing new manufacturing technologies will result in regulatory impasse. The Agency is encouraging manufacturers to use the PAT

[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 Center for Drug Evaluation and Research, Center for Veterinary Medicine (CVM), and Office of Regulatory Affairs (ORA).

framework described here to develop and implement new pharmaceutical manufacturing and quality assurance technologies.

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 technological 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.

II. GUIDANCE DEVELOPMENT PROCESS AND SCOPE

This guidance was developed through a collaborative effort involving CDER, the Center for Veterinary Medicine (CVM), and 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) and the PAT-Subcommittee of the ACPS, and several scientific workshops. Discussions covered a wide range of topics including opportunities for improving pharmaceutical manufacturing efficiencies, existing barriers to the introduction of new technologies, possible approaches for removing both real and perceived barriers, and many of the principles described in this guidance.

This guidance addresses new and abbreviated new (human and veterinary) drug application products regulated by CDER and CVM as well as nonapplication drug products. The recommendations in this guidance are not applicable to biological license applications (BLAs) in CDER. Within this scope, the guidance is applicable to all *manufacturers* (e.g., drug substance and drug product manufacture including intermediate and drug product components) over the life cycle of a product. Within the context of this guidance the term *manufacturers* includes new drug and new veterinary drug *sponsors* and *applicants* (21 CFR 99.1(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 innovative tools for a particular product does not mean that similar technologies must be developed and implemented for other products.

[2] This draft guidance is currently not recommended for products regulated by the Center for Biologics Evaluation and Research (CBER). In collaboration with CBER, we may expand the scope of this guidance in the future. Manufacturers should contact the appropriate CBER product office to discuss the applicability of PAT for their specific product and situation.

III. BACKGROUND

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to ensure quality. This conventional approach has been successful in providing quality pharmaceuticals to the public. However, today significant opportunities exist for improving the efficiency of pharmaceutical manufacturing and quality assurance through the innovative application of novel product and process development, process controls, and modern process analytical chemistry tools. Unfortunately, the pharmaceutical industry generally has been hesitant to introduce new technologies and innovative systems into the manufacturing sector for a number of reasons. For example, 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 new technologies. In addition, a number of scientific and technical issues have been raised as possible reasons for this hesitancy. Nonetheless, industry's hesitancy to broadly implement new pharmaceutical manufacturing technologies is undesirable from a public health perspective. The health of our citizens and animals in their care depends on the availability of safe, effective, and affordable medicines. Efficient pharmaceutical manufacturing is a critical part of an effective U.S. health care system.

In the future, pharmaceuticals will have an increasingly prominent role in health care. 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 free industry from its hesitant perspective, 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, respectively

- 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 future state of pharmaceutical manufacturing 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 and

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

This draft guidance, which is part of the Agency's August 2002 initiative, is intended to facilitate progress to this desired state. Once finalized, this guidance will represent the Agency's current thinking on PAT.

IV. PAT FRAMEWORK

For the purposes of this draft guidance, *PAT* is considered 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 understand 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.*

Currently, 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
- The 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 current approach of *building quality into products,* this guidance highlights opportunities for improving manufacturing efficiencies through technological innovation and enhanced scientific communication between manufactures and the Agency. An emphasis on *building quality into products* allows a focus on relevant multi-factorial relationships among material, manufacturing process, and environmental variables and their effects on quality. These relationships provide 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 are obtained through preformulation programs, development and scale-up studies, and from manufacturing data collected over the life cycle of a product.

A desired goal of the PAT framework is to design and develop processes that can 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 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
- Considering the possibility of real time release
- Increasing automation to improve operator safety and reduce human errors
- Facilitating continuous processing to improve ability and manage variability
  - Using small-scale equipment (to eliminate certain scale-up issues) and dedicated manufacturing facilities
  - Improving energy and material use and increasing capacity

Since this guidance primarily focuses on facilitating innovation in manufacturing and quality assurance, discussion in the following sections is directed at process understanding, control, and quality assurance. Although in the following discussions we use some examples of solid dosage forms to illustrate various concepts in the PAT framework, these concepts are applicable to all manufacturing situations.

A. 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 must 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 (e.g., particle shape, size distribution, inter- and intra-particulate bonding) of pharmaceutical ingredients are relatively difficult to characterize, and adverse effects due to inherent quality variability are often not recognized until after manufacture. Establishing effective standards or specifications for physical attributes of raw (e.g., excipients) and in-process materials poses a significant challenge because of the complexities of such attributes (e.g., particle shape and shape variations within a sample) and because of difficulties related to collecting representative powder samples for testing. It is well known that powder sampling procedures that do not take a portion of a powder stream can lead to nonrepresentative results.

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 only be evaluated by testing samples of in-process materials and end products. These tests are performed off line after preparing collected samples for analysis. Currently, different tests, each for a particular quality attribute (e.g., content uniformity, moisture content, dissolution rate), 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 completely take into consideration physical differences in raw materials (e.g., excipients). Processing difficulties can arise that result in failure

of the product to meet specifications, even if certain raw materials conform to established specifications.

Appropriate use of new on- or in-line process analyzers (e.g., vibrational spectroscopy based sensors) that provide information related to both physical (e.g., particle size, morphic form, moisture content) and chemical attributes can not only address the limitation of *time* defined end points discussed above, these tools can improve efficiency of all processes. To be useful, measurements collected from these types of sensors need not be absolute values of the attribute of interest. The ability to measure relative differences in powder materials before (e.g., within a lot, lot-to-lot, different suppliers) and during processing along with current tests for qualifying incoming raw materials will provide useful information for process control. A degree of flexibility in process conditions (e.g., time) should be applied to manage differences in the physical attributes of the materials being processed. Such an approach can be established and justified when differences in physical attribute and process end points are used to control (e.g., feed-forward and/or feed-back) the process. An end point would be determined based on the desired attributes of the materials necessary for the next unit operation (e.g., acceptable blend uniformity, granule size, moisture control).

1. PAT Tools

There are many current and new tools available that enable 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, develop risk-mitigation strategies, achieve continuous improvement, and share information and knowledge. In the PAT framework, these tools can be categorized according to the following:

- 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

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 Data Acquisition and Analysis

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

This knowledge base can be helpful to support and justify flexible regulatory paths for innovations in manufacturing and postapproval changes. Opportunities need to be identified to improve the usefulness of available relevant product and process knowledge during regulatory decision making — without affecting a manufacturer's development program. A knowledge base can be of most benefit when it consists of both a 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). To achieve this benefit, some manufacturers use 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 (e.g., factorial design 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 effectively address interactions between product and process variables. Interactions essentially are the inability of the one factor to produce the same effect on the response at different levels of another factor.

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-cycle of a product. Information from such structured experiments support 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.

Today's information technology infrastructure makes the development and maintenance of this knowledge base practical. When used appropriately, the tools described above can help identify and evaluate product and process variables that may be critical to product quality and performance. The tools may also help in identifying potential failure modes and mechanisms and quantify their effects on product quality.

The types of knowledge that will be useful when introducing new manufacturing and quality assurance technologies would be expected to answer the following types of questions (examples):

- 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?
- Where in the process should the controls be instituted?

b. Process Analyzers or Process Analytical Chemistry Tools

Process analytical chemistry as a discipline has grown significantly during the past several decades, due to an increasing appreciation for the value of collecting process data during production. Chemical industry drivers of productivity, quality, and environmental impact have supported major advancements in this area. Available tools have evolved from those that take simple process measurements, such as pH, temperature, and pressure, to those that measure chemical composition and physical attributes. Some modern process analysis tools provide nondestructive measurements that contain information related to both physical and chemical attributes of the materials being processed. These measurements can be:

- off-line in a laboratory
- at-line in the production area, during production close to the manufacturing process
- on-line where measurement system is connected to the process via a diverted sample stream; the sample may be returned to the process stream after measurement
- in-line where process stream may be disturbed (e.g., probe insertion), and measurement is done in real time
- noninvasive, when the sensor is not in contact with the material (e.g., Raman spectroscopy through a window) in the processor, the process stream is not disturbed

Many of these recent innovations make real-time control and quality assurance during manufacturing feasible. However, multivariate mathematical approaches are often necessary to extract this information from complex signatures and to correlate these results to a primary method of analysis. A comprehensive statistical and risk analysis of the process is generally necessary to assess the reliability of the predictive mathematical relationship prior to implementation. Based on the estimated risk, a correlation function may need further support or justification. This may be in the form of mechanistic explanation of causal links between process, material measurement, 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 interface are critical to ensuring that collected data are relevant and representative of process and product attributes. Robust design, reliability, and ease of operation are important considerations.

A review of current practice standards (e.g., ASTM) for process analyzers in other industries can provide useful information and facilitate discussions with the Agency. A few examples of such standards are listed in the bibliography section. 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.

c. Process Monitoring, Control, and End Points

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

Therefore, 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 pre-established process endpoints to ensure consistent quality of the output materials and the final product.

Within the PAT framework, a process endpoint need not be a fixed time, but can be 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. Process end points intended for use in *real time release* should be considered more critical than those that are only used for in-process control.

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. Multivariate Statistical Process Control can be feasible and valuable to realizing the full benefit of real time measurements. Similarly, rigorous statistical principles should be used for defining acceptance criteria for end product attributes (e.g., content uniformity) that take into consideration differences in the nature of the test (e.g., continuous monitoring) and sample size between an on-line test and a current laboratory test.

Real time or near real time measurement tools typically generate large volumes of data. Only portions of these data are likely to be relevant for routine quality assurance and regulatory decisions. Batch records therefore should include sufficient scientific information (e.g., mean, standard deviation, confidence intervals, of charts) and procedural information. Ease of secure access to these data is important for real time manufacturing control and quality assurance. Installed information technology systems should accommodate these intended functions.

Technologies that incorporate greater product and process understanding can provide a high assurance of quality on every batch and provide alternative, effective mechanisms to achieve validation. In a PAT framework, 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.

Installation of process analyzers on existing process equipment in production should be done after risk-analysis to ensure this installation does not adversely affect the process or product quality (i.e. qualified equipment and validated process). Based on this assessment, it should be decided if the existing process should be revalidated or not.

Risk-based approaches are suggested for validation of PAT hardware and 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 and Good Automated Manufacturing Practices (GAMP) listed in the bibliography section.

d. Continuous Improvement and Knowledge Management

Continuous learning through data collection and analysis over the life cycle of a product is important. Data can contribute to justifying proposals for postapproval changes including introduction of new technologies. 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.

2. 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 ranges of acceptance criteria established for materials used, process parameters, and 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.

The emphasis on process understanding provides a range of options for qualifying and justifying new technologies such as modern on-line process analyzers intended to measure and control physical and/or chemical attributes of materials to achieve *real time release.* For example, if process knowledge is not shared or communicated when proposing a new process analyzer, 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. In some cases, this approach

[3] FDA/CDRH final guidance for industry and FDA staff, *General Principles of Software Validation,*

may be too burdensome and may discourage the use of some new technologies (e.g., use of acoustic measurement patterns or signatures for process controls). An emphasis on process knowledge can provide less burdensome approaches for validating new technologies for their intended use.

Transfer of laboratory analytical methods to on/in-line or noninvasive methods using test-to-test comparisons may not necessitate a PAT approach. Existing regulatory and compendial approaches and guidances on analytical method validation should be considered.

Structured product and process development on a small scale, using experiment design and an on- or in-line process analyzer to collect data in real time for evaluation of kinetics on reactions and other processes such as crystallization and powder blending can provide valuable insight and understanding for process optimization, scale-up, and technology transfer. Process understanding then continues in the production phase when possibly other variables (e.g., environmental and supplier changes) may be encountered. Therefore, continuous learning through data collection and analysis over the life cycle of a product is important.

3. 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. 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. This is currently under discussion as part of the broad FDA Risk-Based initiative.

4. 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.

5. 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 analytical data. Typically, the PAT component of *real time release* can include a validated combination of assessed material attributes (in-process and/or product at final process stage), process controls, process end-points, and other critical process parameters. Material attributes can be assessed using direct and/or indirect (e.g., correlated) process analytical methods. The combined process analytical measurements and other test data gathered during the manufacturing process can serve 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 testing* to be an example of *alternative analytical procedures* for final product release.

Real time release as defined in this guidance builds on *parametric release* for terminally sterilized drug products, a practice in the United States since 1985. In *real time release,* material attributes are measured and controlled along with process parameters. *Real time release* as defined in this guidance may fulfill the requirements of *parametric release* for all dosage forms as defined by other regulatory authorities.[4]

The Agency's approval should be obtained prior to implementing *real time release* for final products. 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. *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.

B. Regulatory Strategies

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 new strategies. Regulations can effectively support innovation (e.g., new drugs and drug delivery systems) as long as clear communication mechanisms exist between the Agency and industry, for example, in the form of meetings or informal communications between the Agency and manufacturers during drug development.

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[4] *Note for Guidance on Parametric Release* issued by the European Agency for the Evaluation of Medicinal Products (EMEA/CPMP/QWP/3015/99, 1 March 2001, London)

The first component of the PAT framework described above addresses many of the uncertainties with respect to new technologies and outlines broad principles for addressing anticipated scientific and technical issues. This information should assist a manufacturer who is proposing to the Agency innovative technologies that may call for a new regulatory path. The Agency encourages such proposals and has developed new regulatory strategies to consider such proposals. The Agency's new regulatory strategy includes (1) a PAT team approach for CMC review and CGMP inspections; (2) joint training and certification of PAT review, inspection and compliance staff; (3) scientific and technical support for the PAT review, inspection and compliance staff; and (4) the recommendations provided in this guidance.

The recommendations provided in this guidance are intended to alleviate the fear of delay in approval as a result of introducing new manufacturing technologies. 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.

We also encourage the use of PAT strategies for the manufacturer of currently approved products. 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.

When using new measurement tools, such as on/in-line process analyzers, certain data trends that may be intrinsic to the current acceptable process may be observed. Manufactures should scientifically evaluate these data to determine how or if such trends affect quality and implementation of PAT tools. Research data collected for the purposes of evaluating the suitability of an experimental PAT tools on an existing product would not be reviewed by the Agency during routine inspections similar to the way the Agency does not review internal quality assurance program audits (Compliance Policy Guide Sec. 130.300).[5] As research progresses toward validation and implementation phases, it should be recognized that sound statistical analysis might be necessary to evaluate data collected in real time because only approved regulatory methods should be used for quality assurance. Appropriate statistical analyses to evaluate sources of variability

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

and/or differences in sample size to establish equivalence between continuous real-time measurements and laboratory test should be considered.

V. PAT REGULATORY PROCESS

One goal of this guidance is to tailor regulatory scrutiny of innovative PAT proposals 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 assurance. For the Agency to be able to do this, manufacturers should communicate important scientific knowledge to the Agency and resolve related technical issues in a timely manner. Because we anticipate that PAT would be used during the life cycle of a product, we have developed a team approach for reviewing and inspecting. Our goal is to facilitate a flexible regulatory assessment involving multiple Agency offices with varied responsibilities.

To determine a regulatory path for innovative proposals, this guidance recommends communication between the manufacturer and the Agency's PAT review and inspection staff. Communications can occur over the life cycle of a product to discuss the particular proposal or issue at hand. To facilitate efficient communication prior to a meeting or telephone conference, manufacturers are asked to provide a written summary of the proposed technology, its validation and implementation strategies, and the preferred regulatory path.

Any written correspondence and subsequent submissions should be identified clearly as **Process Analytical Technology** or **PAT**. We recommend that all PAT-related correspondence directed to CDER and CVM be copied and sent to the FDA PAT Team.

For nonapplication drug products and all PAT questions and issues not pertaining to a specific submission or application, manufactures should contact the FDA PAT Team at the address below.

FDA Process Analytical Technology Team
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For currently approved products, manufacturers should consider the effects of the PAT proposal on the current process, in-process controls, and specifications. In some cases, manufacturers may not need to make a formal submission, but can propose to the Agency a new regulatory path. This guidance does not provide recommendations on the specific information that should be developed by an applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product as they may relate

to the safety or effectiveness of the product.[6] An applicant should consider all relevant FDA guidance documents for recommendations on the information that should be submitted to support a given change.

This guidance encourages research to explore suitability and validation strategies for new technologies prior to proposing and implementing PAT-based manufacturing. If this research is conducted in a production facility, it should be under the facility's own quality system. In this case, the Agency need not be notified before initiating PAT research. Information generated from this research along with other information that provides process understanding can be used to formulate and communicate an implementation proposal to the Agency. Proposals for implementation and regulatory assessment of PAT can be agreed to with the Agency through the communication channels outlined above. A proposal should be risk based and can include the following options:

- Implementation under the facilities quality system and CGMP inspections by the Agency and notification of implementation to the Agency in an *Annual Report* (if appropriate)
- Implementation following CGMP inspection by the PAT team. The PAT team can assist manufacturers with pre-operational review of the PAT manufacturing facility and process (ORA Field Management Directive NO. 135).[7] The recommendations in the inspection report will serve as a summary basis of final approval of the process and be filed in the relevant application and facility databases within the Agency. The manufacturer would then keep the Agency updated through the *Annual Report* (if appropriate).
- A supplement (CBE, CBE-30 or PAS) is submitted to the Agency prior to implementation, and, if necessary, inspection by a PAT team or only PAT certified investigator before implementation. Following implementation, the manufacturer would then keep the Agency updated through the Annual Report.
- A *comparability protocol*[8] 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 adopted for implementation.

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[6] FDA/CDER guidance for industry *Changes to an Approved NDA or ANDA*.

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

[8] FDA *Draft* Guidance for Industry, *Comparability Protocols – Chemistry, Manufacturing, and Controls Information*, issued February 2003

It should be noted that for certain PAT proposals that do not affect the current process or require a change in specifications, several options can be considered. Several options are suggested, and manufactures are asked to evaluate and propose the most appropriate option for their situation.

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A. Industry Consensus Standards

1. ASTM Standards

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

D 6624-01: Standard Practice for Determining a Flow-Proportioned Average Property Value (FPAPV) for a Collected batch of Process Stream Material Using Stream Analyzer Data

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 178 - 02: Standard Practice for Dealing with Outlying Observations.

E 1655 - 00: Standard Practices for Infrared Multivariate Quantitative Analysis.

E 1866 - 97: Standard Guide for Establishing Spectrophotometer Performance Tests.

E 131-00a: Standard Terminology Relating to Molecular Spectroscopy

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

2. International Society of Pharmaceutical Engineers

GAMP Guide for Validation of Automated Systems, issued on December 2003

3. 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://fda.gov/cder/OPS/PAT.htm.