

# Bristol-Myers Squibb Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000

609 252-5992 Fax: 609 252-3619

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Laurie Smaldone, M.D.  
Senior Vice President  
Worldwide Regulatory Affairs

**January 3, 2001**

**Dockets Management Branch  
Food and Drug Administration, HFA-305  
5630 Fishers Lane, Room 1061  
Rockville, MD 20857**

**Re: Docket No.00D-1562; FDA Draft Guidance/Cancer Drug and Biological Products,  
Clinical Data in Marketing Applications, November 7, 2000**

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1999, pharmaceutical research and development spending totaled \$1.4 billion.

For these reasons, we are very interested in and well qualified to comment on the referenced draft FDA guidance; please find those comments below.

## **GENERAL COMMENTS**

The FDA should be commended for having issued a document which generally reflects a reasonable approach to data requirements for oncology applications, and in many instances, clarifies the needs of the reviewer.

It would seem that, in a great many circumstances, while FDA may not require inclusion of certain data in the submitted database contained within an application, follow-up during the review of an application may require the generation of those data by means of the submission of case report forms. The guidance would benefit from the inclusion of more descriptive language about what data need to be 'collected by the investigator', what data need to be 'collected by the sponsor', (via the case report form), and what data need to be submitted to the FDA in the

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application database. Specific sections where this matter could present as an issue are highlighted in the comments below.

Finally, throughout the guidance reference is made to the use of the National Cancer Institute toxicity grading system; it is suggested that further clarity on database submission of such information coded by MedDRA be provided.

### **II.C BACKGROUND/General Considerations**

(Line 91) If a compound in Phase I shows early evidence of significant activity, a meeting to discuss data requirements for the phase 2 studies may be appropriate, rather than at the end of phase 2. A suggested modification would be to the end of the current sentence: "or sooner if Phase 1/early phase 2 data indicate a potential for "accelerated" approval". Also, some more specific guidance on how Agency personnel would expect that the discussion on data collection should proceed would be helpful, (e.g., submission of annotated case report forms in meeting background).

### **III.D. RECOMMENDATIONS FOR DATA COLLECTION/Cancer Treatment History**

(Line 141) It is suggested that a revision be incorporated here to clarify that for full approval of a drug in the metastatic disease setting details other than the identities of previous chemotherapies are generally not necessary. This will help to distinguish the requirements for data on this matter relative to those in the *refractory* metastatic disease setting, (as described in the second paragraph in this section).

(Lines 146-156) It would seem vital that data be collected on dates of progression following prior therapy as this relates directly to the prescribed definition of 'refractory disease'. Such information is, in fact, more important than best response to prior therapy (as suggested should be collected, line 153) because you must show that patients progressed on therapy or within an agreed upon time period post therapy per the prospective definition for 'refractory'.

### **III.E. RECOMMENDATIONS FOR DATA COLLECTION/Laboratory Tests**

Sample collection of laboratory data presents very practical potential issues to both sponsors and FDA. For example, for any laboratory value which is collected that is not judged immediately by the investigator to represent, in and of itself, a 'serious' event, collection according to grading of events is subject to varying interpretations across studies. As a consequence, the analysis of laboratory abnormalities will be confounded. (And accurate denominator frequency counts would be very difficult because there may be no means by which a sponsor or FDA can determine if missing values mean no severe results or that the tests were not performed.)

Generally, much more accurate information about laboratory abnormalities will be generated if all laboratory test results are collected and then calculation of grades is performed by the sponsor. The guidance would benefit from the inclusion of a caveat which addresses this matter.

(Lines 160-162) Was the statement "all original applications should contain a database of all laboratory tests from a specified number of patients" meant to imply that this is a requirement only for NDA's as opposed to supplemental applications? Clarification is suggested.

(Lines 185-187) It is suggested that the statement that it may be appropriate to rely upon the investigator's opinion about which labs to collect (in those circumstances where 'a drug has been adequately studied for toxicity in previous applications') be revised to clarify that the sponsor has the responsibility for assessing the need for such data collection based upon both the adequacy of the existing safety database and any evolving safety issues, and that the final decision should be generated out of a consultation between sponsor and investigator and detailed prospectively in the protocol. (Please see prefacing comment above for this section of the guidance.)

(Lines 183-189) It is unclear whether 'follow-up test' data should be included in the database or merely collected on the CRF. Clarification is suggested.

(Lines 191-196) It is suggested that this section on laboratory tests 'corresponding to severe toxicities' be clarified to describe the toxicity grading scale which is referenced. If reference is being made here to the NCI CTC scale, grade 5 events are fatal events. We would suggest that fatal events be graded from 1-4 based on severity/characterization, with the outcome recorded as death. Use of 'grade 5' as the descriptor would cause the loss of other descriptive information that the grades 1-4 provide. Finally, for some events simply indicating that the event resolved may not be adequate. For example, the duration of an event could be important (e.g., neuropathy). Clarification on this point is suggested.

### **III.F RECOMMENDATIONS FOR DATA COLLECTION/Physical Examination**

(Lines 200-203) Weight is often needed to ensure that appropriate doses have in fact been administered (for those patients in which detailed dosing data is being collected), and such information can become critical in those cases where an unusual adverse event occurs. Further, performance status and weight information during patient treatment on study can yield hard data which can support quality of life determinations. It is suggested that the guidance be clarified to include these caveats.

### **III.H. RECOMMENDATIONS FOR DATA COLLECTION/Cancer Drug Dosing**

(Lines 238-245) This section would benefit from some guidance on the data which should be submitted in electronic form vs. the data which should be collected on the case report form.

(Lines 241-243) It is suggested that the third sentence in this section be revised as follows for clarity: " In all patients, data should be collected to document the date of the initial dose, the dose, and the dates of subsequent doses, as well as the dates for any dose decreases and reasons ".

### **III.I RECOMMENDATIONS FOR DATA COLLECTION/Toxicity**

The collection of only sample toxicity information from clinical studies raises some potential practical issues for sponsors such as combining results from a group of studies for analyses and labeling. (See similar concern reflected for sample collection of laboratory data.) It is suggested that the guidance include some cautionary statement to this effect.

(Lines 249-258) Please see point made for lines 191-196 regarding grade 5 toxicities. Also, while this section as a whole goes into some detail where the collection of grade 1-3 toxicities in patient samples is concerned, no where in the section is it specified that ordinarily complete information on grade 4-5 toxicities will not only have to be collected, but that such information

must also be submitted within a marketing application. Clarification on this point is suggested.

(Lines 270-271) Clarification is requested on whether the statement that 'Data on investigator attribution of toxicity is not necessary' was meant to imply case report form collection or database submission. Investigator attribution is always considered by the sponsor in safety reporting decisions (serious events) and should always be collected.

(Lines 273-275) While the objective of minimizing unnecessary data collection is laudable it would seem appropriate that the guidance add a caveat that a 'preplan' for collection of data on 'selected toxicities' may ultimately render an assessment of risk versus benefit difficult, since registrational studies with oncology drugs are often initiated without a clear understanding of what might present as a safety issue. Further, if the guidance is meant to imply that the collection of grade 1-2 toxicity information might be necessary in those cases where a sponsor's objective is to demonstrate that a new drug has 'marginal clinical benefit' (e.g., in non-inferiority study designs) then further clarification along these lines would be helpful.

### **III. J. RECOMMENDATIONS FOR DATA COLLECTION/Concomitant Medications**

(Lines 287-300) It is suggested that this section be expanded to clarify that, given the broad range of supportive therapies that patients with cancer receive, often information on drug interactions cannot be adequately ascertained prior to the initiation of registrational studies. As the section is currently written it may be interpreted to mean that the investigator need not record concomitant medications on the case report form; it is only assumed that the guidance meant to state that detailed and comprehensive information on concomitant medications need not be submitted in the database.

### **IV.A. HYPOTHETICAL EXAMPLE**

While the example provided is no doubt intended to be helpful, it would be greatly improved if more specific justification for the adequacy of the described information is provided. For example:

(Lines 332-342) Why might detailed safety data from only one of the two *first-line therapy for metastatic E cancer* randomized trials be considered adequate? (Especially given that the original safety database was very small and cardiac toxicity had been observed in Phase 2.)

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,



Laurie Smaldone, M.D.  
Senior Vice President  
Regulatory Science and Outcomes Research

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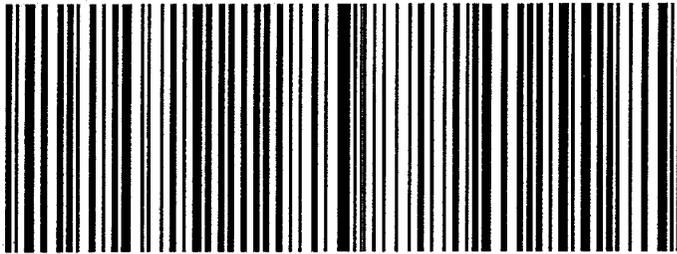
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