November 3, 2003

Via fax and UPS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0380
Draft Guidance for Industry on Process Analytical Technology – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance [Federal Register Volume 68, No. 172, page 52781, September 5, 2003]

Dear Sir/Madam:

Aventis appreciates the opportunity to comment on the above-referenced draft guidance entitled "*Process Analytical Technology – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance*".

The Agency states that the draft guidance explains a science-based, risk-based framework for developing and implementing innovative manufacturing technology. The guidance is intended to encourage innovative pharmaceutical manufacturing and quality assurance.

We offer the following comments and questions for your consideration.

GENERAL COMMENTS:

This guidance is a valuable high-level introduction for industry that outlines broad principles and concepts. However, for clarity, we suggest adding text to explain the elements of PAT implementation approaches in more detail. This explanation should include scientific and technical issues as well as regulatory concepts. Additional explanation or clarification of terms, definitions and approaches are suggested in the following areas: specification setting, analytical validation requirements for PAT methods, equipment qualification requirements, etc.

The description of scientific and technical principles and concepts in this guidance appear to be focused on development products and processes. However, the description of regulatory mechanisms does not reflect this focus. We suggest adding text regarding regulatory mechanisms that reflect the focus of development products and processes.

2003D-0380 C12

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Process variability is a key concept described in this guidance. However, we suggest that the guidance more clearly state that the observed process variability is a product of analytical method variability and the actual process variability, since this aspect impacts directly or indirectly the concepts of specification setting, sampling or statistical evaluation.

SPECIFIC COMMENTS:

Lines 67-70: *"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."*

Recommendation: Will the Agency issue a guidance document on biotechnology products?

Lines 76-79: *"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."*

Recommendation: For clarity, we suggest adding text that explains that developing and implementing PAT tools at a certain site does not mean that similar technologies developed and implemented at other sites or on other manufacturing lines within a particular site.

Lines 133-134: *"The approach is based on science and engineering principles for assessing and mitigating risks related to poor product and process quality."*

Recommendation: For clarity, we suggest that text be added to further elaborate on "mitigating risks related to poor product and process quality".

Lines 140-141: *"Product and process specifications are based on a mechanistic understanding of how formulation and process factors affect product performance"*

Recommendation: For clarity, we suggest rephrasing Lines 140-141 to read as follows: *"Specifications are based on a mechanistic understanding of how materials, components, formulation and process factors affect product performance."*

Also, we question how this differs from the current validation and experience with a product. Therefore, we suggest adding text to provide examples for further clarity.

Lines 148-149: *" – the capability of process control strategies to prevent or mitigate the risk of producing a poor quality product"*

Recommendation: For clarity, we suggest adding text to define *"poor quality product"*.

Lines 163-166: *"The goal of PAT is to understand and control the manufacturing process, which is consistent with out current drug quality system: quality cannot be tested into products; it should be built-in or should be by design."*

Recommendation: In some instances, final product testing is accepted to determine quality parameters besides or in place of built-in-quality (e.g., sterility at release, container-closure integrity at shelf-life, etc.). Therefore, we suggest adding text that indicates such instances.

Lines 177-179: *"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"*

Recommendation: For clarity, we suggest adding text to define the *"principles of engineering, science, and quality assurance"*.

Lines 196-197 and Line 202: *"Gains in quality, safety and/or efficiency will vary depending on the product and are likely to come from: ...Considering the possibility of real time release"*

Recommendation: The draft guidance describes potential PAT benefits from a conceptual viewpoint rather than to explicitly identify incentives for industry that are related to both development and commercial processes. For instance, we suggest that the guidance indicate that real time release of products without final testing is acceptable to the Agency.

Lines 210-212: *"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."*

Recommendation: For clarity, we suggest that examples be expanded to include, as appropriate, other formulation types (i.e., liquid formulations, inhalants, etc.) and API.

Lines 214-253: Section: *"A. Principles and Tools"*

Recommendation: Lines 214-253 provide rationales rather than a description of PAT tools and/or principles. We suggest adding a corresponding sub-header for clarification.

Lines: 302-305: *"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."*

Recommendation: For clarity, we suggest adding text to provide specific information on how and by whom the opportunities would be identified.

Lines 309-313: *"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."*

Recommendation: The approaches described here seem to be multifactor, rather than multivariate approaches. Therefore, we suggest using the word "*multifactor*" in place of "*multivariate*". In addition, for clarity, we suggest defining the technical terms *"response surface methodologies"* and *"pattern recognition tools in conjunction with knowledge management systems"* in a glossary.

Lines 317-320: *"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."*

Recommendation: For clarity, we suggest defining the technical terms *"Methodological experiments (e.g., factorial design experiments) based on statistical principles of orthogonality, reference distribution, and randomization"* in a glossary.

Lines 386-387: *"Based on the estimated risk, a correlation function may need further support or justification."*

Recommendation: Correlation is a weak form of modeling. Therefore, we suggest adding text indicating that all correlation models should be accompanied with a scientific rational.

Lines 402-404: *"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."*

Recommendation: For clarity, we suggest adding more detailed text to explain the ASTM standard reference with regard to:

- Aspects of interest
- What is relevant for discussion with the Agency
- What is relevant with regard to PAT submissions

Lines 435-436: *"Within the PAT framework, a process endpoint need not be a fixed time, but can be the achievement of the desired material attribute."*

Recommendation: For clarity, we suggest adding text to point out that process end points can also be connected to certain signatures rather than a set of specific material attributes.

Lines 448-449: *"Thus, an opportunity to use more rigorous statistical principles for a quality decision is provided."*

Recommendation: The meaning of *"more rigorous statistical principles"* is not obvious. Therefore, we suggest adding text to clarify what is meant by this term.

Lines 468-474: *"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."*

Recommendation: For clarity, we suggest adding text to point out whether this statement negates the need for "classical" process validation on a predetermined number of batches.

Lines 475-479: *"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."*

Recommendation: *"Risk-analysis"* and assessment of the validation status are an integral part of change control procedures.

Line 504-505: *"The ability to predict reflects a higher degree of process understanding."*

Recommendation: For clarity, we suggest adding text or providing examples to further elaborate on the *"ability to predict"*.

Lines 505-507: *"Although retrospective process capability data are indicative of a state of control, these alone may be insufficient to gauge or communicate process understanding."*

Recommendation: Process capability does not indicate a state of statistical control. Therefore, we suggest deleting this sentence.

Lines 519-520: *"An emphasis on process knowledge can provide less burdensome approaches for validating new technologies for their intended use."*

Recommendation: For clarity, we suggest adding text or providing examples to define "*less burdensome approaches*". In addition, we suggest highlighting which conventional validation requirements would not be relevant for PAT methods.

Lines 522-523: *"Transfer of laboratory analytical methods to at-line methods using test-to-test comparisons may not necessitate a PAT approach."*

Recommendation: Replacing existing laboratory tests with new methods that can be used at-line should be encouraged. In that respect, we are unclear as to the meaning of "... may not necessitate a PAT approach". We suggest adding text for clarification.

Lines 541-543: *"For processes that are well understood, opportunities exist to develop less restrictive regulatory approach to manage change."*

Recommendation: For clarity, we suggest adding text to further explain "less restrictive regulatory approaches". For example, would simpler specifications be acceptable under a PAT approach?

Lines 562-563: *"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."*

Recommendation: For clarity, we suggest rephrasing Lines 562-563 to read as follows: *"Real time release corresponds to the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process analytical data."*

Lines 574-579: *"Real time release as defined in this guidance builds on parametric release for heat terminally sterilized drug products, a practice in the United States since 1985. In real time release, material attributes 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."*

Recommendation: For clarity, we suggest adding text to point out that Material attributes are not always directly measured, but predicted upon extensive correlative information (e.g., predicting tablet hardness with NIR).

Lines 586-587: *"Real time release as defined in this guidance meets the requirements of testing and release for distribution (21 CFR 211.165).*

Recommendation: For clarity, we suggest adding text to indicate the applicability of 21 CFR 211.165 to API production.

Lines 589-592: *"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."

Recommendation: For clarity, we suggest adding text to explicitly point out whether this statement negates the need for "classical" process validation on a predetermined number of batches.

Lines 599-603: *"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."*

Recommendation: For clarity, we suggest adding text to elaborate on the mechanisms for development projects. Which will be additional opportunities for FDA feedback other than meetings such as Pre-IND and EOP2? Does the submission need to be identified as "PAT Related"?

Lines 607-610: *"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."*

Recommendation: For clarity, we suggest adding text to provide examples of *"new regulatory paths"*. Also, we suggest adding text to inform industry of the Agency's new regulatory strategies to consider innovative technology proposals.

Lines 619-622: *"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."*

Recommendation: We suggest adding text to further discuss and clarify the process and approach to establish regulatory specifications in development, for instance, with regard to the required *"mechanistic basis"*. Also, we suggest adding text to provide information on how the concept of interim specifications should be applied in a PAT framework.

Lines 626-633: *"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 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."*

Recommendation: We suggest adding text to further clarify whether the implementation options encompass PAT implementation without corresponding regulatory submission, for instance, as an additional test.

Lines 637-638: *"Manufactures should scientifically evaluate these date to determine how or if such trends affect quality and implementation of PAT tools."*

Recommendation: We suggest the correction of a typographical error. The word *"Manufactures"* should be replaced with *"Manufacturers"*.

Lines 656-657: *"To be able to do this, manufacturers should communicate important scientific knowledge to the Agency and resolve related technical issues in a timely manner."*

Recommendation: For clarity, we suggest adding text to further define the mechanisms and objectives of communicating scientific data to the Agency.

Lines 704-721: *"In general, PAT implementation plans should be risk based. We are proposing the following possible implementation options:*

- *PAT can be implemented under the facility's quality system; CGMP inspections by the Agency follow.*
- *PAT can be implemented following CGMP inspection by the PAT Team. ...*
- *A supplement (CBE, CBE-30 or PAS) can be submitted to the Agency prior to implementation, and if necessary, an inspection can be performed by a PAT Team or PAT certified investigator before implementation.*
- *A comparability protocol can be submitted to the Agency outlining PAT research, validation and implementation strategies and time lines. Following approval of this comparability protocol by the Agency, one or a combination of the above regulatory pathways can be adopted for implementation."*

Recommendation: The guidance implies that PAT approaches that are not risk based are acceptable. We suggest adding text to further clarify the following points:

- Whether the implementation options encompass PAT implementation without corresponding regulatory submission to the agency, for instance, as additional tests.
- Procedures to handle submission that include PAT methods for certain process steps along with conventional test concepts for others.

In addition, we suggest that the guidance include text to outline the regulatory mechanisms and responsibilities within FDA for PAT submission on development products in more detail. For instance, would EO2 or pre-NDA meetings be suitable time points to discuss PAT approaches?

Lines 724-725: *"manufactures should evaluate and discuss with the Agency the most appropriate option for their situation."*

Recommendation: We suggest the correction of a typographical error. The word *"manufactures"* should be replaced with *"Manufacturers"*.

On behalf of Aventis, we appreciate the opportunity to comment on the *Draft Guidance for Industry on Process Analytical Technology – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance* and are much obliged for your consideration.

Sincerely,

for S.C.

Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs