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November 3, 2003

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

Re: Docket No. 2003D-0380; Proposed Draft Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, *[68 Federal Register No. 172, page 52781 (September 5, 2003)]*

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2002 alone, Bristol-Myers Squibb dedicated $2.2 billion for pharmaceutical research and development activities. The company has more than 5,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline is comprised of approximately 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on this Draft FDA Guidance for Industry on Process Analytical Technology. Bristol Myers Squibb is appreciative to have one of its personnel be a part of the FDA subcommittee to advise, shape and communicate the thinking behind the agency's perspective on PAT. We hope that further regulatory development on this important subject consider a similar approach.

Bristol Myers Squibb encourages and supports this Guidance as a unique technical way to improve our processes with supportive regulatory direction.

We commend the U.S. FDA for the following direction as stated in the draft guidance:

- The introduction recognizes that regulatory uncertainty has been a barrier to the implementation of state of art technology in the pharmaceutical industry in the United States. The guidance does a commendable job of creating a regulatory environment directed toward the implementation of new technology.

- The definition of Process Analytical Technology that implies a holistic approach to the improvement of product quality rather than it being simply about analytical measurements.

- The inclusion of experience, practices and standards from other industries and regulatory agencies, such as those in Europe, into the development of PAT processes for pharmaceuticals represents the positive collaborative intention of the guidance. This implies intent toward harmonization of PAT practices.

However, there are several aspects toward the improvement of the draft guidance, which we have cited below:

- Under the PAT tools, section C, Process Monitoring, Controls and End Points the following statement should be added at line 441:

  "Interim process parameters should be used until the process dynamics are better understood and well established."

  Rationale: This will provide support for continuous improvement activity and latitude for industry implementations to enhance process understanding.

- Additionally, under the PAT tools, section C, Process Monitoring, Controls and End Points the following statement should be added at line 441:

  "The batch record, once a paper based representation, becomes increasingly electronic-based with the implementation of PAT technology. The data and information making up the electronic batch record should be clearly defined by the business process through policy and procedure for each process using PAT."

  Rationale: This addresses questions of what a batch record should be as electronic PAT data is collected and maintained. It leaves appropriate leverage of what needs to be maintained to represent the batch record.

- Under the PAT tools, section C, Process Monitoring, Controls and End Points the following statement should be added after line 452:

  "It is not expected that all data points collected electronically during real time measurement be maintained for extended periods of time. Providing a summary of the information representing the quality of the material to be included as part of the batch record is considered an acceptable practice. The summary, format and retention requirements of such data should be identified based on a documented risk assessment. The recommendations provided by the FDA Guidance Part 11: Scope and Application should be considered."

Rationale: The FDA should speak directly to any expectation to maintain the ability to reprocess data over the GMP record retention requirements. Such decisions should be part of a product quality risk assessment. The comment also provides an important reference to the Part 11 Scope and Application Guidance not currently found in the PAT Draft Guidance.

Additional recommendations are provided, although we consider them to be relatively minor:

- Line 36 – change the word "fear" to "concern".
- Line 195 – change the word "preventing" to "minimizing".
- Line 211 – change the word "modulate" to "transform".
- Line 212 – change the word "modulate" to "manufacturing".

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Mauricio Futran, Ph.D.
Vice President, Process R&D

Susan Voigt
Vice President, Environment, Health and Safety & Corporate Product Quality

William Winter, Ph.D.
Vice President, Analytical Development

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