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Bristol-Myers Squibb Company

December 18, 2003

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

Re: Docket No. 2003D-0385; Draft Guidance for Industry: Comparability Protocols - Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information, [68 Federal Register 52776-52777 (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 comprises of approximately 50 compounds under active development of which several are therapeutic proteins.

For these reasons, we are very interested in and well qualified to comment on the FDA draft guidance for industry entitled "Comparability Protocols - Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information".

Our comments are provided in bullet format below:

General Comments:

- The scope of the guidance document is restricted to post approval CMC changes. A sentence to direct sponsors to the 1996 FDA Guidance Concerning Demonstration of Comparability of Human Biological Products Including Therapeutic Biotechnology-derived Products for guidance on how to handle comparability for changes made during development would be helpful.
- The draft guidance emphasizes the use of comparability protocols to lower the reporting category. It would be important to clearly state the filing mechanism for obtaining FDA review and comment when a reduction in reporting category is not requested. Lines 260-262 of the guidance state that comparability protocols are not recommended for CMC changes that require PK/PD data to evaluate the effect of the change. In addition, lines 272-274 state that it may be possible to design a comparability protocol for a move to a manufacturing site however, the FDA may be limited in their ability to designate a reporting category other than

PAS. Historically, sponsors were encouraged to submit comparability protocols to the FDA for comment even for changes that require PK/PD or that remain a PAS due to the need for an inspection. We would anticipate that these comparability plans could still be submitted to the FDA for review and comment outside the realm of this new guidance.

- Please provide further clarification of "detailed description" as listed in line 386 - "a detailed description of the proposed changes clearly.....". Too much granularity in the detailed description can actually limit the usefulness of a given protocol since it will be difficult to anticipate every change that is to be made in the future as a result of development work.

Specific Comments:

- Following line 223, add a sentence stating, "Except where noted, the below examples refer to changes made to drug substance manufacturing processes."
- In regards to lines 335-346, please modify the language to define types of changes that would require a prior approval supplement for protocol revision. As one example, we would recommend that a new assay for non-routine characterization testing that is more appropriate because of technical advancement should be substituted in an approved comparability protocol without filing the amended protocol as a prior approval supplement.
- Modify the sentence in line 562 to include the bolded phrases, "We recommend that you **assess the effect of upstream changes on the downstream process and where appropriate**, discuss in your comparability protocol how to ensure that the ~~entire~~ manufacturing process is adequately controlled."

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

Sincerely,

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