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

Re: Docket No. 2005D-0122, Draft Guidance for Industry on Exploratory IND Studies; Vol. 70, No. 71, Federal Register 19764-19765 (April, 14, 2005)

Dear Sir/Madam:

The following comments on the above draft guidance are submitted on behalf of Eli Lilly and Company. In preparation of the final guidance, the following comments are submitted for Agency consideration.

General Comments

We agree with the general message of the guidance and appreciate the agency's efforts to clarify the approaches that can be taken when planning exploratory IND studies in humans. Overall the guidance is reasonable and is generally consistent with recommendations contained in the CHMP microdose guideline and the PhRMA Exploratory IND proposal.

We understand and support that these draft guidelines are also intended to facilitate development of radiolabeled ligands for the sole purpose of serving as biomarkers in drug development. However, in these instances, such ligands will never be developed as therapeutic agents, nor be part of "expanded clinical testing". Is it the Agency's intent that sponsors open an Exploratory IND for each study using this ligand? Alternatively, can one Exploratory IND for a single radiolabeled ligand include several sub-therapeutic dosed studies? Is there then a time limit for how long an Exploratory IND may be in effect in the case where several studies may be conducted?

It appears that the Agency's intent within this guidance is to inform sponsors that before further clinical testing is initiated (beyond the study conducted under the Exploratory IND), a traditional IND must be opened within the appropriate Division. It is ambiguous as to whether the traditional IND is to be a separate entity, or if supplementing the Exploratory IND with the additional information is sufficient (lines 174-177) to proceed into expanded clinical testing.

Answers That Matter

2005D-0122

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Preclinical Comments

The guidance outlines a flexible approach to the animal safety studies required to support exploratory IND studies in humans. Clarification, as suggested in the tabular set of detailed comments below, would make the guidance more useful for sponsors and reviewers.

In multiple areas the document refers to scaling based on body surface area. Lilly suggests that scaling based on pharmacokinetic / pharmacodynamic modeling may be appropriate, depending on the nature of the development program and data available for modeling.

Therapeutic biological products are included in this draft guidance, but the majority of the recommended toxicology studies (genotoxicity studies, use of primates as the primary species, use of a second species) are primarily relevant for small molecule therapeutics. Please clarify that biological drugs should be developed according to ICHS6 and removing reference to biologic drugs from some parts of the document.

CM&C Comments

From a chemistry, manufacturing, and controls perspective, the exploratory IND does not offer regulatory relief from existing Phase 1 guidance (Content and Format of Investigational New Drug Applications for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products). However, reiteration of the flexibility in existing regulations is recognized and appreciated.

In Section B.2, it is helpful guidance that the use of the same batch of candidate product in toxicology studies and clinical trials represents an opportunity to provide less characterization data.

The comments within the table that follows refer to individual sections or lines within the draft guidance.

Sincerely,
Eli Lilly and Company

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Eli Lilly and Company

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Eli Lilly and Company

Detailed Comments Table 1.0

Section	Guidance Line	Comment
I. Introduction	21	For additional clarity and consistency, reword to, "...clinical; chemistry, manufacturing, and controls; and preclinical approaches..."
II. Background	90	For additional clarity and consistency, reword to, "...clinical; chemistry, manufacturing, and controls; and preclinical approaches..."
	97-98	Please clarify if these types of studies are limited to healthy volunteers. Would microdose studies be appropriate in patients, despite the fact that there is no therapeutic intent?
	114	Please clarify the use of "limited" as used to describe the number of subjects, dose range and period of time for exposure. For instance, would a limited number of subjects be restricted to 5, 10 or 25?
	Footnote 6	The footnote states that generally these studies would not be conducted in pediatric patients or in pregnant or lactating women. Please clarify if women of child bearing potential should also generally be excluded from exploratory IND studies.
III A Clinical	174-177	Please clarify with regards to the timing of expanding an exploratory IND to a traditional IND. If a sponsor chooses to amend an exploratory IND with data to support a traditional Phase 1 plan, at what point can the clinical studies proceed (i.e. is there a 30-day wait similar to an initial IND)? Alternatively, is the intention of this guidance to advise sponsors to submit an entirely separate traditional IND for a selected compound that was subject to an Exploratory IND.
	176	For increased clarity, change "supplement" to "amend"

Section	Guidance Line	Comment
	182, footnote 9	Footnote 9 appears to discuss the use of a known radiolabeled ligand (published at least once) outside the Exploratory IND. Is it the intent then that this Exploratory IND will not apply to subsequent studies using radiolabeled ligands that have been developed solely for the purpose of imaging work at sub-therapeutic doses? This is assuming that an Exploratory IND may have been used for the first study (unless it was conducted outside the US) and the results have been published.
III C 1 Tox PK/Imaging	317	Request clarification that if the clinical study involves only male subjects, the animal studies can be conducted in male animals only, consistent with the CHMP position paper.
	322	Request clarification regarding the endpoints collected. For those categories listed, is it the agency's expectation that the parameter list (tissue list, clinical pathology parameters) be identical to that routinely used for toxicity studies supporting a traditional IND?
	322	Please add a statement that toxicokinetic data are not required in the microdosing studies since the doses are usually too low for routine detection of plasma concentrations.
	332	Please clarify if safety pharmacology data are required under this scenario.
III C 2 Tox Pharm	359	For the toxicokinetic measurements, clarify that the assays used would need to be proven, but not have the same state of GLP validation as the assays that would support a traditional IND.
	363-364	Similar to comment on line 322, request clarification of parameters selected. Recommend that they be consistent between these approaches.
	367	Please clarify the safety pharmacology parameters required. Does citation of the S7A guideline indicate that the endpoints must be consistent with the requirements in the S7A? For example, must respiratory assessments be quantitative?

Section	Guidance Line	Comment
	372-377	We request modification of the genetic toxicology section as following starting at line 373: "...to be studied. The genetic toxicology tests should include a bacterial mutation assay using all five tester strains with and without metabolic activation and a test with a cytogenetic endpoint. This second test may be a test for chromosome aberrations in vivo or in vitro. An in vivo micronucleus test performed in conjunction with a repeat dose toxicity study would also be acceptable; however, to accurately interpret this test the doses administered would need to be sufficiently high (maximum tolerated or limit dose)."
3. MOA studies	404-407	Additional clarification is requested regarding the minimal endpoints, which would indicate a sufficient assessment of toxicity. Examples include genotoxicity testing, safety pharmacology parameters, and clinical and morphologic pathology parameters. It may be sufficient to indicate that novel approaches may be utilized and recommend that these approaches be discussed with the review division in advance of executing the animal studies.
Attachment		Modify to include the genotoxicity testing recommended in comment on line 372 above.
Comments specific to Biological Drugs	308 - 387	The microdose and pharmacological effects examples are based on small molecules rather than biological drugs. For instance, a biological drug with a 2-week half-life could have a single 2-week study in cynomolgus monkeys supporting the first single-dose study in humans under a traditional IND. In addition, the rodent is frequently not an appropriate species for biological drugs based on a lack of pharmacology, but the rodent is the preferred species in the examples used in the guidance. Finally, lines 372-377 recommend genotoxicity testing, which usually isn't appropriate for biological drugs. Therefore, please clarify that the first 2 examples in lines 308-327 are focused on small molecules rather than biological drugs.
	388-425	The third example includes an antibody as an example of a biological drug. Thus, the single species use for toxicology studies (lines 402-03) is appropriate. Clarification of, "...using the specific candidate intended for the clinical investigation" is needed, since it's fairly common to have separate lots for toxicology and clinical studies. Suggest modifying this sentence to "...using similar material as

Section	Guidance Line	Comment
		<p>that intended for clinical investigation.” Also, consideration should be given to how much testing is needed for biological drugs toward the same target, but with different potencies and/or structural changes that alter pharmacokinetics. For example, could different levels of pegylation of the same primary structure be tested without comprehensive toxicology studies of each variant? Would it be possible to demonstrate comparable in vitro potency and toxicology studies only of the variants with the shortest and longest half-lives? Clinical studies would then focus on finding the variant with optimal single dose pharmacokinetics and pharmacodynamics. Another potential example is multiple antibodies that have structural differences that alter pharmacokinetics and/or potency but are directed toward a common target. Could the toxicology program for these variants include tissue binding for all variants, but toxicology studies for only the most potent and longest half-life variants? Please consider incorporating these or similar examples into the guidance.</p>
	445 - 449	<p>Consistent with prior comments the Table Attachment is specific for small molecules and isn't relevant for biological drugs. Recommend clarifying the title by clearly indicated the table is only appropriate for NMEs.</p>