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January 23, 2001

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

Dear Sir or Madam:

Subject: Docket No. 00D-1563; Draft Guidance for Industry on Carcinogenicity Study Protocol Submissions, 65 Federal Register 66757 (November 7, 2000)

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For these reasons, we are very interested in and well qualified to comment on this FDA Draft Guidance for Industry on Carcinogenicity Study Protocol Submissions. We commend the FDA for providing to industry guidance on the types of information that the agency relies on to evaluate carcinogenicity protocol design. Knowing what the FDA's needs and expectations are for these reviews will allow us to provide the information more efficiently and clearly. However, some of the requirements in the current draft guidance will create a substantial scientific and resource burden very early in the drug development process that we believe will do little to guide dose-selection decisions. We provide the following specific comments:

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II. Background

We recommend that it be clarified that "45 days" (lines 42 and 52) refers to calendar days, not business days. Similarly, "30 days" (line 75) should specify "30 calendar days". Also, line 42 notes that the "FDA will evaluate within 45 days...". To be consistent with the November 12, 1997 letter that is referenced in the Guidance, this should be changed to "FDA will provide a written response within 45 days...".

III. A. Information Important to Facilitate Protocol Review

1. "A toxicology study report should be included..." (line 96). We request that the guidance should specify that an unaudited draft report (containing summary tables, individual animal data, and overall study summary) would be acceptable.
2. "Metabolic profiles should be provided..." (line 103). To be consistent with the ICH Guideline, "Dose Selection for Carcinogenicity Studies of Pharmaceuticals," we suggest that the guidance specify that *in vitro* generated comparative profiles would suffice in the absence of *in vivo* metabolism data.
3. "Data (point estimates as well as individual animal values)...(lines 108 and 109). It should be recognized that exposure measures are usually derived from composite rather than individual animal profiles. Therefore, individual animal values will represent concentrations only at selected time points. Also, it is unclear what the phrase "point estimates" means; it would be helpful if this were defined or reworded.
4. "Exposure (steady state Cmax and AUC[0-24]) data should be provided for the parent and for the major metabolites..." (lines 112-115). Again, we recommend that the guidance should specify, per ICH guidelines, that *in vitro* information on metabolites is acceptable. In that case, there will be no Cmax or AUC data on metabolites. Further, information from clinical trials on exposure to the parent compound at steady state may not be available when the carcinogenicity protocol is submitted. A lack of such information may preclude the use of the multiple of human systemic exposure and limit dose endpoints, but the toxicity dose selection endpoint should be acceptable. We suggest that this be clarified in footnote 8. Please also note that "MHRD" on line 115 should be "MRHD."
5. "Plasma protein binding data should be provided for the parent drug and the major human metabolites (to the extent feasible)..." (lines 119-122). The added value of protein binding determinations for metabolites is not apparent. We feel this recommendation should be dropped.
6. "A summary of the investigations into the genotoxic potential of the drug and its major human metabolites should be included." (lines

124 and 125). Genotoxicity testing of metabolites is felt to be unnecessary since the activation system (S9) that is routinely added to genetic toxicity assays should provide that information. In addition, *in vivo* genotoxicity testing (e.g., micronucleus assay) in rodents should ensure adequate evaluation of the genotoxic potential of metabolites. It is recommended that this requirement be deleted.

E. Presentation of Data from Rangefinding or Other Toxicity Studies

"Clinical pathology tables should include the group mean value and range for each parameter reported." (lines 164 and 165). It is not clear if "range" means within study range or historical range. Most automated clinical pathology systems do not currently calculate or tabulate either of these ranges, and reprogramming them to do so will be resource and time constrained. We suggest the requirement to report ranges be made optional.

F. Use of the Limit Dose

"One of those criteria is that it can be ensured that the rodent exposure to the drug and metabolites at 1500 mg/kg/day exceeds systemic human exposure (AUC) at the MRHD by greater than an order of magnitude." (lines 171-173). The ICH guideline does not specifically require a 10-fold multiple for every metabolite. The need to exceed human exposure for metabolites by an order of magnitude will be problematic, since metabolism can vary so much from species to species. The request for metabolite analysis will also have implications for sample volumes, and may increase the number of animals necessary to harvest an adequate volume of plasma for multiple analyses. Thus, we recommend that this requirement be reconsidered.

"For the purposes of this guidance, CDER considers this has been demonstrated if the lower 95 percent confidence limit for AUC in the rodent..." (lines 173-176). In rodent studies, AUCs are determined by sampling different animals at each time point, and obtaining a single composite AUC on all of the animals. There is no estimate of individual-animal AUCs, and it is impossible to determine a 95% confidence limit. Therefore, we suggest that this requirement be dropped.

Table: The Types of Data Useful for Evaluation of Carcinogenicity Bioassay Protocols (lines 180-182).

In this table, we recommend that a footnote be added to the columns titled "Animal AUC" and "Human AUC" to reflect that unbound values should be calculated when protein binding is high and the unbound fraction is greater in humans than in rodents (as per the previously cited

ICH Guidelines). The word 'unbound' should be removed from the titles of these two columns.

We appreciate the opportunity to provide these comments and respectively request that the FDA give them careful consideration. We would be glad to provide additional information as may be requested.

Sincerely,

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and Veterinary Sciences

Sincerely,

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