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**MEMORANDUM**

**FDA DRAFT GUIDANCE ON EXPLORATORY IND STUDIES**

On April 14, 2005, the Food and Drug Administration (“FDA”) announced the availability of a draft “Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies” (“Exploratory IND Guidance” or “Guidance”).<sup>1</sup> The draft Guidance describes some early Phase 1 (i.e., “Phase 0”) clinical exploratory approaches to enable sponsors to more efficiently identify and develop promising compounds under an Investigational New Drug Application (“IND”), based on a more limited preclinical data set than that required for a traditional Phase 1 study. Comments on the draft Guidance should be submitted to FDA by July 13, 2005.

The draft Exploratory IND Guidance was issued pursuant to FDA’s March 2004 “Critical Path Initiative,” which, among other things, announced the need for new drug development tools early in the development process to identify promising compounds

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<sup>1</sup> A copy of the draft guidance document is available at <<http://www.fda.gov/cder/guidance/6384dft.pdf>>; see also FDA, Notice, Draft Guidance for Industry on Exploratory Investigational New Drugs Studies; Availability, 70 Fed. Reg. 19,764 (Apr. 14, 2005) (available at <<http://www.fda.gov/OHRMS/DOCKETS/98fr/05-7485.pdf>>).

and increase time and resource efficiencies.<sup>2</sup> However, even before the announcement of the “Critical Path Initiative,” the agency had already begun to discuss early drug development tools permissible under its IND regulations at 21 C.F.R. Part 312. For example, in May 2001, FDA issued a Manual of Policies and Procedures (“MaPP”) describing “screening INDs” (i.e., a single IND submitted for the limited purpose of comparing the properties of closely related moieties to screen for the best development candidate).<sup>3</sup> The agency also considered proposals in the European Union for “Microdose INDs” (i.e., studies intended to collect pharmacokinetic information in human subjects by administering “microdoses” — 1/100<sup>th</sup> of the dose calculated to yield a pharmacological effect — of selected compounds) as it developed the draft Exploratory IND Guidance.<sup>4</sup> In this respect, the Exploratory IND (“ExpIND”), which includes these types of exploratory trials, is not truly a “new” drug development tool, but rather a clarification of the preclinical and clinical approaches that a sponsor may consider under current IND regulations when developing compounds and exploring their clinical utility under an IND.

The Guidance defines an “exploratory IND study” to mean a clinical trial that is conducted very early in phase 1 “prior to the traditional dose escalation, safety, and tolerance studies that ordinarily initiate a clinical drug development program,” and that “involves very limited human exposure [(e.g., 7 days)], and has no therapeutic intent.” Guidance at 1. Examples of uses for ExpIND studies include:

- Obtaining information on pharmacokinetics, including biodistribution
- Selecting the most promising lead product from a group of candidates designed to interact with a particular therapeutic target
- Exploring a product’s biodistribution characteristics using imaging technologies

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<sup>2</sup> See FDA, “Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products,” (Mar. 16, 2004) (available at <<http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>>).

<sup>3</sup> See FDA, MaPP 6030.4, “Screening INDs,” (May 2001) (available at <<http://www.fda.gov/cder/mapp/6030-4.pdf>>).

<sup>4</sup> See European Medicines Agency, “Position Paper on Non-Clinical Safety Studies to Support Clinical Trials with a Single Microdose,” CPMP/SWP/2599/02Rev 1, (June 2004) (available at <<http://www.emea.eu.int/pdfs/human/swp/259902en.pdf>>).

- Understanding the relationship between a mechanism of action and the treatment of a disease.

Although the ExpIND procedure outlined in the Guidance may be used to develop compounds for any indication, “it is particularly important for manufacturers to consider this approach when developing products to treat serious [or life-threatening] diseases.” *Id.* at 4.<sup>5</sup> In addition, ExpINDs are not usually intended to be permanent, but temporary. Sponsors must describe their plans to withdraw ExpINDs once studies are completed, or to supplement the application with additional data to permit expanded clinical testing typical for a traditional IND.

Because of the exploratory nature of clinical investigations carried out under an ExpIND (*i.e.*, administration of sub-therapeutic doses of a compound or doses that produce a pharmacological but not toxic effect), FDA flexibly interprets the IND information requirements to allow these clinical studies to proceed based on a more limited data base than that required for a traditional Phase 1 study. Despite this flexibility, however, an applicant must provide the agency with enough information for FDA to determine that human subjects will not face undue risk of harm. The major types of information that must be included in an ExpIND are: (1) clinical development plan information; (2) chemistry, manufacturing, and controls (“CMC”) information; and (3) pharmacology and toxicology information. FDA’s approach to each of these information types, which depends on the scope and intended goals of the clinical study, is described below.

*Clinical Development Plan Information.* Because studies to be conducted under an ExpIND focus on a limited study or group of studies necessary to identify and further develop a promising compound, applicants must articulate a rationale for selecting the compound rather than providing a more detailed development plan. The draft Exploratory IND Guidance identifies single- and multiple-dose studies as two potentially useful ExpIND study designs. Single-dose studies could include the administration of a sub-pharmacologic (*e.g.*, a “microdose”) of a compound to a limited number of study subjects to collect pharmacokinetic information and/or perform imaging studies, or a

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<sup>5</sup> FDA generally regards a disease or condition to be “serious” if it is “associated with morbidity that has substantial impact on day-to-day functioning,” FDA, Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review, (Sept. 1998) at 4, and “life-threatening” if “the likelihood of death is high unless the course of the disease is interrupted” or if there is a “potentially fatal outcome.” 21 C.F.R. § 312.81(a).

pharmacologic dose to collect information on pharmacological effects. Dose-escalation studies conducted under an ExpIND should be designed to investigate a pharmacodynamic endpoint, rather than to determine tolerability limits (typically performed under a traditional IND).

*CMC Information.* The scope of CMC information that should be included in an ExpIND is perhaps the one area most similar to a traditional IND. The Guidance refers to the agency's "Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products," (Nov. 1995) (available at <<http://www.fda.gov/cder/guidance/clin2.pdf>>) for general CMC information. In addition, an applicant should submit a summary report on the specific compound or group of compounds to be studied that includes, for example, a physical and chemical description of the compound, the grade and quality of manufacturing excipients and product components, and stability information.

If drug from a particular batch that was used in nonclinical toxicology studies is to be used in the clinical setting, FDA will consider the material to be qualified for human use based on the general CMC information included in the ExpIND. However, if the compound used in nonclinical studies is not the same material that will be used in humans, applicants should provide certain analytical testing data demonstrating that the material is representative of drug from batches used in nonclinical toxicology studies.

*Pharmacology and Toxicology Information.* The amount of data from nonclinical testing that should be included in an ExpIND depends on the scope and intended goals of the clinical study.<sup>6</sup> The Guidance discusses three study scenarios: (1) pharmacokinetic or imaging studies; (2) pharmacological studies; and (3) mechanism of action studies.

ExpINDs for pharmacokinetic or imaging studies (i.e., "microdose" studies) may include data from an extended, single-dose toxicity study in a single mammalian species that measured *in vitro* metabolism, and if the applicant provides comparative data on *in vitro* pharmacodynamic effects. ExpINDs for pharmacological studies require more extensive preclinical safety data, because they are intended to select a safe starting dose (and maximum dose) for a clinical study. For example, the ExpIND may include data from "a 2-week repeat dose toxicology study in a sensitive species accompanied by toxicokinetic evaluations." Guidance at 9. To support an ExpIND for clinical studies intended to evaluate a compound's mechanism of action, "FDA will accept alternative, or

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<sup>6</sup> FDA anticipates that all preclinical safety studies supporting an ExpIND will be performed consistent with Good Laboratory Practices. See 21 C.F.R. Part 58.

modified, pharmacological and toxicological studies to select clinical starting doses and dose escalation schemes. For example, short-term, modified toxicity or safety studies in two animal species based on a dosing strategy to achieve a clinical pharmacodynamic endpoint can in some instances serve as the basis for selecting the safe clinical starting dose for a new candidate drug.” Id at 11.

The draft Exploratory IND Guidance applies only to IND content. The ExpIND submission procedures described in FDA’s regulations are the same as those for a traditional IND. Therefore, for example, an ExpIND does not become effective until thirty days after FDA receives the application, and clinical studies conducted under an ExpIND may be placed on “clinical hold.” See 21 C.F.R. §§ 312.40, 312.42.

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If you have any questions about this memorandum or would like additional information on GRMPs or drug development issues, please contact Kurt Karst (202.737.7544; krk@hpm.com).