Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

REVISED DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Office of Regulatory Affairs (ORA)

December 2003
Pharmaceutical CGMPs

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Guidance for Industry
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 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. Working with existing regulations, the Agency has developed a new innovative approach for helping the pharmaceutical industry address anticipated technical and regulatory issues and questions.

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 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 as well as joint training and certification of a PAT review and inspection staff,

Together with the recommendations in this guidance, this strategy is intended to address and, where it can, alleviate the concerns among manufacturers that introducing PAT-based control technologies into manufacturing will result in a regulatory impasse. The Agency is encouraging manufacturers to use the PAT framework described here to develop and implement PAT-based systems into pharmaceutical manufacturing and quality assurance.

[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).

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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). 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. In addition, a first draft was published, and a public docket, 2003D-0380, was opened with an initial 60-day comment period for interested persons to comment on the first draft. Based on a review of the cogent comments made to Public Docket 2003D-0380 on that draft, a second draft was published with a 120-day comment period. After reviewing the comments to the second draft, this guidance was finalized and published.

This guidance addresses new and abbreviated new (human and veterinary) drug application products regulated by CDER and CVM as well as nonapplication drug products, with certain exceptions – the guidance is currently not applicable to products in the CDER's Office of Biotechnology Products. Within this scope, the guidance is applicable to all manufacturers of drug substances and drug products (including intermediate and drug product components) over the life of their products. Within the context of this guidance the term *manufacturers* includes new drug and new veterinary drug *sponsors* and *applicants* (21 CFR 99.10). 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 not applicable for products regulated by the Center for Biologics Evaluation and Research (CBER). Manufacturers should contact the appropriate CBER product office to discuss the applicability of PAT for their specific product and situation. In collaboration with CBER, the Agency may expand the scope of this guidance in the future.

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III. BACKGROUND

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to ensure quality. For more than two decades, this evolving conventional approach has been used in providing 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 approaches, process controls, and modern process analytical 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 often-cited reason is *regulatory uncertainty*, which derives from the misperception that our existing regulatory system is rigid and discourages the introduction of new technologies. In addition, a number of scientific and technical issues have been raised as possible reasons for this hesitancy. In reality, the main reason for this hesitancy is the same as the underlying reason for the industry's reluctance to comply with any regulation governing their conduct, the up front and ongoing costs that such activities incur. However, given the significant recent non-compliance costs that some pharmaceutical firms have incurred, the industry has begun to see that the costs of non-compliance can far outweigh the costs of compliance.

Furthermore, any failure to fully comply with CGMP or to broadly implement better pharmaceutical development, manufacturing, and quality assurance technologies is undesirable from a public health perspective. The health of our citizens and animals in their care depends on the availability of unadulterated, safe, effective, and affordable medicines. The efficient CGMP-compliant manufacturing of high-quality pharmaceuticals is a critical part of an effective U.S. health care system.

For the foreseeable 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 current hesitancy, 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 should, if attained, help improve the American public's access to quality pharmaceuticals and health care services. The goals of that initiative are intended to ensure:

- The most up-to-date concepts of statistics-based risk management and quality systems approaches are incorporated into the manufacture of pharmaceuticals while maintaining full compliance with all current good manufacturing practice ("CGMP") **minimums**

- Manufacturers are encouraged to use the latest proven scientific technology (best practical technology [BPT]) in pharmaceutical manufacturing

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- The Agency's submission review and inspection programs operate in a coordinated and synergistic manner

- The Agency consistently enforces all applicable regulations and the manufacturers consistently meet, or exceed, all of the CGMP regulations applicable to their operations.

- Management of the Agency's "Risk-Based Approach" in a manner that encourages scientifically sound innovation in the pharmaceutical manufacturing sector

- Agency resources are used effectively and efficiently to help the industry attain and maintain CGMP compliance so that the industry can provide the data needed for the Agency to use scientifically sound risk management to address the most significant health risks

Pharmaceutical manufacturing continues to evolve with increased emphasis on science and engineering principles. Effective use of valid population statistics, statistical quality control, and the most current pharmaceutical science and engineering principles and knowledge – throughout the life 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 a CGMP-compliant, science-based integrated systems approach to regulating pharmaceutical product quality. The approach used is based on the manufacturer's using the appropriate sound science and fundamental engineering principles for assessing and mitigating the 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 CGMP-compliant manufacturing processes
- Product and process specifications are based on a CGMP-complaint population-statistics-based understanding of how formulation and process factors affect product performance
- Near-real-time quality assurance
- Relevant regulatory policies and procedures are tailored to accommodate the most current level of scientific knowledge and the current recognized consensus target and CGMP-minimum levels for quality
- Risk-based regulatory approaches recognize
  - the CGMP-required *minimum* level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and
  - the capability of CGMP-compliant population-based statistical process control strategies to prevent, or minimize 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 guidance, PAT is considered to be a CGMP-compliant system for assisting in the designing, analyzing, and controlling manufacturing through timely evaluations (i.e., during processing) of critical quality and performance variables and attributes of raw and in-process materials, product, and processes with the goal of ensuring final product quality. It is important to

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note that the term *analysis* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner using population statistics to define the controls, control specifications, and material acceptance specifications required to attain and maintain CGMP compliance. 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*. However, for the foreseeable future, statistical population assessment (21 CFR 211.165(d)) is the way to ensure that each batch or lot of product is, *as the FDC Act requires*, CGMP compliant.

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 characteristics listed above
- The design of manufacturing processes using principles of engineering, material science, and quality assurance to ensure acceptable and reproducible:
  - incoming component lots that have their critical variable properties appropriately constrained,
  - in-process material batches or lots from each phase of production having well-defined characteristics.
  - processing controls that are resistant to the permissible changes in the manufacturing environment and the materials input to each step, and
  - batches or lots of product that all meet, or exceed, their accepted quality and performance expectations 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 the components, materials, manufacturing process steps and controls, and environmental variables and their effects on quality. Provided valid, number-sufficient, population-representative data sets are collected for all factors that may adversely affect the process and the product, and appropriate statistics-based experimentation and modeling is used to establish the validity of any relationships proposed, these proven 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). When the effects of scale are properly addressed and sufficient population representative data is collected at each stage, the data and information to help understand and elucidate these relationships may be obtained through preformulation programs, development and scale-up studies as well as from manufacturing data collected over the life of a product.

A desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined CGMP-compliant, or better, level of quality at the end of the manufacturing process.

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Such procedures would be consistent with CGMP and 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 evaluations and controls
- Minimizing the risk of rejects, scrap, and re-processing
- Considering the possibility of near-real-time release
- Increasing automation to improve operator safety and reduce human errors
- Facilitating continuous processing to improve efficiency and manage variability
  - Using small-scale equipment (to eliminate or minimize certain scale-up issues) and dedicated manufacturing facilities (to minimize setup, changeover, and cleaning disruptions)
  - Improving energy and material use and increasing throughput

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

A. Principles and Tools

0. Introduction and Rationale

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 characteristics of incoming materials and their processability for each unit operation. During the last 3 decades, significant progress has been made in developing analytical methods for chemical characteristics (e.g., identity and purity). Similar progress has been made in assessing the physical characteristics of both components and material mixtures (e.g., particle size distribution, material flow, agglomeration, segregation, density, intrinsic viscosity, particle morphology, and porosity). However, manufacturers have not been equally diligent in characterizing and controlling certain physical variables factors (e.g., particle shape, size distribution, inter- and intra-particulate bonding) that are known to adversely affect the performance of pharmaceutical ingredients. Some have even chosen to claim that such: a) are relatively difficult to characterize and b) are out of the manufacturer's control ("must take what supplier supplies"). Thus, the adverse effects due to a lack of adequate controls on the inherent quality variability in the components are often not recognized until after manufacture. These manufacturers claim that establishing effective standards or specifications for physical characteristics of the raw (e.g., active ingredients and excipients) and in-process materials pose a significant challenge because of the**:** a) complexities of such variables (e.g., particle shape and shape variations within a sample) and b) difficulties related to collecting representative powder samples for testing. It is well known that the typical powder sampling procedures

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used by the pharmaceutical manufacturers are prone to sampling biases.

Formulation design strategies exist that provide robust processes that are not adversely affected by differences allowed by the manufacturer in the physical characteristics of the raw materials used to produce their products. For formulations of solid dosage forms, for example, these strategies fall into three (3) well-defined categories:

- Wet granulation (using aqueous, nonaqueous or mixed aqueous/non-aqueous solvents)
- Dry granulation (using one or more compaction, milling, and screening steps to appropriately bind otherwise "incompatible" [in size, density, and/or binding affinity] components together)
- Direct blending of the ingredients

Because using these defined strategies (instead of the *ad hoc* approaches that many use) generally increases the costs (time and money), some have tried to portray these strategies-as not generalized and based on the experience of a particular formulator. However, the published "state of the science" *vis-à-vis* formulation and process development seems to be at odds with the preceding. In any case, the quality of these formulations can only be assessed by appropriately evaluating samples of the components, in-process materials and end products. Currently, these evaluations are usually performed off line after preparing collected samples for analysis. Different tests, each for a particular quality variable factor (e.g., content uniformity, moisture content, dissolution rate), are needed when, for materials defined by multiple variables, such evaluations only address one variable factor (e.g., level 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 analytical technologies are now available that can acquire information on multiple variable factors with minimal or no sample preparation. These technologies provide an opportunity to assess multiple variable factors, often nondestructively.

Currently many pharmaceutical processing steps are based on *time-defined* end points (e.g., blend for 10 minutes). However, in some cases, because of the lack of adequate material controls and weaknesses in the development of the process, these *time-defined* end points do not properly take into consideration physical differences in the components and materials used in a given process (i.e., active ingredients, excipients and in-process intermediates). Moreover, processing difficulties can arise that result in failure of the product to meet specifications, even when all materials conform to their established specifications. This is the case because the manufacturer, for whatever reason, fails to have adequate controls on the raw materials and/or the processing conditions.

Appropriate use of suitable on- or in-line process analyzers (e.g., vibration-spectroscopy-based systems) that provide information related to both physical (e.g., particle size, morphic form, moisture content) and chemical characteristics can, in some cases, not only address the limitation of time-defined end points discussed above, but also these systems can improve the efficiency of some process steps.

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To be useful in cases where the use of such is scientifically sound (21 CFR 211.160), the evaluations generated by these types of systems need not be absolute values of the variable factors of interest. However, they must be reproducible, precise, appropriately accurate, and material-representative (location, container, or batch) assessments of the variable factors of interest.

The ability to accurately evaluate lot-shipment-representative (21 CFR 211.84(b)) relative differences in powder materials before (e.g., within a lot, lot-to-lot, different suppliers) and during processing along with current tests, where necessary[3], for qualifying incoming raw materials can provide useful information for process control. A pre-established degree of flexibility in process conditions (e.g., time) can be applied to manage differences in the physical characteristics of the materials being processed provided the flexibility is supported by scientifically sound and appropriate process development studies. Provided sufficient material-representative evaluations are made, such an approach can be established and justified when differences in physical characteristics and process end-point evaluations are used to control (e.g., feed-forward and/or feed-back) a given process step. In such cases, *as it often is currently for moisture level in drying operations*, an end point would be determined based on the desired variable factor characteristics 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 may enable scientific, risk-managed pharmaceutical development, manufacture, and quality assurance. These tools, when used within an adequately characterized 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 as follows:

- Multivariate data acquisition and analysis tools
- Modern process analyzers or process analytical tools
- Process and endpoint monitoring and control tools

[3] To meet the requirements of CGMP, at least one "**identity test**" (21 CFR 211.84(d)(1)) must be performed when full testing is performed on lot-representative samples (21 CFR 211.84(b)) and, when a vendor's "**report of analysis**" (or "certificate of analysis") is being used to accept components, the regulations require the manufacturer to perform "**at least one specific identity test**" (21 CFR 211.84(b)(2)) on lot representative samples (21 CFR 211.84(b)). When the on-, in-, or at- line analyzer used does not truly measure identity but instead classifies a material as "acceptable" or "unacceptable," as, for example, most Near-Infra-Red (NIR) analyzers do, the evaluation, while it may be useful to providing assurance that each container of a component is "comparable" to some training set of acceptable materials" is not a "**specific identity**" test. In such cases, the CGMP testing requirements must be met or the product produced will be adulterated. For such, the manufacturers should perform the requisite tests if they wish to even offer their drug products for sale in the United States.

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- 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. However, the scientifically sound and appropriate strategies fall into two (2) broad categories, a) designed condition-spanning experimentation (most typically using factorial or sub-factorial experimental designs) or b) direct-search condition spanning experimentation (a category that is little used in the pharmaceutical industry). In both scientifically sound strategies, once the region or regions where acceptable uniformity and performance are identified, mapping algorithms augmented, where needed, by confirmatory experiments are used to define the systems relationships from which the needed control levels, control specifications, and material acceptance specifications can be established and justified. The success of such developmental strategies hinges on the adequacy of the controls on the:

- Incoming components,
- Environmental conditions (e.g., temperature, humidity, particulate level, microbial load),
- In-process materials and product,
- Equipment used, and
- The individual process steps

These are crucial to the successful development of the process. Provided the developmental strategy used is scientifically sound and appropriate, the knowledge acquired in these development programs can validly be used as 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 a scientific understanding of the relevant multi-factorial relationships (e.g., among the properties of the component, formulation, process, and product quality factors) 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.

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Provided the variability in the components used in the system are adequately defined and controlled, the applicability and reliability of knowledge in the form of mathematical relationships and models can be assessed by statistical evaluation of model predictions *vis-à-vis* the actual observed product outcomes.

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 component, product and process variables. Though not commonly used, multivariate direct-search approaches, like Simplex optimization, that do not rely on factor orthogonality, are less affected by non-uniformities in factor space and generally require fewer experiments than even fractional factorial designs when several variables are concomitantly studied. Such direct-search Simplex studies may provide a more rapid means of identifying the optimum region for the material levels and processing conditions used in a given process step than factorial designs.

Traditional one-factor-at-a-time experiments do not effectively address interactions (also known as, confounding factors or factor non-orthogonalities) between product outcomes and the levels selected for the process variables. This is the case because such experimentation strategies provide no means of identifying or estimating the effects of interactions when, as is usually the case, such exist. In multivariate experiments, interactions (or confounding factors and factor non-orthogonalities) are those parts of the effects observed (results) that, though identified, cannot be accounted for solely by the levels of the factors studied in the experiments when factor analysis is applied to the results data generated by such experiments.

Unfortunately, pharmaceutical systems are complicated by the variability in the components assigned as factors in such studies. Thus, the apparent interactions identified may be partially connected to the usually "not well characterized" variability in the specific component aliquots used in each experiment. However, many of the commercially available statistical programs used do not even consider, much less, warn the user to consider and/or allow the user to adequately address, this reality. To properly address component variability, iterative replication of a significant number of the designed experiments (using various combinations of components from different [unrelated] lots) is required to separate component variability from component and processing interaction effects. Regrettably, the experimental development studies conducted by many firms seem to ignore, or, at best, minimally address, this "factor level uncertainty" reality.

Nonetheless, experiments conducted during product and process development can serve as the building blocks for the understanding of the process that can evolve to accommodate a higher degree of complexity as the factor and results data sets grow throughout the life of a product. Information from such structured experiments can be used to support the development of a knowledge system for a particular product and its processes, provided the experiments are scientifically sound and the permitted variability in the components used in the process is properly addressed.

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This information, along with information from other similarly sound development projects, can then become part of a scientifically sound and effective overall institutional knowledge base. As this institutional knowledge base grows in coverage (range of components, processes, 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 component, 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 in quantify their effects on both process capability and 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 impacts of process changes upon the active transport, degradation, and dissolution properties of the component, intermediate, drug substance, or drug product being manufactured?
- What are the components and processing steps that should be used to manufacture the initial, clinical, and projected approved dosage forms to ensure that each dosage form will meet the appropriate standards of quality?
- What sources of variability are critical?
- For the clinical and projected approved dosage form, what are the key physical and chemical properties of the components selected, the controls needed for the key components, and the control ranges needed for each key property of each component?
- What are the effects of product material levels and processing conditions on *product* quality *and product acceptability*?
- Where in the process should the process and product controls be instituted?

b. Process Analyzers and Process Analysis Tools

The use of process analytical technology (PAT) has grown significantly during the past several decades. The increase in the usage of PAT has been driven by an increasing appreciation for the value of collecting process data during production and the advances in instrumentation, sensors, and data acquisition, storage, and processing power. Beginning with the oil industry in the 1970's, the chemical industry drivers, including the need to a) address and minimize the effects of feed variability, b) increase productivity, c) improve quality, and d) minimize adverse environmental impacts, have supported major advancements in this area. Available tools have

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evolved from those that take simple process measurements, such as pH, temperature, and pressure, to those that measure chemical composition (e.g., GC-TCD/EC/MS, LC-UV/RI/MS, ICP-Light Adsorption/MS, and NMR) and physical variable factors (e.g., color, density, viscosity, particle size distribution, flow). Some modern process analysis tools provide nondestructive evaluations that contain information related to both the physical and chemical variable factors of the materials being processed. These evaluations can be:

- off-line, in a laboratory, where the samples are removed from the processing area, transported to the lab, and evaluated
- at-line, in the production area, where the samples are evaluated during production in an area close to the manufacturing process
- on-line, where the evaluation system is connected to the process via sample stream diverter; periodically, a sample from the process is diverted and evaluated; and, in favorable cases; the sample is returned to the process after evaluation
- invasive in-line**,** where the process is disturbed (e.g., probe insertion), and evaluation is done in real time
- noninvasive in-line, where the sensor is not in contact with the material (e.g., Raman spectroscopy through a window in the process equipment) and the process 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. The most critical problem in this area is ensuring that the correlations found are truly correlations between the changes in the samples and the test results observed. For example, when using Near-Infrared ("NIR") system to assess component purity, the Near-IR adsorption bands chosen must be directly relatable to the structural features of the compound. If this is not the case, future batches, as has been found in more than one instance, may be improperly classified as failing when they do not or, worse, passing when they fail. The second most critical problem in this area, especially for complex material mixtures, is having analyzer training sets that include representative examples of both passing/conforming materials and failing/non-conforming materials that appropriately span the entire possible ranges. The third critical problem is the evaluation of sufficient population representative samples to insure that the overall classification arrived at by the trained validated evaluation systems is valid. [**Note:** Typically, in dynamic systems equipped with short-range sensors in much wider vessels, some significant multiple of the number of evaluations required in static systems will need to evaluated.] In the discrete entity case, the numbers in the recognized attribute inspection (sampling and evaluation) plans (e.g. ***ANSI/ASQ Z 1.4***) for the "process variability unknown case"[4] can be used as the

[4] The restriction to the "process variability unknown case" arises because the variabilities in the key physical property factors of the components used in the process are: **a)** not, for whatever reason, rigorously controlled and/or **b)** the allowed variabilities in said properties, and not just the levels of the components and their interactions, can be significant factors in determining the outcomes observed.

basis number with the multiplier being determined by the level of residual variability in the system.

When the validity of the correlations~~,~~ and the adequacy of the training sets have been established, and sufficient population representative evaluations have been made, a comprehensive statistical analysis of the process is generally necessary to assess: **a)** the reliability of the predictive mathematical relationships established and **b**) the risks associated with the failure of the each of the correlations thus established prior to implementation. Based on the estimated risk and the level of confidence in the correlations generated, a correlation function may need further support or justification. This support or justification may be in the form of mechanistic explanation of the causal links between the inputs (components and/or prior step materials), the processing steps, and the evaluated outputs as they impact and are impacted by the target quality specification~~s~~ *minimums* and acceptance criteria required by CGMP. For certain applications, non-quantitative PAT-based evaluations can provide a useful *material signature* that may be related to the underlying acceptability of the 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 can be established (proven) to reliably relate to product acceptability and/or process capability.

Design, construction, and qualification of the process equipment, the analyzer, and their interface are critical to ensuring that collected data are relevant and representative of process and product variable factors. 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-based process consider a CGMP-compliant, scientific, risk-adverse approach relevant to the intended use of the analyzer in a specific process step.

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 component, material and process variable factors "that may be responsible for causing variability in the characteristics of in-process material and the drug product" (21 CFR 211.110(a))
- Design a process evaluation system to allow real time or near-real time (e.g., on-, in-, or at-line) monitoring of all critical variables that developmental studies establish can affect the acceptability of the product produced in a given step
- Design process controls that permit pre-established adjustments to ensure adequate control of all critical variable factors and process outcomes

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- Develop valid mathematical correlation relationships between product the product's quality requirements (regulatory and commercial) and the results from the in-depth evaluation of all critical component, material, and process variables

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 component, material, and product variables. Process monitoring and control strategies are intended to monitor and validate (21 CFR 211.110) the state of a process and, within pre-established limits, actively manipulate it to maintain the required outcomes. Strategies should explicitly address: a) the critical variable factors for the input components and materials, b) the ability and reliability of process analyzers to evaluate the critical variable factors, and c) the achievement of pre-established process endpoints to ensure consistent batch conformance to specifications for each batch of the output materials and the final product. Within the PAT framework, a process endpoint need not be a fixed time, but can, within pre-established limits, be defined by the achievement of a predefined material specification (e.g., a LOD [loss on drying] of less than 1 %). This, however, does not mean that process time is not considered. A range of acceptable process times (processing window), likely to be achieved during the manufacturing phase, should be evaluated, and provisions for addressing significant deviations from the predetermined acceptable process times should be developed. Process end points intended for use in *"near-real-time" release* should be considered more *critically* than those that are only used for in-process control.

Where the use of PAT spans the entire manufacturing process, the fraction of components, in-process materials and final product evaluated during production could be substantially greater than the often non-CGMP-compliant inspection practices used by many firms that minimize laboratory testing by ignoring the explicit requirements set forth in 21 CFR Part 211 for the acceptance inspection (sampling and testing) of**: a)** incoming components (21 CFR 211.84(b) and (d) and 21 CFR 211.160(b)(1)), **b)** in-process materials (21 CFR 211.110(b) and 21 CFR 211.160(b)(2)) **and c)** the drug product (21 CFR 211.160(b)(3) and 21 CFR 211.165(d)). This requirement for an increased number of samples arises occurs because a valid static "classifying" PAT typically requires at least half an order of magnitude more batch-representative evaluations than testing, and a dynamic "classifying" PAT requires several time that number, before a valid assessment of the acceptability of an in-process <u>batch</u> or <u>lot</u> can be reached. Moreover, the drug product CGMP, by explicitly requiring the use of statistical quality control (SQC, 21 CFR 211.165(d)), makes the use of PAT a difficult choice to establish and justify for "product release" (the acceptance of the drug-product batch for release) *even when the firm has rigorous component acceptance controls.* In addition, the in-process findings by a PAT classifying analyzer, even if valid, preclude the *direct* use of that data to reduce the number of samples required for valid SQC assessments. This is the case because such findings provide no *direct* measures of the variability of the in-process batch at each stage. However, such classifying analyzers do provide the manufacturer with another opportunity to apply statistical principles to its in-process acceptance/rejection decision practices. Thus, multivariate Statistical

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Quality Control (SQC) is feasible and, when properly applied, can be a valuable adjunct to realizing the full benefit of real-time and near-real-time evaluations.

Similar statistical principles should be used for defining the acceptance specifications for end product variable factors (e.g., content uniformity). These should take into consideration the:

- Testing requirements of the CGMP regulations
- Differences in the nature of the evaluation (e.g., measurement, or examination and/or classification)
- Differences in the minimum number of samples required for a valid evaluation
- Intrinsic sample volume or mass differences between an on-, in-, or at- line evaluation and a current laboratory test

Real-time or near-real-time evaluation tools typically generate large volumes of data. In a PAT environment, batch records should include the same CGMP-complaint scientific and procedural information that establishes the acceptability of the process and the product as that required currently. However, the volume of data should be:

– *at least half* an order of magnitude or more larger for *static* PAT-based "classifying" analysis systems than the volume of data required to show CGMP compliance in the current "laboratory" environment, and

– several times more than the amount required for static systems when comparable *dynamic* PAT-based "classifying" analysis systems are used.

For example, when the on-, in-, or at- line systems truly make measurements, the batch records should include a series of charts displaying the measurement results obtained in terms of their acceptance ranges and confidence interval estimates as well as intra- batch charts showing data distribution plots, and the inter-batch control charts, updated global process envelope tabulations, and trend charts. When the on-, in-, or at- line analyzers classify the samples, the batch records should include the appropriate attribute counterparts to the variable charts. Ease of secure access to these data is important for real-time manufacturing control and near-real-time quality assurance. In such cases, the firm's installed information technology systems should be fully compliant with all of the applicable recordskeeping requirements of 21 CFR 211 and the electronic records and electronic signature strictures of 21 CFR Part 11 and fully support of all the requisite functions.

Technologies that facilitate the provision of greater product and process understanding can provide a high assurance of CGMP compliance for every batch and provide alternative, effective mechanisms to establish the validity of the process. In a PAT framework, process validity can be enhanced and CGMP-compliance assurance can be increased when each process step is continually monitored, its conformance to targets is concomitantly evaluated, and, within pre-established limits, parameters and time frames, adjusted using validated in-process evaluations (tests and examinations), controls, and process endpoints.

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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, validated process, and CGMP-compliant product). Based on this assessment, it should be decided if any part of the existing process should be additionally qualified or not.

Risk-assessment-based approaches are suggested for the validation of PAT software systems. The recommendations provided by other FDA guidances such as General Principles of Software Validation[5] should be considered. Other useful information can be obtained from consensus standards, such as ANSI, ASQC (now ASQ), ASTM, IEC, ISA, ISO, and Good Automated Manufacturing Practices (GAMP) listed in the bibliography section.

d. Continuous Improvement and Knowledge Management

Continuous learning through the continual analysis of the batch-representative data collected over the life of a product is important. The appropriate analysis of the batch-representative data collected can contribute to justifying proposals for postapproval changes including the introduction of new technologies. Approaches and information technology systems that support knowledge acquisition from such data collections are valuable for the manufacturers and can also facilitate the sharing of scientific information with the Agency.

2. *Process Understanding*

A process is generally considered well understood when (1) all critical sources of variability are identified, properly controlled, and understood; (2) the permissible component and process variabilities are managed by the process; and (3) product quality variability can be accurately and reliably predicted to be within the acceptance specifications established by the materials used, process parameters, manufacturing environment and other conditions. The ability to accurately predict the outcomes of changes within the validated process envelope requires a high degree of process control and understanding. Although retrospective process capability data can be indicative of a state of control (provided sufficient batch-representative data is available for each batch or lot produced), 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 evaluate and, when active feedback and feed-forward mechanisms are included, control physical and/or chemical variable factors of the materials to achieve *near-real-time* acceptability for 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., on-line automated UV/visible active uniformity assessment system) and a conventional test method (e.g., a wet chemical test) on collected samples may be the only available option. Similarly,

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

Derived from: http://www.fda.gov/…/…/3996gdl00001.pdf

when proposing a new process analyzer, the evaluation-to-test comparison between an on-line classifying analyzer (e.g., NIR spectroscopy for content uniformity confirmation) and a conventional test method (e.g., a wet UV/visible content uniformity test) not only requires an extensive comparison between collected samples but also requires the preparation of comparable "known definitely passing," and "known definitely failing" training sets for the initial signature identification and training of the analyzer as well as "known marginally passing" and "known marginally failing" samples sets for the confirmatory training of the analysis system. In addition, unless all of the data produced is properly collected with an appropriate environmental reference corrector, **a)** the "marginal" training sets will need to be reevaluated by the classifying analyzer before each use to verify the "classification" accuracy of such analyzers and, *in any case*, **b)**, periodically, the in-process "wet test" will need to be performed on batch-representative in-process samples to confirm the accuracy of such analyzers' findings. Finally, to comply with CGMP (21 CFR 211.165(d)), release testing must be done on representative samples from each batch — when the process analyzer does not test (e.g., NIR spectroscopy systems), the manufacture ***may*** still ***be*** required to perform the requisite release testing. In some cases, this approach may be too burdensome and may discourage the use of some new technologies (e.g., use of acoustic *pattern evaluations* or "signatures" for in-process controls). Accumulated process knowledge derived from appropriate batch-representative test data for each variable factor in each batch can, in many cases, greatly reduce the burdens incurred in defining the requisite training sets, performing the requisite training, and verifying the suitability of a variable-classifying technology for its intended use.

Transfer of a current laboratory analytical test method (e.g., an HPLC method for content) to a comparable in-line or at-line test method (e.g., an automated sample-preparation [sampling, weighing and dilution] UV/Visible test system for content) using test-to-test comparisons may not necessitate a PAT approach. Existing regulatory and compendia1 approaches and guidances on analytical method validation should be considered in such cases.

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. The maturation of such firms' process understanding then continues in the production phase where other variables (e.g., environmental and supplier changes) may be encountered. Therefore, continuous learning through data collection and analysis over the life 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 provided the components, environmental conditions, equipment, and process steps are adequately controlled. For processes that are well understood, well controlled and CGMP-compliant, opportunities exist to develop less restrictive regulatory approaches to manage change than the most restrictive approach, the

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filing of a prior-approval supplement (PAS), which requires in-depth formal review, possible on-site inspection, and the issuance of a formal acceptance letter by the Agency. Thus, a focus on process understanding, control and compliance 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.

4. Integrated Systems Approach

The fast pace of innovation in today's information age necessitates integrated systems thinking for the in-depth evaluation and timely application of efficient, CGMP-compliant tools and systems that protect public health and safety, promote improved product quality and regulatory compliance and satisfy the needs of 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 that is fully CGMP-compliant as well as compliant with 21 CFR Part 11. Therefore, upper management support for these initiatives is critical for their successful implementation.

5. Near-Real-Time Release

Given the requirement that all drugs must be CGMP-compliant, *near-real-time* release is the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on the on-line, electronic, QCU review and acceptance of all applicable batch production and control records in conjunction with an appropriate review and acceptance of the process analytical evaluation data. Typically, the PAT component of *near-real-time release* includes a validated combination of assessed material characteristics (in-process and/or product), process controls, process end points, CGMP-required test data and test data assessments, and other critical process parameters. While in-process variable factors can be assessed using direct and/or indirect (e.g., correlated) process analytical methods, **a)** the CGMP regulations explicitly require identity testing on lot-shipment representative samples and test result acceptance for incoming components (21 CFR 211.84(b), 21 CFR 211.84(d) and 21 CFR 211.160(b)(2)), and **b)**, for drug product release, CGMP requires the use of statistical-quality-control-based testing of batch-representative sample units and states that "**statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels**" (21 CFR 211.165(d)). Thus, whatever a regulated firm elects to do, the aforementioned evaluations must include the explicitly required testing (not just evaluations correlated thereto) for incoming component identity acceptance and for drug-product release. The combined process analytical evaluations (including classification or examination outcomes) and other CGMP-mandated test data gathered during the manufacturing process can serve the basis for the *near-real-time release* of the final product that demonstrates that each batch conforms to established regulatory requirements.

The Agency's approval should be obtained prior to implementing *near-real-time release* for final products. Process understanding, control strategies, plus on-, in-, or at-line evaluation of the critical variable factors that relate to product quality can provide a scientific risk-based

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approach to justify how near-real-time quality assurance augmented by the requisite CGMP testing may be equivalent to, or better than, the prevalent laboratory-only-based testing and quality-control-unit test result assessment on today's collected samples.

Near-real-time release as outlined in this guidance can meet the requirements of testing and release for distribution (21 CFR 211.165) and production record review (21 CFR 211.192) that must be met before a manufacturer's quality control unit can release the batch or lot of product for introduction into commerce. The CGMP requirements ***minimums*** can be met provided the explicit requirements are satisfied for:

- at least one "**identity test**" or "**specific identity test**" on representative samples of each shipment of each lot of each incoming component acceptance (21 CFR 211.84) and
- a statistical quality control test and test acceptance assessment against appropriate AQL criteria are conducted on an appropriate number of batch representative units from each batch (21 CFR 211.165(d)).

When all of the requisite reviews have been accomplished on line, all item expectations have been met, and the batch or lot has been found to be acceptable for release, the manufacturer's quality control unit (QCU), by a secure electronic signature procedure, can then sign off on the official "certificate of analysis" for the batch or lot and issue an "on-line release" authorizing the release of that batch for distribution [**Note:** Any discrepancy or unexpected finding must be thoroughly investigated and the investigation completed before the QCU signs off on any release or release-related document that the firm's quality system includes in its validated computerized "release for distribution" module.]

For near-real-time quality assurance, the desired process performance and material acceptability can be ensured by using process-appropriate, CGMP-compliant, real-time process and near-real-time material assessment during the manufacture of each batch. As required by 21 CFR 211.110, the test and examination data from production batches still serves "**to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product**." In addition, this data contributes to the body of knowledge that defines the overall integrity of the process and serves to establish the relative importance of each factor or factor interaction so that that information is available and can be used to facilitate the investigation of any process, material or product deviation from its predefined expectation limits or ranges.

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.

The first component of the PAT framework described above addresses many of the uncertain-

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ties 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 direction. The Agency encourages such proposals and has developed new regulatory strategies to consider such proposals. 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 industry's concerns about a 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 CGMP-compliant *scientifically sound* and *appropriate* statistics-based regulatory specifications for their products. These statistics-based *specifications* for the manufacturer's final product must be:

1. **Based on** the **evaluation of sets of** *batch-representative* ***samples*** and
2. **Derived from** the **USP**'s lifetime **post-release "*any article*" *requirements***.

Because only a small percentage of each batch of the product is evaluated, the manufacturer's statistics-based specifications must be appropriately inside of the **USP**'s limit and range values. In general, the fewer batch-representative samples that a firm's inspection plan evaluates, the further the manufacturer's acceptance criteria must be inside of the appropriate **USP**'s limit values or ranges.

We also encourage the use of PAT strategies for the manufacture 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 be used to assess the potential adverse impacts, if any, on product quality before installation is initiated. 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 evaluation tools, such as on/in-line process analyzers, certain data trends (that may be intrinsic to the current accepted process) may be observed. Manufacturers should scientifically evaluate these data to determine how, or if, such trends indicate an adverse product quality impact and/or an adverse impact attributable to the implementation of the PAT tools being studied. In cases where the data observed clearly indicate an underlying process control problem, that problem must be investigated in the same manner as required for any other such problem. Except where it is part of a CGMP-mandated problem investigation, the Agency does not intend to

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inspect research data collected on an existing product for the purpose of evaluating the suitability of an experimental process analyzer or other PAT tools. The FDA's general 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: **a)** their being part of a problem investigation or **b)** exceptional situations similar to those outlined in Compliance Policy Guide Sec. 130.300[6]. Those data used to support validation or regulatory submissions will be subject to inspection in the usual manner.

V. REGULATORY APPROACH TO PAT USAGE

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 assurance. To facilitate achieving that goal, manufacturers should communicate important scientific knowledge to the Agency and resolve related technical issues in a timely manner. The Agency's goal is also to facilitate a flexible regulatory assessment involving multiple Agency offices with varied responsibilities.

This guidance provides a broad perspective on the Agency's 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: **a)** communication between manufacturers and the Agency will continue over the life of a product and **b)** communication will be in the form of meetings, telephone conferences, and written correspondence. Any 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***.

We recommend general correspondence related to PAT be directed to our new FDA PAT Team. Manufacturers can also contact the PAT Team regarding any PAT questions or issues related to nonapplication drug products or not pertaining to a specific submission or application at the address below.

FDA Process Analytical Technology Team
Office of Pharmaceutical Science, HFD-003
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857"

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

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For currently approved products, during the planning phase for adding one or more PAT-based analyzers to a process, manufacturers should consider the effects of PAT on the current process, in-process controls, and specifications. When consulting with the Agency, manufacturers may want to discuss not only specific PAT plans, but also their thoughts on a possible CGMP-compliant regulatory path to implementing those plans.

This guidance is also intended to encourage research to explore suitability and validation strategies for new technologies prior to planning and implementing PAT-based manufacturing. If research is conducted in a production facility, it should be conducted under the facility's existing CGMP-compliant quality system. Information generated from this research along with other information that provides process understanding can be used to formulate and communicate implementation plans to Agency staff. Plans for implementing and regulatory assessment of PAT can be agreed to with the Agency through a variety of communication channels.

Section 116 of the 1997 Food and Drug Administration Modernization Act amended the Food, Drug, and Cosmetic Act by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. We recommend that manufacturers continue to consider all relevant FDA guidance documents for recommendations on the information that should be submitted to support a given change.[7]

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

- PAT can be implemented under the CGMP-compliant facility's quality system; CGMP inspections by the Agency *will* follow.

- PAT can be implemented following an acceptable 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)[8]. The recommendations in the inspection report will: a) serve as a summary basis ~~of~~ in the Agency's final review and approval of the process and b) be filed in the relevant application, where needed, ~~and~~ as well as the facility databases within the Agency.

- A supplement (CBE-0, 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[9] can be submitted to the Agency outlining PAT research, validation and implementation strategies and time lines. Following approval of this

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

[8] FDA Field Management Directive 135. http://www.fda.gov/ora/inspect-ref/fmd135a.html

[9] FDA draft 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.

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comparability protocol by the Agency, one or a combination of the above regulatory pathways can be adopted for implementation.

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.

Derived from: http://www.fda.gov/…/…/3996gdl00001.pdf

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ISO 11843-3:2003 Capability of detection – Part 3: Methodology for determination of the critical value for the response variable when no calibration data are used

ii. Calibration

ANSI/ASQC M1-1996: American National Standard for Calibration Systems

ISO 11095:1996 Linear calibration using reference materials

ISO Guide 32:1997 Calibration in analytical chemistry and use of certified reference materials

ISO 12713:1998 Non-destructive testing -- Acoustic emission inspection -- Primary calibration of transducers

ISO 12714:1999 Non-destructive testing -- Acoustic emission inspection -- Secondary calibration of acoustic emission sensors

d. REFERENCE STANDARD MATERIALS

ISO Guide 30:1992 Terms and definitions used in connection with reference materials

ISO Guide 31:2000 Reference materials – Contents of certificates and labels

ISO Guide 33:2000 Uses of certified reference materials

ISO Guide 34:2000 General requirements for the competence of reference material producers

ISO Guide 35:1989 Certification of reference materials – General and statistical principles

e. GENERAL QUALITY SYSTEM RELATED

ANSI/ISO/ASQC Q10011-1994 Series: Guidelines for Auditing Quality Systems

ANSI/ASQC E2-1996: Guide to Inspection Planning

ANSI/ISO/ASQC Q10006-1997: Quality Management - Guidelines to Quality in Project Management

ANSI/ASQ Z1.13-1999: Quality Systems Guide for Research

ANSI/ISO/ASQC Q9003-1994: Model for Quality Assurance in Final Inspection and Test

ASQC Q2-1991: Quality Management System and Elements for Laboratories - Guidelines

ANSI/ISO 17025-1999 General Requirements for the Competence of Testing and Calibration Laboratories

f. RISK MANAGEMENT

ISO/IEC Guide 73:2002 Risk management – Vocabulary -- Guidelines for use in standards

ISO 14971:2000 Medical devices – Application of risk management to medical devices

g. OTHER

ANSI/IEC/ASQC D601123-1997: Reliability Testing – Compliance Test Plans for Success Ratio

Derived from: http://www.fda.gov/…/…/3996gdl00001.pdf

ANSI/IEC/ASQC D601070-1997: Compliance Test Procedures for Steady-State Availability

ISA-TR91.00.02-2003: Criticality Classification Guideline for Instrumentation

2. 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

3. International Society of Pharmaceutical Engineers

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

4. 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

Derived from: http://www.fda.gov/…/…/3996gdl00001.pdf

B. STATUTORY AND REGULATORY REFERENCES

1. 21 U.S.C. Title 9—Federal Food, Drug, and Cosmetic Act ("FDC Act") Sections

- **a. 301** Short title (and brief legislative history)
- **b. 321** Definitions, generally
- **c. 321b** "Package" defined
- **d. 331** Prohibited acts
- **e. 332** Injunction Proceedings
- **f. 333** Penalties
- **g. 334** Seizure
- **h. 335** Hearing before report of criminal violation
- **i. 335a** Debarment, temporary denial of approval, and suspension
- **j. 335b** Civil penalties
- **k. 335c** Authority to withdraw approval of abbreviated drug applications
- **l. 351** Adulterated drugs and devices
- **m. 352** Misbranded drugs and Devices
- **n. 355** New Drugs
- **o. 356a** Manufacturing Changes
- **p. 358** Authority to designate official names
- **q. 360** Registration of producers of drugs and devices
- **r. 360b** New animal drugs
- **s. 371** Regulations and hearings
- **t. 372** Examinations and investigations
- **u. 374** Inspection
- **v. 377** Revision of United States Pharmacopoeia; development of analysis and mechanical and physical tests
- **w. 379** Confidential information
- **x. 379d** Automation of Food and Drug Administration
- **y. 393** Food and Drug Administration
- **z. 394** Scientific review groups

2. 21 CFR—Food And Drugs Parts

- **a. 5** DELEGATIONS OF AUTHORITY AND ORGANIZATION
- **b. 7** ENFORCEMENT POLICY

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c.	**10**	ADMINISTRATIVE PRACTICES AND PROCEDURES
d.	**11**	ELECTRONIC RECORDS; ELECTRONIC SIGNATURES
e.	**20**	PUBLIC INFORMATION
f.	**26**	MUTUAL RECOGNITION OF PHARMACEUTICAL GOOD MANUFACTURING PRACTICE REPORTS, MEDICAL DEVICE QUALITY SYSTEM AUDIT REPORTS, AND CERTAIN MEDICAL DEVICE PRODUCT EVALUATION REPORTS: UNITED STATES AND THE EUROPEAN COMMUNITY
g.	**58**	GOOD LABORATORY PRACTICE FOR NONCLINICAL LABORATORY STUDIES
h.	**201**	LABELING
i.	**207**	REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN COMMERCIAL DISTRIBUTION
j.	**210**	CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL (applies to Parts 210 – 226 and others)
k.	**211**	CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS
l.	**310**	NEW DRUGS
m.	**312**	INVESTIGATIONAL NEW DRUG APPLICATION
n.	**314**	APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG
o.	**315**	DIAGNOSTIC RADIOPHARMACEUTICALS
p.	**316**	ORPHAN DRUGS
q.	**320**	BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS
r.	**514**	NEW ANIMAL DRUG APPLICATIONS
s.	**600**	BIOLOGICAL PRODUCTS: GENERAL
t.	**606**	CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS
u.	**610**	GENERAL BIOLOGICAL PRODUCTS STANDARDS
v.	**640**	ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS
w.	**820**	QUALITY SYSTEM REGULATION (CGMP for Devices for Human Use)

Derived from: http://www.fda.gov/…/…/3996gdl00001.pdf

C. TEXTS and REFERENCE BOOKS

1. "**STATISTICAL QUALITY ASSURANCE METHODS FOR ENGINEERS**," Stephen B. Vardeman and J. Marcus Jobe, 1999, John Wiley & Sons.

2. "The Guidelines for The Development and Validation of Near-Infrared Spectroscopic Methods in the Pharmaceutical Industry" in the "**HANDBOOK OF VIBRATIONAL SPECTROSCOPY,**" John M. Charmers and Peter R. Griffiths (Editors), 2002, John Wiley & Sons Ltd

3. "**STATISTICAL METHODS IN MANUFACTURING**," Richard B. Clements, 1991, Prentice-Hall

4. "**STATISTICS**," David Freeman, Robert Pisani and Robert Purvis, 1978, WW Norton & Company

5. "**EXPERIMENTAL STATISTICS, Handbook 91**," Mary Gibbons Natrella (Editor), 1966, National Bureau of Standards reprint of "experimental statistics" portion of Army Material Command's "*AMC Engineering Design Handbook*" series

6. "Encarta World English Dictionary," Anne H. Soukhanov (US General Editor), 1999, St. Martin's Press

D. LITERATURE

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

Derived from: http://www.fda.gov/…/…/3996gdl00001.pdf

GLOSSARY

A. Terms Defined By Regulation

1.	***"Acceptance criteria"***	**21 CFR 210.3(b)(20)**
2.	***"Active ingredient"***	**§§ 210.3(b)(7)**
3.	***"Batch"***	**§§ 210.3(b)(2)**
4.	***"Component"***	**§§ 210.3(b)(3)**
5.	***"Drug product"***	**§§§ (b)(4)**
6.	***"Inactive ingredient"***	**§§§ (b)(8)**
7.	***"In-process material"***	**§§§ (b)(9)**
8.	***"Lot"***	**§§§ (b)(10)**
9.	***"Manufacture, processing, packing, or holding of a drug product"***	**§§§ (b)(12)**
10.	***"Quality control unit"***	**§§§ (b)(15)**
11.	***"Raw data"***	**21 CFR 58.3(k)**
12.	***"Representative sample"***	**21 CFR 210.3(b)(21)**
13.	***"Strength"***	**§§ 210.3(b)(16)**

B. Terms or Phrases Defined By Statute

1.	***"Abbreviated drug application"***	**21 U.S.C. 321 (aa)**
2.	***"Adulterated drug"***	
	(contaminated with filth)	**21 U.S.C. 321 (a)(1)**
	(made under filthy conditions)	**(a)(2)(A)**
	(CGMP non-compliant)	**(a)(2)(B)**
	(in a contaminated container)	**(a)(3)**
	(contains "unsafe" color)	**(a)(4)**
	(contains "unsafe" animal drug)	**(a)(5)**
	(feed containing "unsafe" animal drug)	**(a)(6)**
	(strength, quality, or purity differs from official compendium)	**(b)**
	(misrepresented strength, quality, or purity	**(c)**
	(mixed with or substituted with another substance)	**(d)**
3.	***"Counterfeit drugs"***	**21 U.S.C. 321 (g)(2)**

Derived from: http://www.fda.gov/…/…/3996gdl00001.pdf

4. "Current good manufacturing practice" **21 U.S.C. 351 (a)(2)(B)**

"A drug … shall be deemed to be adulterated —if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with ***current good manufacturing practice*** to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess; …"

5. "Drug" **21 U.S.C. 321 (g)(1)**

6. "Drug Product" **21 U.S.C. 321 (dd)**

7. "New animal drug" **21 U.S.C. 321 (v)**

8. "New drug" **21 U.S.C. 321 (p)**

9. "Official compendium" **21 U.S.C. 321 (j)**

10. "Safe" **21 U.S.C. 321 (u)**

C. Terms or Phrases Defined For Use In This Guidance

1. "***Analysis***" in "Process Analytical Technology" ("PAT") is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner *using population statistics to define the controls****,*** *control specifications, and material acceptance specifications required to attain and maintain CGMP compliance.*

2. "***Attribute***," as used in statistics, means a quality of something and, accordingly assessments of an attribute are qualitative in nature; antonym: variable.

3. "***Characteristic***" means any qualitative or quantitative defining feature.

4. "***Classify***" means to *assign* things *to groups*.

5. "***Correlation***," as used in statistics, means the degree to which two or more variables are related and change together. "Correlation coefficient" means a number or function (having a value of between –1 and +1) that indicates the probable degree of correlation between two variables.

6. ***"Critical,"*** *as that term applies to pharmaceutical products and processes****,*** is an adjective that applies to any process or product *characteristic* that is *required to be controlled in a manner that complies with, or pertaining to any applicable requirement defined in, the drug CGMP as set forth in* ***21 CFR 210*** *through* ***21 CFR 226***. ***Non-critical****, in the same context,* is an adjective that applies to any process or product *characteristic that is above* or *in addition to* the ***minimums*** established in the drug CGMP.

7. "***Evaluate***" means to consider or examine something in order to judge its value, quality, importance, or condition.

8. "***Examine***," means to study something in detail – *the drums were opened and their contents examined for the presence of foreign particulate matter.*

Derived from: http://www.fda.gov/…/…/3996gdl00001.pdf

9. "***Factor***" means something that contributes to or has an influence on the result of something.

10. "***Factor analysis***" is a statistical technique used to determine the relative strength of the various influences on an outcome.

11. "***Factorial design***" refers to the plan selected to carry out a *factorial experiment*.

12. "***Factorial experiment***" is an experiment that consists of a series of trials in which the trials are made up of predefined combinations of set variants of several factors.

13. "***Identification***" means the act of recognizing *something by evaluating* of one or more of *its characteristics*.

14. "***Identity***" means the *fact* or condition *of being the same* or *exactly alike*.

15. "***Material signature***" is a complex response elicited from a material that while not directly proportional to the exact level of one or more characteristics of the material (i.e., not quantitative) can validly be used, *under some carefully defined conditions*, to classify the acceptability or non-acceptability of a sample of the material based on the "semi-quantitative" complex responses recorded by an appropriately qualified analysis system.

16. "**Measure**" means to find out the size, length, quantity, or rate of something using a suitable instrument or device, or to assess the quality of something by comparing it to some standard.

17. "***Multivariate***" means used to describe or related to a statistical distribution that involves a number of random but often related variables.

18. "***Near-real-time quality assurance***" means a valid integrated quality system that dynamically assesses the critical quality characteristics of materials and all batch production and control records appertaining thereto as they proceed from step to step in a process, and uses the near-real-time results produced by the dynamic process controls incorporated into the process and their records' review findings to determine the acceptability of the material or materials produced by each stage in the process.

19. "***Near-real-time release***" is the use of *near-real-time quality assurance* to effect the release on incoming components, in-process materials and product.

20. "***Orthogonality***" means the degree to which the outcomes (results) of any process step for different levels of two or more input or process factors are independent of each other.

21. "***Poor quality product***" means any product that does not consistently meet, or exceed, all of its pre-established batch (or lot) *specifications*, including *acceptance criteria* (as that term is defined in **21 CFR 210.3(b)(20)**), any of its sample specifications or, where applicable or required by **21 CFR 211.165(d)**, any of its batch (or lot) statistical quality control criteria (as per **21 CFR 211.165(d)** which is required for drug products and generally applicable to the drug substance and other components used in a drug product formulation [since under the FDC Act, said components are drugs]).

Derived from: http://www.fda.gov/…/…/3996gdl00001.pdf

22. "***Process Analytical Technology***" ("PAT"), for this guidance, is considered to be a *CGMP-compliant system* for *use in* designing, analyzing, and*/or* controlling manufacturing through timely *evaluations* (i.e., during processing) of *the* critical quality and performance *variables and* attributes of *the* raw and in-process materials, ***product,*** and processes *along with the batch production and control records appertaining thereto* with the goal of ensuring final product quality.

23. "***A 'Process Analytical Technology' (PAT) analysis***" is any analysis that uses an analyzer that significantly automates, by any means, the analysis of any variable parameter such that the analysis is faster than the corresponding manually analysis and the data produced by the analysis system performing that analysis is automatically acquired, processed, reported and stored in a CGMP-compliant manner along with the processing parameters and any ancillary information input to it or acquired by it (like temperature and humidity to establish the environmental conditions during the analysis period).

24. "***Processing window***" is the predefined time window that establishes the minimum and maximum times within which a given end point must occur.

25. **"*Purity*"** means the absence, or degree of absence, of anything of a different type – *tests to establish the purity of the water in the holding tank.*

26. "***Quality***" means an essential identifying property of something.

27. "***Randomization***" means the process of selecting or arranging (ordering) items so that so that no specific pattern or order determines the selection process or the resulting arrangement – *After the set of trials in a given* ***factorial experiment*** *was determined in the factorial design, randomization was used to ensure that the sequential experiment trials were not performed in any time-related order (such as, Trial 1, Trial 2, Trial 3, Trial 4, Trial 5, Trial 6, Trial 7, Trial 7, Trial 8, Trial 9) and the order selected was Trial 5, Trial 9, Trial 1, Trial 7, Trial 2, Trial 5, Trial 6, Trial 7, Trial 3, Trial 8, Trial 4, and Trial4 so that both within-trial and between trial variability could be assessed.*

28. "***Specification***" means a detailed description of a component, material, intermediate, product, or control in terms of the numerical limits, ranges or acceptance criteria that defines what can be accepted for**: a)** use **or b)**, in the "product" case, for introduction into commerce. For the pharmaceutical industry, such specifications must be designed to ensure that the each batch product manufactured by a given firm meets scientifically sound and appropriate specifications that define the identity, strength, quality and purity of each dose such that, *after the batch is released into commerce*, **a)** each dose can validly be represented to be safe and efficacious **and b)** any **USP** (or **NF)** *article* in said *batch* will, if tested, meet the explicit and implicit commercial requirements set forth in the **USP** (or the **NF**) for that product. [**Note:** The term controls includes both the equipment used to effect the control required and the permissible limits, ranges, and/or acceptance and other criteria used to establish that a given control is functioning or has functioned as it was designed to function.]

29. **"*Test*,"** as a verb, to examine something in order to ascertain the presence of or the properties of a particular substance – *test for bacteria on a surface or test for the level of water in a drug substance.*

Derived from: http://www.fda.gov/…/…/3996gdl00001.pdf

30. "***Variable***" means something that is capable of changing or varying and, in the pharmaceutical industry, the variables are those control and material factors that are known to control or contribute to the variability in the product produced by a given process.

Derived from: http://www.fda.gov/…/…/3996gdl00001.pdf