

July 13, 2005

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



RE: 2005D-0122 Draft Guidance for Industry; Exploratory Investigational New Drugs Studies; Availability

Merck & Co., Inc. is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck Research Laboratories (MRL), Merck's research division, is one of the world's leading biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. We have extensive experience in the development, licensure, and marketing of products and have used that experience to author the comments below. Our general comments on the draft guidance follow.

Merck commends the Food and Drug Administration (FDA) for providing draft guidance on the use of the exploratory Investigational New Drug (exp-IND) program for the manufacture of drug products. The draft guidance states that the purpose of the exp-IND program is to support studies with limited human exposure and no therapeutic intent, such as screening and microdosing studies of limited duration (e.g., 7 days). The draft guidance states that investigations can be initiated with less or different preclinical support than that required for traditional IND studies because the studies are expected to utilize a range of doses (from sub-therapeutic to therapeutic doses) with pharmacological and pharmacodynamic effects (but not toxicologic effects), and are not expected to explore tolerability. We agree with the Agency that the "traditional" IND approach is not always cost and time efficient. Further, we support this and all efforts by FDA to persuade sponsors to take a more streamlined approach to early drug development, when appropriate.

We concur with the overall direction of the draft guidance in that preclinical testing programs for exp-IND studies can be more flexible than traditional IND programs. While we agree with this approach, we want to ensure that timelines are met and that sponsors gain Agency agreement with "tailored" preclinical safety assessment programs to support exp-IND studies. Therefore, we recommend a mechanism (e.g., pre-exp-IND

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meetings) to ensure agreement between the Agency and sponsors before companies move forward with a particular program.

Additionally, the development of imaging tools that facilitate early proof of biology (target and mechanism) decision making on novel therapeutics has the potential to speed the selection of safe and effective molecules and doses for proof-of-concept clinical trials. Furthermore, early elimination of molecules unlikely to have therapeutic benefit will enhance human research subject safety. This initiative aligns well with the goals of the FDA Critical Path Initiative.

We have provided the following additional recommendations related to specific sections of the document for the Agency to consider as it finalizes this draft guidance.

Line 170

The guidance indicates that an exp-IND can support a “circumscribed study” or group of studies. It is assumed that the exp-IND will include an entire protocol for the initial opening IND study. However, it is not clear how much information is required for the other studies to be supported by the initial exp-IND.

We recommend that FDA allow the sponsor the option of submitting a complete protocol for each study or provide a complete protocol for the initial study to be conducted under the exp-IND with general outlines of subsequent protocols, containing information such as: objective/rationale of conducting study, number of individuals to be enrolled, and duration and dose(s) (upper and lower bounds) of the drug to be evaluated. The full protocols for subsequent studies to be conducted under the exp-IND would be submitted to FDA prior to the initiation of the clinical studies.

Lines 174-177

The draft guidance states, *“This section should also describe ...the intent to supplement the exp-IND with the appropriate complement of preclinical data to permit expanded clinical testing.”*

We applaud the FDA for allowing the flexibility to supplement an exp-IND with the appropriate complement of preclinical data, if further clinical studies are indicated. The above statement from the draft guidance suggests that with additional information it may be possible to extend or convert an exp-IND to a traditional IND without a formal IND resubmission. We recommend that FDA provide more clarity on how this conversion can be completed. For example, the Agency should clarify whether sponsors need to ask for formal permission to convert the exp-IND to a traditional IND, the type of documentation required to implement a conversion, and the time period during which additional studies could not be initiated following submission of additional preclinical data to support traditional IND studies.

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Line 181-183

The draft guidance states: *“In single-dose studies, a sub-pharmacologic or pharmacologic dose is administered to a limited number of subjects.”*

It is not clear if exp-IND studies may be conducted in patients. Use of this exploratory approach should be allowed in patients under certain circumstances. For example, when the characteristics of the compound make a benefit-risk ratio unfavorable in healthy subjects (i.e., a chemotherapeutic drug that may have a genotoxicity preclinical profile or a CNS active compound that may have considerable adverse events (AEs) when given to a healthy subject), or to gain an understanding of the relationship between mechanism of action (MOA) and treatment of a disease requires evaluation in patients. Therefore, we recommend that FDA clarify the term “subjects” to explicitly include patients.

Line 204

The draft guidance refers to the inclusion of a discussion of whether the chemistry of the candidate product presents any signals of potential human risk “in the beginning of the exp-IND application.”

We request that the Agency provide clarification regarding whether this requirement reflects the requirement for traditional INDs that stipulates sponsors must include whether a product presents any signals of potential human risk. We believe the scope of the requirement for exp-INDs should mirror the requirement for traditional IND programs in this aspect and not require additional information.

Lines 210-213

We eagerly await FDA guidance explaining and/or defining the level of CMC information that will be useful for product development.

Lines 308-332

The first example, *Clinical Studies of pharmacokinetics or imaging*, defines a microdose as less than 1/100th of the dose calculated to yield a pharmacological effect of a test substance, and a maximum of ≤ 100 micrograms. The draft guidance states: *“Because microdose studies involve only single exposures to microgram quantities of test materials and because such exposures are comparable to routine environmental exposures, routine genetic toxicology testing is not needed”.*

We concur that genetic toxicity studies are not needed. In practice, many PET tracer studies involve administration of the tracer several times in a given study (typically 3, maybe up to 4 administrations). However, we recommend that the wording in this section be altered to accommodate a small number of administrations rather than define this strictly as a single dose. This is especially important for pharmacodynamic markers because more patients will be required for studies if only single-dose administration is allowed and pre- and post-dose treatment with an intervention agent is part of the assessment. Also, in typical imaging studies, multiple doses of a radioactive research

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probe are given to subjects who could also receive multiple doses of an investigational new drug candidate. In typical imaging studies, multiple doses of a radioactive research probe are given to subjects who could also receive multiple doses of an investigational new drug candidate. These studies are designed to (1) quantify the duration of drug action as either (a) time-on-target (e.g., blockade of a receptor or inhibition of an enzyme) or (b) duration of a pharmacodynamic effect (e.g., inhibition of an enzyme product or promotion of signal transduction); or (2) characterize a dose-response curve as either a (a) dose-versus-target occupancy curve or (b) dose-versus-pharmacodynamic effect curve.

Therefore, we believe the definition should state that the total quantity administered should not exceed 100 micrograms in a given day, and that several administrations should be allowed over a period of 3-4 days, not to exceed a total of 250ug. Additionally, some tracer imaging studies require tracer injections over two week intervals. Therefore, we suggest the following wording in paragraph 1: “A microdose is defined as less than 1/100th of the dose calculated to yield a pharmacological effect of a test substance, and a maximum of <100 micrograms in a given day, and a total of up to 250 ug/day over several administrations with appropriate washout periods between administrations.

Additionally, in paragraph 2, we suggest that the final guidance state: “Because microdose studies involve exposures to microgram quantities of test materials and because such exposures are comparable to routine environmental exposures, routine genetic toxicology testing is not needed”.

Further, we request that FDA allow microdosing in combination with another investigational compound at the higher exp-IND repeat dose study levels. Otherwise, sponsors will have to fully develop either the biomarker compound or the potential drug before they could be combined and dosed in a single patient. We believe microdosing in combination is justified as the microdose compound adds no significant risk to subjects over that of the allowed high-dose treatment paradigms included in the exp-IND.

Lastly, we believe FDA should allow sponsors the flexibility in choosing doses based on molar units versus molecular weight because doses based on mass may differ due to the weight of a molecule. This issue is an example of a topic that can be addressed by the Agency and the sponsor during the pre-exp-IND meeting suggested above.

Line 336-344

It appears that the Agency did not include a provision that, when evaluating several compounds to choose the best development candidate, would allow up to 10 days of total treatment within a single subject with appropriate washout periods between candidate compound administrations. This approach was included in PhRMA’s proposal and we request that FDA include this provision in the final guidance to enable sponsors to facilitate candidate selection with clinical data.

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Lines 348-353

The guidance suggests that the observation of a gender difference in the rodent study would require both genders to be assessed in the non-rodent study. If differences are observed in gender-specific organs in rodent studies, and if humans of both genders (or the targeted gender) are planned for inclusion in the clinical trials, then it may be appropriate to conduct the non-rodent study to include either both genders (or the targeted gender). Absent this clinical circumstance, or absent effects on a gender-specific organ, there is no basis to include both genders in the non-rodent study. There is no evidence that, for general toxicity, gender differences in susceptibility in animals translates to similar gender differences in susceptibility in humans. Thus, such data have no relevance to the decision process. We would ask that the language be changed to indicate that either gender of non-rodents is acceptable and that gender-based differences in susceptibility as a factor in preclinical and clinical study design only apply to gender-specific organ toxicities.

Lines 349-351

The draft guidance states that: *“The numbers of animals 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.”*

We note that current traditional guidelines on non-rodents do not, in general, use animal numbers that attain statistically meaningful comparisons. Thus, the draft guidance would seem to indicate that large numbers of animals of each gender would still be necessary. We do not agree that this is the case given the objective of the non-rodent study within the exp-IND. Therefore, we recommend that the final guidance state the following:

“... fewer than normally used to attain statistically meaningful comparisons, but sufficient to rule out any toxicologically significant increase in sensitivity compared with rodent, (e.g. 3 – 4 non-rodents in the treatment group).”

Lines 372-373

In the second example, *“Clinical trials to study pharmacological effects”* the draft guidance states: *“In general, each product in this type of exploratory IND should be tested for potential genotoxicity unless such testing is not appropriate for the population to be studied.”*

With regard to the phrase: *“...such testing is not appropriate for the population to be studied,”* we recommend that the Agency provide examples of what is meant by this phrase (e.g., terminally ill patients) as it is unclear from the current draft language.

Lines 373-375

The draft guidance states: *“The genetic toxicology tests should include a bacterial mutation assay using all strains and exposure conditions¹⁸, as well as a test for chromosome aberrations either in vitro or in vivo.*

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We believe this is an entirely reasonable approach. We note that the ICH guidelines would allow a mouse lymphoma cell mutation assay as an alternative to the in vitro chromosome aberration assay, therefore, we request that FDA's final guidance maintain consistency with the ICH guidelines for genotoxicity. Additionally, the ICH guideline requires that the bacterial mutation assay be done twice. We propose that the FDA guideline for exp-INDs state that a single assay is sufficient, provided that it meets all criteria for an acceptable assay under current guidelines.

With regard to Footnote 18 on line 375, there is an apparent error as it refers to the S7A Safety Pharmacology guideline rather than the ICH genotoxicity guideline. We request that FDA change the footnote to accurately indicate it is referring to ICH S2B.

Lines 375-377

The draft guidance states that if the in vivo test for chromosome aberrations is used, *"The in vivo test can be performed in conjunction with the repeated dose toxicity study in the rodent species. The high dose in this case should be the maximally tolerated dose."*

We recommend that the final guidance state that an upper limit of 1000 mg/kg/day would be appropriate for studies of 14 days or longer. This change would be consistent with the Organisation for Economic Co-operation and Development (OECD) guideline on the mammalian erythrocyte micronucleus test (475, section 23) cited in the ICH guidelines. We also recommend that the guideline state specifically that a test for chromosome aberrations in vivo includes the bone marrow micronucleus assay in rodents.

Line 384

"(3) the dose that produces a pharmacological response or at which target modulation is observed in the clinical trial."

We request further clarification by FDA regarding the 3rd criteria. Specifically, we recommend that the Agency change this sentence to state: "(3) the dose that produces a pharmacological and/or pharmacodynamic response..."

Line 385

We suggest FDA change the wording in this line from "proposed stopping dose" to "proposed maximal clinical dose."

Lines 388-406

In the third example from section C. Safety Program Designs - Examples, entitled *"Clinical studies of MOAs related to efficacy"*, the draft guidance discusses dose selection for clinical studies based on pharmacodynamics (kinetic and pharmacological knowledge from animal studies) so that the emphasis of the pre-clinical studies is not a determination of frank toxicity in animals but might be based, for example, on a dose known to saturate a receptor. The draft guidance makes no statement about any requirement for genetic toxicology studies.

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We recommend that, since antibodies are mentioned in the draft guidance, the final guidance should state that, for biologics, genetic toxicology testing would not be required and FDA should provide additional guidance regarding requirements for small molecules.

Additionally, the preclinical rodent toxicity study discussed in example 3 of Section C. may not reach a maximally tolerated dose. We request that, for this example, FDA consider the same recommendations we stated above with regard to the second example in Section C, but without the requirement for a maximally tolerated dose or limit dose in the in vivo study (provided the in vitro results are negative). We suggest the following text as a new sentence on line 406: “The genetic toxicology tests should include a bacterial mutation assay using all strains and exposure conditions, as well as a test for mutation in mammalian cells in vitro or for chromosome aberrations either in vitro or in vivo. The in vivo test can be performed in conjunction with the repeated dose toxicity study in the rodent species designed to establish safe levels.” We also suggest providing guidance as in the second example, that such genetic toxicity studies might not be required for certain patient populations, such as terminally ill patients.

Lines 417 to 424

The guidance states: *“...certain of the GLP provisions may compromise proper science. For this reason, sponsors should provide a factual basis for exemptions from conformity with GLP provisions (21 CFR 312.23(a)(8)(iii). Sponsors are encouraged to discuss the necessity of exemptions from GLP provisions with the FDA prior to conducting safety related studies.”*

In Line 421, we recommend changing the text from “...compromise proper science” to “...may not be necessary”. Additionally, we suggest deleting the last sentence (lines 423-424). These changes would make the final guidance for exp-IND programs consistent with traditional IND requirements where studies that do not follow all GLP provisions may be included with appropriate explanation.

Page 13 – Attachment

We recommend changing the section of the flowchart on the bottom-right from “Clinical equivalent of ½ of rat or nonrodent AUC – whichever is lower” to “Clinical equivalent of the nonrodent AUC or ½ of the rat AUC – whichever is lower.”

In summary, we commend the Agency for its effort to streamline the drug development process. We believe the exp-IND program can enhance the drug development process and agree with FDA’s overall approach of the exp-IND guidance document. We hope our recommendations help the Agency as it finalizes this important regulatory document.

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We appreciate the opportunity to work with the Agency on this important initiative. Please feel free to contact me if you should encounter any questions regarding our comments.

Sincerely,



Brian M. Mayhew

U.S. Regulatory Policy