



Bristol-Myers Squibb Company

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August 4, 2005

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

Re: Draft Guidance for Industry, Investigators, and Reviewers on “*Exploratory IND Studies*”

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the *Draft Guidance for Industry, Investigators, and Reviewers on “Exploratory IND Studies”*. Our company’s mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. For this reason, we are interested in commenting on the *Draft Guidance for Industry, Investigators, and Reviewers on “Exploratory IND Studies”* released for comment in April, 2005.

We commend the FDA for this initiative to provide guidance to Industry on the development of novel therapeutic agents. BMS anticipates that this FDA guidance, when finalized, will result in a well-defined, consistent and efficient framework that will support the effective development of novel treatments and clear regulatory decision-making which can ultimately lead to the availability of new, safe and effective treatment options for a variety of diseases.

BMS appreciates the opportunity to comment on this draft guidance. Upon careful review, BMS has identified several aspects of the draft guidance that require further clarification and are cited below.

BMS Comments on the Draft Guidance

General overview

BMS requests the Agency to provide additional clarity related to the following topics described in the draft guidance:

1. The Agency states in the draft guidance that existing IND regulations allow a great deal of flexibility in terms of the amount of data needed and that sponsors have not taken full advantage of that flexibility. Providing additional comments (possibly with examples) to illustrate specific areas where the Agency believes that sponsors have missed opportunities to

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utilize the existing flexibility in regulations would be very useful. Such guidance would facilitate improvements in efficiency during early clinical development of investigative compounds. Also, BMS requests that the Agency explore opportunities for interaction between the sponsor and FDA within the framework of this draft guidance.

2. BMS requests that the Agency clarify the interplay between an exploratory IND and a traditional IND. For example:
 - a. Can the same investigational product simultaneously be the subject of an exploratory and traditional IND?
 - b. It is possible that an exploratory IND may become appropriate after a traditional IND is in effect. In such a case, is the filing of an exploratory IND still feasible?

Specific BMS Comments

Line 84: Existing regulations allow a great deal of flexibility in terms of the amount of data that need to be submitted with any IND application, depending on the goals of an investigation, the specific human testing being proposed, and the expected risks. The Agency believes that sponsors have not taken full advantage of that flexibility.

Considering the flexibility in what may be acceptable under the Exploratory IND process, and the intention of this guidance to facilitate early development, there is an opportunity to specify if special mechanisms for communication with FDA are part of the process. For example, FDA could encourage a pre-Exploratory IND teleconference with sponsors to agree upon the toxicology package and study objectives in advance, and waive or reduce the standard 30 day IND review period if the toxicology studies meet the pre-defined objectives and the starting and maximum dose are specified according to the guidance.

Line 97: Exploratory IND studies, which usually involve very limited human exposure and have no therapeutic intent, can serve a number of useful goals. For example, an exploratory IND study can help sponsors:

The term "no therapeutic intent" is understood to mean that the exposure to investigative product would not be intended to treat a disease. However, this does not necessarily mean that the early clinical studies would be conducted in healthy volunteers. There may be times when the exploratory studies would be best conducted in subjects with active disease, such as when the endpoint of interest is most readily ascertained in subjects. We request clarification to include such a possibility.

Line 107: Explore a product's biodistribution characteristics using various imaging technologies.

'Biodistribution' is also limited by the PK-based problem, namely extrapolation of results from microdose PK to therapeutic-dose PK. IV dosing, with occupancy rates by PET, might be helpful for some drugs, but the PK considerations (eg. p-glycoprotein at the blood brain barrier) may still be difficult to interpret.

Line 155: Previous human experience with the investigational candidate or related compounds, if there is any.

Information on related compounds is a good idea, but, the standard should not be stricter here than in any other IND.

Line 169: The exploratory IND studies discussed here focus on a circumscribed study or group of studies and plans for which will provide information needed to plan further development of a single candidate or to select appropriate candidates from a group of related candidates.

Clarify that these studies may be used to select more than one candidate. That is, the Exploratory IND process is not restricted to the studies required to select a single candidate for further development.

Line 174: This section should also describe the plan to withdraw the exploratory IND application after completing the outlined study or studies, or the intent to supplement the exploratory IND with the appropriate complement of preclinical data to permit expanded clinical testing.

We recommend using the following wording to help clarify how the Agency wants sponsors to submit additional information to an exploratory IND: "...after completing the outlined study or studies, or the intent to amend the exploratory IND with the appropriate complement of preclinical data to permit expanded clinical testing."

BMS also requests greater clarity from the FDA on this issue. An exploratory IND followed by a 'traditional' IND submission will need to be a continuous process with no significant loss of time for a successful candidate, otherwise this route will be rather unattractive relative to the current approach. Footnote 8 says that the withdrawn IND can be referenced in the 'traditional IND'. BMS requests that the Agency clarify how the study reports should be handled to facilitate the withdrawal of the exploratory IND, and/or incorporation in a traditional IND.

Additionally, Exploratory INDs that are pursued may be converted to full INDs by amendment of the exploratory IND with the information required to initiate full early development studies.

Line 219: Information on the candidate product (i.e., the active ingredient) can be submitted in a summary report containing the following items.

Please clarify what is required when more than 1 candidate is subject to the Exploratory IND.

Line 299: The level of preclinical testing performed to ensure safety will depend on the scope and intended goals of the clinical trials.

See comment for line 84.

Line 301: We recommend that the requirements for GLP testing paragraph of lines 417-424 be moved to starting line 301.

Line 302: The document provides safety program designs and provides 3 examples. Lines 302-305 address broad objectives for which the preclinical safety programs may be tailored, with one example as "validating a clinical model in healthy volunteers."

We suggest including “patients with active disease” as well as healthy volunteers when the endpoint of interest is most readily ascertained in these specific populations.

Under the initial example of clinical studies of pharmacokinetics or imaging:

Line 313: The agency recognizes that the “potential risk to human subjects is very limited” and that line 323, “endpoints evaluated should include histopathology.”

We believe that additional guidance needs to be provided and a “cause for concern” approach can be employed. We suggest that a “limited” (presumptive target organs and gross lesions) histopathological assessment be conducted only on controls and high-dose animals, especially in the context of no significant changes in the informative endpoints of clinical chemistry and hematology. If histopathological changes exist in the high dose group, then lower dose groups would be evaluated until the establishment of a NOEL / NOAEL.

Line 332: Because microdose studies involve only single exposures to microgram quantities of test materials and because such exposures are comparable to environmental exposures, routine genetic toxicology testing is not needed.

Using the same rationale as for genetic toxicology testing, we suggest that cardiovascular safety assessment can be limited for microdose studies, and that cardiovascular safety assessment only be conducted as part of the repeat dose toxicity study in nonrodents.

Under the second example of clinical trials to study pharmacological effects:

Line 345-346: The rat is the usual species chosen for this purpose, but other species might be selected. If a rodent species is used, additional studies in nonrodents, most often dogs, can be used to confirm that the rodent is an appropriately sensitive species.

If it is known and documented in the literature that the rodent is the most relevant species for a specific class of compounds intended for clinical investigation, we suggest that toxicity testing in a nonrodent species be omitted. Conversely, if the nonrodent were the most relevant species, we suggest that toxicity testing in rodents be omitted.

Lines 349-351: The numbers of animals used in the confirmatory study can be fewer than normally used to attain statistically meaningful comparisons, but of sufficient number to meaningfully identify a toxic response.

The sentence referring to the number of animals that can be used in the confirmatory study is vague, and we request that the Agency provide specific definition as to the exact number of nonrodents/sex that should be used. This also provides an example of an issue suitable for discussion at a pre-EIND meeting.

Line 379: The results from the preclinical program may be used to select starting and maximum doses for the clinical trials. The starting dose is anticipated to be no greater than 1/50 of the NOAEL from the 2-week toxicology study in the sensitive species on an mg/m2 basis.

This NOAEL refers to the dose, not the exposure obtained.

Line 380: The starting dose is anticipated to be no greater than 1/50 of the NOAEL from the 2-week toxicology study in the sensitive species on an mg/m2 basis.

This NOAEL refers to the dose, not the exposure obtained, and requires additional clarity.

Line 385: Escalation from the proposed stopping dose should only be performed after consultation with and concurrence of the FDA.

There is an opportunity for FDA to clarify an expedited review and communication process when Exploratory INDs reach this step, in the spirit of Critical Path.

Under the third example of clinical studies of mechanisms of action related to efficacy:

Lines 405-406: Although the production of frank toxicity is not the primary intended goal of the nonclinical study, many informative endpoints (e.g., hematology and histopathology) typically incorporated into toxicity studies should be investigated at all doses.

We suggest that a "limited" (presumptive target organs and gross lesions) histopathological assessment only on control and high-dose animals can be allowed, especially in the context of no significant changes in the informative endpoints of clinical chemistry and hematology.

If histopathological changes exist in the high dose group, then lower dose groups would be evaluated until establishment of a NOEL/NOAEL. There is currently no guidance on the need for genotoxicity, and we suggest that the need to perform these types of studies largely depends on the intended patient population.

Attachment:

Some boxes beyond line 449 should be included to complete the flow diagram. More specifically, conduct the Exploratory IND first-in-man study, consult with the FDA, withdraw the original IND (and presumably close it out by finalizing the necessary reports), complete the needed toxicology reports and other non-clinical work, file the 'traditional IND', and then resume Phase I could be some of the additional boxes.

Chemistry, Manufacturing, and Controls Information

For consistency, FDA MAPP 6030.4 (5/09/01) "INDs: Screening INDs" allows a similar approach to exploratory INDs and references the same guidances, and would need to be updated (eg. the requirement to 'withdraw' the screening IND and open a full IND should be deleted)

Line 215: *General Information refers to both the drug substance and the drug product. It would be more appropriate to separate these two items and their requirements.*

Line 257: *This is valid only if we use the same formulation. Often, formulation for toxicology studies will be different from the clinical formulation. Stability protocol can be substituted for 4 week stability data, if available, in exploratory INDs.*

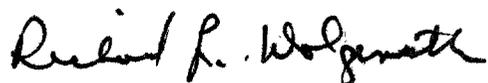
Line 288 Assay for potency (biologic):
Please provide clarification.

Line 285 Assay for purity vs. Assay for potency

Most commonly, assay for purity or potency should be identical. Please provide clarification.

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 by the FDA.

Sincerely,

A handwritten signature in black ink, reading "Richard L. Wolgemuth". The signature is written in a cursive style with a large initial "R".

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Pharmaceutical Research Institute
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