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July 12, 2005

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

**Re: Docket Number: 2005D-0122**  
**Comments on Draft Guidance for Industry on Exploratory IND Studies**

The Johnson & Johnson family of companies (J&J) is the world's most comprehensive and broadly based manufacturer of health care products for the consumer, pharmaceutical and medical devices and diagnostics markets. J&J has more than 200 operating companies in 57 countries around the world employing approximately 109,000 employees and selling products in more than 175 countries.

J&J is actively pursuing technologies and initiatives that can identify potential drug candidates earlier in the development process, hastening their development and ultimately their availability to the public.

On behalf of J&J, we are providing the following general and specific comments in response to the FDA's draft "Guidance for Industry, Exploratory IND Studies," released for comment on April 14, 2005:

**General Comment/s**

Overall we believe that the draft guidance captures many of the important requirements for safely expediting drug development. We also understand that although this is a relatively detailed guidance, there will be more specific discussions between FDA and industry as we develop more experience with this initiative.

**Specific Comments**

**Section II: Background**

Lines 138-142: The Agency encourages sponsors to consider an exploratory IND for drugs targeting serious diseases. It would be useful to clarify whether the Agency will require the same level of pre-clinical data for an exploratory IND for a new drug candidate intended for a serious disease, compared to a new drug candidate intended to treat a less serious disorder (*presumably the same*).

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### **Section III: Content of IND Submissions**

#### **A. Clinical Information**

##### *1. Introductory statement and general investigational plan*

Lines 168-177: The Agency should clarify if a 30-day review period (as for conventional IND applications) also applies to exploratory IND submissions. The Agency should also clarify if an additional 30-day review period is required when the exploratory IND is supplemented to permit additional clinical testing.

Lines 174-177: The Sponsor should not have to declare at the time of initial application whether the exploratory IND will be withdrawn or amended since the action related to the exploratory IND would likely be driven by the results of the exploratory studies. The exploratory IND should be viewed as a first step in an evolving drug development program. As such, a mechanism is needed whereby an exploratory IND, once appropriately amended, becomes a traditional IND rather than a distinct submission.

#### **B. Chemistry, Manufacturing and Controls Information**

Lines 210-213: This cGMP guidance will be critical to the implementation of the Exploratory IND concept. As the production of cGMP materials can be a rate-limiting step in entering the clinic quicker, we urge the FDA to finalize the guidance in the near future.

##### *1. General information for the candidate product*

Lines 215-261: Footnote 5 states that, "For the purposes of this guidance, the term *candidate*, or *candidate product*, is used to describe a drug or biologic that is being testing in early exploratory studies under an IND. In contrast to other Agency guidances, this guidance does not distinguish between a *drug product* and a *drug substance*." However in Section III.B.1 the term "candidate product" is defined as the active ingredient while the terms "product", "candidate product", "candidate drug product" appear to be used interchangeably to describe the test article. For clarification and to reduce confusion, the Agency should consider using the term "test article" as mentioned in line 419 consistently throughout the guidance when referring to the dosage form.

Lines 215-261: Please clarify if a single summary report should be included for both the active pharmaceutical ingredient and test article of each "candidate". For example, if the goal of the Exploratory IND is to compare the hydrochloride, citrate and free base forms of an active pharmaceutical ingredient, would three individual summaries be expected? If so, would all three forms need to be described and analytically characterize to the same extent? Recognizing it is the free base form that would be systemically available, would safety programs and ancillary CM&C support be expected for all three forms? Line 366 appears to imply that this is the requirement only if the study is designed to elicit a pharmacological effect.

Lines 230-231: Please specify if an excipient approved for use by another major health authority but considered as a novel excipient by FDA is acceptable for use in exploratory IND studies.

Lines 257-258: With regards to supportive stability studies, the use of the term “product” is interpreted to refer to the test article. Does this imply that stability of the drug substance is not required? Again, clarification is required on the terminology to reduce confusion.

Lines 259-260: There is a general uncertainty regarding sterility and pyrogenicity testing requirements for test articles that are nasally and orally inhaled. Dosage forms for inhalation should be distinguished to indicate nasal versus oral inhalation into the lungs if requirements differ. A footnote for clarity is suggested.

## 2. *Analytical characterization of candidate product*

Lines 268-269: The guidance “recommends” establishing the impurity profile for future reference; assurance that FDA reviewers will not require this information from sponsors as part of the exploratory IND would be helpful.

Lines 275-278: In those situations where a batch of “candidate product” is different from that employed in nonclinical toxicology studies, would the appearance of a new impurity that is below the qualification threshold be considered “representative” of batches included in previous nonclinical studies? Under what conditions would the Agency consider imposing a Clinical Hold if a new impurity is observed?

## C. Safety Program Designs – Examples

The three examples provided in this section characterize the generally flexible approach the Agency is encouraging for exploratory IND safety programs. Given that flexibility, as sponsors contemplate submitting an exploratory IND, there will likely need to be preliminary consultation with the FDA on the particulars of a specific drug program, e.g., to gain consensus on acceptable exposure limits, etc. Does the Agency envisage a mechanism whereby sponsors might rapidly obtain Agency feedback (apart from a traditional pre-IND meeting) on their specific plans for an exploratory IND safety package and for a preliminary clinical study design?

### 1. *Clinical studies of pharmacokinetics or imaging*

Lines 310-311: “*A microdose is defined as less than 1/100<sup>th</sup> of the dose calculated to yield a pharmacological effect.....*” An alternative definition might consider a microdose as 1/100<sup>th</sup> of the expected therapeutic dose. That somewhat more liberal definition could allow sponsors to employ more readily implemented analytical methods than AMS, which has technical and logistical limitations.

### 2. *Clinical trials to study pharmacological effects*

Lines 342-364: Please clarify that the nonrodent is a confirmatory species for safety assessment and therefore a very limited number of animals is required. Consideration should also be given to only studying the gender planned for use in the clinical studies in the nonrodent studies even if gender differences are present (e.g.: If females are not being used in early clinical studies, the nonrodent study should not be required to study females).

To be consistent with general toxicology programs, please clarify that any standard rodent or nonrodent species may be used.

3. *Clinical studies of MAOs related to efficacy*

Lines 390-406 It would be helpful to more explicitly define in the guidance those circumstances under which the Agency considers it appropriate to implement their proposal: "...*in some cases, a single species could be used if it is established as the most relevant species based on scientific evidence....*". Also, what alternative or modified study designs are being referred to in the statement "...alternative, or modified, pharmacological and toxicological studies to select clinical starting doses and dose escalation schemes"?

**Summary**

J&J appreciates the opportunity to provide input to the Agency on this important critical path initiative. We believe this is a significant opportunity for the FDA to work together with its stakeholders to provide this flexible drug development option to expedite drugs along the critical path and enhance the drug development process while ensuring human subject safety.

In closing, we would like to thank the Agency in advance for its thoughtful consideration of our comments/recommendations. If we can provide further assistance, please do not hesitate to contact us at 908 927 2800 (telephone line dedicated for FDA use).

Respectfully submitted,



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