David W. Blois, Ph.D.
Senior Vice President
Global Regulatory Policy

Merck & Co., Inc.
West Point PA 19486
E-Mail: david_blois@merck.com
Tel 484 344 2304
215 652 5000
Fax 484 344 2335

November 4, 2003

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

Docket No. 2003D-0380
Draft Guidance for Industry: Process Analytical Technology—A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

Merck & Co., Inc. is a leading worldwide, human health product company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many of the important pharmaceutical products on the market today.

The Food and Drug Administration (FDA) is encouraging industry to develop and implement innovative pharmaceutical manufacturing and quality assurance. The draft guidance, Process Analytical Technology (PAT), presents a scientific, risk-based framework to help manufacturers develop and implement new efficient tools for use during pharmaceutical development, manufacturing and quality assurance. Merck strongly supports the development of this draft guidance and applauds the Agency for its efforts. Because of Merck's experience in real time monitoring of certain parameters in its manufacturing processes, we are well qualified and very interested in the draft guidance and provide the following comments:

GENERAL COMMENTS:

The preparation of a guidance document on PAT is strongly supported by the pharmaceutical industry and by Merck. In fact, we support further broadening of the PAT initiative to encompass therapeutic proteins recently transferred to the Center for Drugs and all biologics regulated under the Center for Biologics. This draft guidance provides a broad overview of the role of PAT in pharmaceutical development and manufacturing. However, it is difficult to understand many of the concepts in the guidance without a specialized background in PAT; and it is not clear how these concepts would be implemented from a regulatory perspective. It would be helpful if a brief description of how the Agency would review a PAT submission were included; clarifying roles and responsibilities of inspectors and the Center. During review of the draft document, we found many vague statements that could promote misunderstanding of the concepts inherent to PAT. We cite examples of indefinite wording throughout our

comments. We suggest that the inclusion of a glossary would be beneficial in providing clear and consistent definitions of PAT terminology that could be easily referenced.

Additionally, we encourage efforts toward the international harmonization of the PAT initiative. Without worldwide agreement on the utility of PAT, any headway concerning real time product release would be diluted by still having to perform the entire battery of release testing for international regulatory agencies. A sponsor who develops a process with extensive PAT such that it can justify real time release to the FDA would still need an entire quality lab dedicated to providing traditional product release testing to satisfy other worldwide agencies.

Real time monitoring, multivariate data acquisition and calibration generate large volumes of data. The industry needs guidance on how to handle such large data sets including: a) types of data that need to be retained; b) retention time of large data sets; c) handling of data outliers; and d) retention of PAT data as part of the batch record.

This draft guidance does not put enough emphasis on how PAT in an R&D setting could be used to justify selection of the subset of analytical controls needed for routine production. Although the guidance recognizes the inverse relationship between the level of process understanding and the risk of producing a poor quality product, it is not clear how the link can be used to facilitate regulatory decisions based on reduced risk that ultimately lead to less testing.

The importance of laboratory based reference methods should also be captured in this guidance. It is essential to have a set of validated reference methods that can periodically challenge the PAT methods and also for disaster recovery situations where one may need a fall back position to ensure continuity of product supply.

SPECIFIC COMMENTS:

Line 199-207: ***PAT Framework***
Comment: The following gains were not listed, yet featured prominently later in the document:

- Use of in-process control and feedback
- Process understanding

Line 358-379: ***Process Analyzers or Process Analytical Chemistry Tools***
Comment: The Agency should provide a more concise statement on what is considered a PAT method. It is confusing that in-process, off-line lab methods were included under the PAT umbrella. It appears that the non-destructive nature of some process analysis tools is the qualifying criteria for their inclusion as a PAT.

Line 359 – 408: ***Process Analyzers or Process Analytical Chemistry Tools***
Comment: Appropriate guidance should be provided regarding PAT analytical method validation. This could be specifically addressed in the FDA's draft analytical method validation guidance.

Line 390-395: ***Process Signature***
Comment: Clarification of what constitutes a PAT-derived process signature would be helpful. The industry needs guidance on how to justify release of product using an abstract variable or set of variables.

Line 463: ***Process Monitoring, Control and End Points***
Comment: A greater level of detail is provided here than is found in the rest of this draft guidance documentation. It is suggested that less detail would be appropriate, particularly regarding the PAT data content of batch records.

Line 560-592: ***Real Time Release***
Comment: The possibility of real-time release is a major shift in paradigm for the industry and the regulatory agencies. The guidance should elaborate on this concept and provide overall structure of its implementation.

The last paragraph (lines 589-592) of this section needs clarification. It is unclear what FDA suggests for use of production batches in validation. While PAT can enhance the process validation by providing better process understanding, the ultimate goal of process understanding is to design a consistent process that leads to less routine testing in the end.

Line 594-725: ***Regulatory Strategies***
Comment: Conclusions derived from applications of PAT in R&D for process development and optimization may be provided in a regulatory filing to justify the selection of in-process and release tests used in production. The supporting PAT data would still be considered research data.

Bibliography

It would be useful to include the following as a literature reference:

- 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) John Wiley & Sons Ltd, Chichester, 2002

We welcome the opportunity to provide feedback on the *Draft Guidance for Industry: Process Analytical Technology — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance.*

Sincerely,

David W. Blois, Ph.D.
Senior Vice-President
Global Regulatory Policy