Bristol-Myers Squibb
Pharmaceutical Research Institute

P O Box 4000 Princeton, NJ 08543-4000
Tel 609 252-5992 Fax 609 252-3619
laurie.smaldone@bms.com

1203 '03 MAR 14 A9:18

Laurie Smaldone, M.D.
Senior Vice President
Global Regulatory Sciences

11-Mar-2003

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

Re: Docket No. 02D-0492; Draft Guidance for Industry and Reviewers. Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers [Federal Register Vol. 68, No. 11 (January 16, 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 2001 alone, Bristol-Myers Squibb dedicated $2.1 billion for pharmaceutical research and development activities. The company has nearly 6,000 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 more than 50 compounds under active development.

For these reasons, we are very interested in and well qualified to comment on this FDA draft guidance for estimating safe starting doses in clinical trials for therapeutics in adult healthy volunteers.

Summary of BMS Comments on Proposal

General Comments: We were pleased to have the opportunity to review the U.S. FDA's draft guidance on estimating safe starting doses for first-in-human (FIH) trials. We believe that this guidance will establish consistent terminology for discussing the starting dose for FIH trials and also commend the FDA for establishing common conversion factors for body surface area scaling. However, we believe that this guidance does not give due consideration to other commonly used approaches for estimating starting doses in FIH trials and also are concerned that rapid attainment of FIH trial objectives may not always be possible by the use of this proposed algorithm alone.

02D-0492

C6

Pharmacokinetic-based extrapolation methods were considered to be of limited utility because their use would require multiple untested assumptions. Multiple untested assumptions are also encountered when scaling by body surface area, and this method has not been proven superior to other extrapolation methods. Pharmacokinetic-based methods are currently being used to guide starting dose selection for FIH trials, and a recent review article provided detailed descriptions as well as critical assessments of these methods.[1] Given that pharmacological and toxicological responses are better related to systemic exposure than dose, the use of pharmacokinetic-based extrapolation methods is warranted and should be discussed in detail within the guidance.

Scaling by body surface as proposed by this guidance provides ".. a more conservative starting dose estimate". While it is agreed that safety is the primary consideration in FIH trials, starting doses that are too conservative may require multiple escalations to reach a clinically meaningful dose. Concerns about starting doses that are too conservative could be alleviated by using exposure-guided dose escalation; however, this guidance does not address dose escalation. Input from the FDA on this topic would be welcomed in this guidance.

Specific Comments (Items that Need Clarification & Recommended Actions)

Page 1, Section II. Scope, Lines 34-35: The sentence "This document is not pertinent to prophylactic vaccines or endogenous proteins (i.e., recombinant clotting factors) used at physiologic concentrations" needs clarification. Without having prior pharmacokinetic data for an endogenous protein in humans, how would one know in advance what doses of a protein would achieve concentrations in the "physiologic" range? Also, it is not exactly clear why proteins alone are being excluded. If the characteristics "endogenous" and "physiologic concentrations" are the main rationale, why would not all endogenous compounds, whether or not a protein, be exempted if "used at physiologic concentrations"? Is it assumed that the toxicity of a human protein can never be fully tested in animals? Therefore, the algorithm used in this paper, which is based on animal toxicity data, is not relevant. In that case, the sentence should exempt all endogenous proteins, irrespective of whether they are "used at physiologic concentrations".

> ***Recommendation:*** FDA should clarify why endogenous proteins (and not other endogenous compounds) are being excluded and why the phrase "at physiologic concentrations" is needed.

Page 2, Section II. Scope, 1st paragraph and footnote 2: The guidance states that using animal pharmacokinetic data for guiding selection of starting doses is useful in only a "limited number of cases" and provides reasons for limited utility of pharmacokinetic extrapolation methods in footnote 2. This footnote states that pharmacokinetic-based methods are not considered valid for estimating starting doses because their use would require multiple untested assumptions. It should be noted that scaling by body surface area also requires the use of multiple untested assumptions [*e.g.*, that the absorption, distribution, metabolism, and elimination processes of a compound scale across species by a pre-determined scaling factor ($W^{0.67}$)]. Limitations clearly exist for all extrapolation methods (hence the use of safety factors), and no one method has been proven superior for estimating starting doses for FIH trials. Pharmacokinetic-based extrapolation methods are particularly appealing since starting dose estimates are derived based on exposures rather than dose,

and a recent review article[1] suggests that pharmacokinetic-based extrapolation methods have been successfully used to estimate starting doses in FIH trials. We believe that pharmacokinetic-based extrapolation methods can be useful in deriving safe starting doses for FIH trials and should be given further consideration in this guidance.

> ***Recommendations:*** The use of pharmacokinetic-based methods for estimating starting doses in FIH trials should be given more consideration in this guidance. A detailed discussion of the utility and limitations of all methods used to estimate starting doses in FIH trials, including scaling by body surface area, should be provided in the guidance.

Page 2, Section II. Scope, Lines 48-55: Starting doses are generally intended to be devoid of pharmacological activity,[1,2] but this important consideration has not been addressed in this section (nor in the remainder of the guidance - also see Page 11, Section VIII. Step 5: Consideration of the Pharmacologically Active Dose (PAD), Lines 422-433).

> ***Recommendation:*** FDA should consider adding statements regarding pharmacological activity of starting doses in this section.

Page 2, Section II. Scope, Lines 63-64: Although this document does not specifically address starting doses in patients, many principles and approaches recommended here have clearly been drawn from the paper entitled "Regulatory considerations for the preclinical development of anticancer drugs".[3]

> ***Recommendation:*** FDA should provide similar details in this guidance regarding the type and design of appropriate toxicology studies that are essential for determining MRSD as well as identifying those studies that, while not essential, are considered extremely valuable for supporting the safety profile.

Page 3, Section III. Overview of the Algorithm, Line 68: Figure 1 does not appear anywhere in this document.

> ***Recommendation:*** This figure should be referenced appropriately in the guidance.

Page 3, Section III. Overview of Algorithm, Lines 96-98: "When information indicates that a particular species is most relevant for assessing human risk (and deemed the *most appropriate species*), the HED for that species should be used in subsequent calculations, regardless of whether this species was the most sensitive." This statement may not be appropriate in situations where irreversible or life-threatening toxicity occurs in a species other than that which is deemed "most appropriate" and yields an HED which is less than the HED derived from the "most appropriate" species.

> ***Recommendation:*** FDA should consider re-wording this sentence so that the MRSD could be appropriately lowered in the event of situations as noted above.

Page 4, Section III. Overview of Algorithm, Lines 133-135: It is not clear what is meant by "pharmacologically active dose (PAD)" in this sentence. Does the definition provided in the Glossary (*i.e.*, the lowest dose tested in an animal species with the intended pharmacologic activity) apply here?

Recommendation: The FDA should clarify what is meant by "pharmacologically active dose" here and in the remainder of the document.

Page 4, Section III. Overview of Algorithm, Lines 138-140: The guidance states that the recommended algorithm "... is supported by a general review and analysis by CDER and CBER examining the results from a number of therapeutics entered into development." What were the criteria utilized to determine that the recommended algorithm is suitable for selecting starting doses for FIH trials? Given that other methods are also used for estimating starting doses for FIH trials,[1] it would be useful to compare the performance of the proposed method *vs.* these other commonly used methods.

Recommendation: FDA should provide the details of and summarize the results of their analysis in the guidance. FDA should consider assessing the performance of the proposed method *vs.* other commonly used methods for estimating starting doses in FIH trials.

Page 4, Section IV. Step 1: No Observed Adverse Effect Level (NOAEL) Determination, Lines 146-147: The guidance states that "The first step in determining the MRSD is to review and evaluate the available animal data so that a NOAEL can be determined for each study." It is unclear if this applies to non-GLP/exploratory toxicology studies. In cases where NOAELs are available from single- and repeat-dose toxicity studies, which NOAEL should be used to determine the MRSD (also applies to Page 8, Section VI. Step 3: Most Appropriate Species Selection, Lines 294-296)?

Recommendation: FDA should specify whether NOAELs derived from non-GLP/exploratory studies should be used to determine the MRSD and provide guidance on deriving the MRSD when multiple NOAELs are available from both single- and repeat-dose toxicity studies.

Page 4, Section IV. Step 1: No Observed Adverse Effect Level (NOAEL) Determination, Lines 147-149: "Several differing definitions of NOAEL exist, but for selecting a starting dose, the following is used here: the highest dose level that does not produce a significant increase in adverse effects." This definition is not consistent with the term "no observed adverse effect level" and also differs from the one given in the Glossary (the highest dose tested in an animal species without adverse effects detected).

Recommendation: FDA should clarify the definition of NOAEL and ensure its consistent use throughout the document.

Page 5, Section IV. Step 1: No Observed Adverse Effect Level (NOAEL) Determination, Lines 167-170: "Measurements of systemic levels or exposure (i.e., AUC or Cmax) cannot be employed for setting a safe starting dose in humans, and it is critical to rely on dose and observed toxic response data from adequate and well-conducted toxicology studies." Evidence to support the notion that systemic levels or exposure cannot be used to set safe starting doses has not been provided in the guidance. As mentioned previously (see comments to Page 2, Section II. Scope, 1st paragraph and footnote 2), we believe that pharmacokinetic-based extrapolation methods can be useful in deriving safe starting doses for FIH trials.

Recommendation: We recommend that the use of pharmacokinetic-based methods for estimating starting doses in FIH trials should be given more consideration in this guidance.

Page 5, Section IV. Step 1: No Observed Adverse Effect Level (NOAEL) Determination, Lines 172-174: The guidance states that "... the lowest saturating dose, not the highest (non-toxic) dose, should be used for calculating the HED." It is unclear what is meant by "lowest saturating dose". Does this mean the dose at which no further increase in exposure is observed?

Recommendation: FDA should be more explicit in describing the lowest saturating dose.

Page 9, Section VII. Step 4: Application of Safety Factor, Lines 339-340: The rationale and basis for the historically derived safety factor of 10 should be provided.

Page 11, Section VIII. Step 5: Consideration of the Pharmacologically Active Dose (PAD), Lines 422-433: The definition of "pharmacologically active dose" should be provided in this section. It is generally accepted practice that the starting dose in FIH trials is pharmacologically inactive;[1,2] however, this has not been addressed in this guidance and deserves further discussion.

Recommendation: FDA should define "pharmacologically active dose" in this section (as well as in the remainder of the guidance) and provide more discussion on the use of pharmacologically active *vs.* inactive starting doses.

Page 18, Appendix B, Analysis of Body Weight Effects on HED Calculations, Table 3: The use of significant figures should be consistent throughout the table.

Page 20, Appendix B, Analysis of Body Weight Effects on HED Calculations, Table 4, Column F, Mouse: The number -22% is incorrect; the correct value is -26%.

Page 25, Appendix E, Selection of Maximum Recommended Starting Dose, Step 4: The text in the box "Choose Safety Factor and Divide HED" is unclear. The following is suggested for clarity: "Choose Safety Factor and Divide HED by This Factor".

Page 26, Glossary, Line 777: "Km: Factor for converting mg/kg dose to mg/m^2 dose" - the "k" should not be capitalized.

Page 26, Glossary, Lines 785-786: The definition for NOAEL presented here is not the same as that given in Section IV lines 148-149.

> ***Recommendation:*** FDA should use a consistent definition of NOAEL throughout the document (we recommend the definition provided in the Glossary).

Page 26, Glossary, Lines 789-790: The acronym "LPAD" is more representative of "lowest dose tested in an animal species with the intended pharmacologic activity" and recommend its use in the guidance.

BMS appreciates the opportunity to provide comments on this draft guidance and requests that the FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Laurie F. Smaldone, M.D.
Senior Vice President
Global Regulatory Sciences

REFERENCES

1. Reigner BG and Blesch KS. Estimating the starting dose for entry into humans: principles and practice. Eur. J. Clin. Pharmacol. 2002; 57: 835-845.
2. Posvar EL and Sedman SJ. New drugs: first time in man. J. Clin. Pharmacol. 1989; 29: 961-966.
3. Degorge JJ, Ahn C, Andrews PA, Brower ME, Giorgio DW, Goheer MA, Lee-Ham DY, McGuinn WD, Schmidt W, Sun CJ, and Tripathi SC. Regulatory considerations for preclinical development of anticancer drugs. Cancer Chemother. Pharmacol. 1998; 41: 173-185.