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US Food and Drug Administration
Division of Dockets Management (HFA-305) 7 '03 NOV -5 A11 :11
Room 1061
5630 Fishers Lane, Rockville, MD 20852

Docket No. 2003D-0380

Re: Guidance for Industry PAT - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance (Draft Guidance, August 2003)

PDA is pleased to provide comments on the recently issued Guidance for Industry entitled PAT - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance. PDA is an international professional association of more than 10,500 individual member scientists having interest and expertise in pharmaceutical manufacturing and quality. A committee of experts in this field prepared the comments that follow.

We are encouraged by the initiative of the FDA to clarify their position on process analytical technology (PAT) and appreciate the rapid pace with which this guidance was prepared. We believe this action will speed the adoption of this beneficial technology in our industry. The PDA supports the development and implementation of PAT for use in the manufacture of pharmaceutical products and offers these comments in a constructive manner.

General Comments:

1. We recommend that the section on the background of PAT *(Section III, lines 82-169)* and other general information regarding the use and benefits of PAT be removed from the body of the guidance. This information may be more appropriate in an appendix or a separate concept paper. Greater emphasis on regulatory expectations is desired in the guidance.

2. The footnotes included in the document provide useful reference to related FDA documents. We recommend further references of this nature. Specifically, reference to applicable sections of the Guideline on General Principles of Process Validation (USFDA, May 1987), Hazard Analysis and Critical Control Point Principles and Application Guidelines (USFDA, USDA, August 14, 1997) and other relevant existing documents would help clarify how this new guidance supports or modifies the agency's positions in these areas.

Additional Information and Clarification Requested:

1. Safe Harbor and Research Exemption. During preliminary and more advanced discussions over the past 18 months on the subject of PAT implementation, the terms "Safe Harbor" and "Research Exemption" were used to convey a concise and central definition to a concept critical to broad use of these technologies. *Lines 632 -633 and 635-647* imply these concepts, but the reader is forced to rely on a tangential interpretation with respect to measurement devices and data quality rather than a direct discussion of the impact of PAT data to a product's compliance with registered specifications. This has been one of the most contentious areas of the PAT initiative and has the potential to slow experimentation with and

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implementation of these technologies. Further clarification that products will be assessed with current methods and against current specifications is desired.

2. Specifications. It is imperative that the agency re-evaluates the current definition of specification limits to ensure that processes that have historically produced acceptable product are not unduly penalized by the increased amount of data available with PAT methods. It is unclear what the status of previously registered methods and specifications will be once a PAT method is initiated. Product release specifications should be set to meet patient safety and efficacy requirements, not process capability as stated in *lines 451-455*. Internal process control limits should be set and re-evaluated periodically as additional process experience is gained and process improvements made as stated in *lines 490-496*.

3. Validation. It is expected that the development and implementation of PAT will drive changes in the way equipment and processes are validated. It would be helpful if this guidance provided validation expectations for PAT methods and equipment. *Lines 519-520* state "An emphasis on process knowledge can provide less burdensome approaches for validating new technologies for their intended use". An example would help demonstrate this point. Further explanation on what is meant by "continuous quality verification" or "continuous real time quality assurance" is desired. A comparison with the current prospective three-batch process validation strategy would be helpful.

4. Chemometrics. The section entitled Multivariate Data Acquisition and Analysis *(Section IV.A.1.a, lines 326-401)* would benefit from a specific discussion on chemometrics and some of the common modeling tools such as Principle Component Analysis (PCA) and Partial Least Squares (PLS). An example or examples, including validation, registration strategy and data retention guidelines would be helpful. Alternatively, such information could be developed with a third party such as PQRI or ASTM and placed in a separate guide or standard.

5. Process Signature. The concept of a "process signature" as discussed in *lines 389-392* should be clarified. If documenting such a signature becomes a regulatory expectation, deviation from this signature should not be treated the same as current process deviations or OOS results. It can be difficult to correlate non-specific changes in process signature with specific changes in product quality. As a result, this approach may be extremely prone to false positives, frustrating the ruggedness of PAT methodology.

6. Life-Cycle. An example showing the use of PAT during product/process development and subsequent deployment at production scale would be instructive. It appears likely that data collected during development could lead to simplified measurement and control strategies in production. Further, with increased production experience, it may be justified to remove a PAT device. Following the regulatory expectations of this evolutionary process would be helpful.

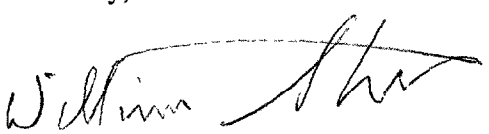
7. Risk Assessment. The guidance refers on several occasions to "risk" and "risk-based" methods and decisions *(e.g. lines 27, 124, 406, 476, 481, 544, and 547)*. There is confusion as to the nature of the risk being managed. Risk associated with product safety and quality and that with resource conservation appear to be used interchangeably. Clarification is needed on how to assess risk. Information such as that provided in ISO 14971: 2000, Application of Risk Management to Medical Devices (February 12, 2002) would eliminate this confusion.

8. Dosage Forms. The guidance appears to focus on the application of PAT to drug products, and primarily solid oral dosage forms. PAT is also applicable to liquid and semi-solid products. Furthermore, the chemical industry has a long history of successful use of these technologies and use in the production of active pharmaceutical ingredients (API) or drug substances by traditional chemical synthesis or fermentation should also be encouraged. These points could be made through selection of examples in the guidance, or a broader scope statement.

9. Regulatory Filing Process. While the regulatory filing process is mentioned in this guidance, the document would benefit from a flow chart showing the different types of filings expected (new or existing product), the desired timing of contact with the agency, who to contact and the information expected at each stage.

PDA appreciates the opportunity to support the FDA in the preparation of sound and science based guidance. Please contact me if you have any questions on this matter.

Sincerely,



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