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Division of Dockets Management [HFA-305]
Food and Drug Administration
5600 Fishers Lane, rm. 1061
Rockville, MD 20852

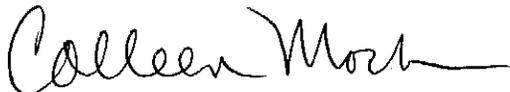
Re: [Docket No. 2006N-0062] -Expanded Access to Investigational Drugs for Treatment Use

We applaud the efforts of the FDA to improve access to investigational drugs in an appropriate and responsible way by clarification of procedures. Lilly appreciates the opportunity to contribute comments, and is open to further discussion of expanded access and other mechanisms which can appropriately bring the benefits of promising treatments to patients as early as possible.

Please feel free to contact me at (317) 277-0199 for clarification of any comments.

Sincerely,

Eli Lilly & Company



Colleen Mockbee
Associate Director, U.S. Regulatory Affairs

Eli Lilly and Company
Comments on Federal Register Notice: Proposed Rule
Expanded Access to Investigational Drugs for Treatment Use
Docket No. 2006N-0062

Lilly respectfully submits the following written comments regarding the December 14, 2006 Federal Register Notice Proposed Rule that would amend regulations on expanded access to investigational new drugs for the treatment of patients.

Lilly is a leading, innovation-driven corporation committed to developing a growing portfolio of best-in-class and first-in-class pharmaceutical products that help people live longer, healthier, and more active lives. We are committed to providing *Answers that Matter* – through medicines and information – for some of the world’s most urgent medical needs. As such, Lilly recognizes the importance of delivering to patients new treatments that will address important health needs as early as possible.

Lilly appreciates FDA’s intent to expand access to unapproved drugs in an appropriate and responsible way by clarification of procedures. As noted by the FDA in the proposed rule, the most efficient and effective way to make a drug widely available is through approval of the drug. Continued availability and appropriate utilization of existing regulatory processes such as fast track development, accelerated approval, and priority review are essential to bringing the most promising treatments to patients with serious, life-threatening conditions as early as possible.

We agree with the emphasis on the importance of the drug development process in understanding the benefit/risk of a drug through science-based approaches. Importantly, there needs to be assurance that clinical trials intended to support registration of new drugs for the treatment of serious or life-threatening illnesses are not detrimentally impacted as a result of expanded access use. However, the criteria for making such determination need to be more explicit.

We support the FDA’s position that the collection of meaningful information should be preserved when establishing treatment INDs. Expanded access protocols have met an important patient need during the time period from demonstration of efficacy and safety in clinical trials to ultimate regulatory approval. Lilly has worked collaboratively with the FDA to establish treatment IND programs prior to receiving marketing authorization for both Gemzar and Alimta that collected meaningful information on the treatment use of these drugs.

Lilly’s specific comments will focus on improving access, clarity of criteria, and reducing burdensome aspects of the process.

Specific Comments

1. In the discussion of benefits of the proposed rule (page 75160) FDA states “In FDAMA, Congress included language in section 561(c) of the act to authorize the Secretary to inform medical associations, medical societies, and other appropriate persons of the availability of investigational drugs under treatment INDs or treatment protocols. FDA believes that this action, along with detailed eligibility criteria and submission requirements established in the proposed rule, would improve access to investigational drugs and result in making expanded access use more widely available to patients regardless of treatment setting”.

Comment: It should be recognized that multiple approaches are needed to continue the education and awareness necessary to improve access to clinical trials, and thereby access to potentially important new investigational drugs.

A concerted and collaborative effort has been made to improve communication of available clinical trials through creation of the Clinical Trials Data Bank on the NIH Public Access Database (www.clinicaltrials.gov). As a result, public information on clinical trials has become more standardized and widely available in the years since the expanded access provisions were initially developed. In spite of these efforts, lack of awareness of available trials remains a key contributing factor for patients not gaining access to clinical trials.

Recommendation: Review of the Clinical Trial Data Bank should be explicitly recognized as a standard criterion for investigators' initiating requests for expanded access and in FDA's determination of whether approving such request would interfere with the conduct of existing studies for which a patient may be eligible (see Comment 2).

2. Under proposed 312.305(a)(3), FDA must determine that providing the investigational drug for the requested use will not interfere with the initiation, conduct or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the development of the expanded access use. Section 561(b)(3) and (c)(5) of the act requires FDA to make this determination.

Comment: The proposed rule does not include specific factors that will be used by the FDA to make this determination and as such may increase the possibility of inequitable access.

Recommendation: To facilitate and establish some consistency in FDA's determination, investigator requests for expanded access should include a statement that the public list of clinical trials has been reviewed and the patient is not eligible or is otherwise unable to participate (e.g., distance) in available studies. The statement should be inclusive of all investigational products for the same use and not only the investigational drug being considered for expanded access. Requiring a statement from the investigator is consistent with the spirit of the rule by providing specific criteria and mitigating potential disparate access to investigational drugs without placing undue burden upon the investigator.

This recommendation is also consistent with the goal of ensuring the enrollment in clinical trials is not adversely impacted by expanded access uses.

3. 312.315(c)(2) – *“If the drug is not being actively developed, the sponsor must explain why the drug cannot currently be developed for the expanded access use and under what circumstances the drug could be developed.”*

Comment: Lilly does not understand the relevance of this requirement in making a determination of whether the expanded access request should be approved. Sponsors develop and submit general investigational plans as part of the IND annual report. Drug development is a process that encompasses years of development and evolves as new information is learned. A statement regarding the sponsor's future development plans will not address the immediate question of access for the particular patient or group of patients included in the intermediate-size expanded access protocol. Additionally, at the earlier stages of drug development the ability to support a broader clinical program than described in the sponsor's general investigational plan may not be feasible for various reasons.

Recommendation: Remove this requirement.

4. 312.315(c)(3)- *“Include an explanation by the sponsor, if the drug is being studied in a clinical trial, of why the patients to be treated cannot be enrolled in the clinical trial and under what circumstances the sponsor would conduct a clinical trial in these patients.”*

Comment: Selecting the best treatment option for each patient is essential and involves many factors. It is our understanding that the investigator should include a statement regarding a patient's eligibility for existing studies. In the case of an existing clinical trial for which the patient appears to be ineligible, Lilly believes the investigator, sponsor, and FDA should be in dialogue to ensure appropriate and consistent interpretation of the criteria prior to an expanded access request. Typically exclusion criteria include measures to protect patient safety and reflect the need to carefully evaluate and monitor for potential drug related adverse events. Broadening inclusion criteria can confound assessment of drug effect if the patient population is too heterogeneous. However, if there are situations in which the patient's safety or the integrity of the study will not be deleteriously affected, Lilly believes the FDA and sponsors should consider existing mechanisms to amend protocols to include such patients.

Recommendation: Remove this requirement.

5. FDA notes that investigators are not selected by the sponsor but can be any physician (sometimes with specified qualifications) as a characteristic of open-label safety studies and this appears to be consistent with treatment INDs (page 51155, Section I). Proposed 312.305(c)(5) includes "ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use."
 - a. **Comment:** It is not clear if the FDA is stating lack of selection of investigators as an issue or if FDA is acknowledging that treatment INDs should be open to any physician (and in some cases with special qualifications). Sponsor selection and qualification of investigators typical of a study conducted under 21 CFR 312 would not be consistent with the goals of expanding access to community based physicians, and increases the sponsor burden for implementing treatment INDs.
Recommendation: Revise proposed 312.305(c)(5) to "in general any licensed physician may participate in an expanded access protocol. Additional specific qualifications may be necessary in some situations." In general, the sponsor collection of the investigator's qualifications utilizing a signed Statement of Investigator (FDA Form 1572) should be considered as adequate to meet the requirements for qualification of investigators requesting expanded access. Clarifying the expectations will reduce the burden for sponsors and facilitate availability of expanded access for a larger number of physicians. Differentiating qualification requirements will also acknowledge implementation of expanded access protocols is driven by a process that is distinct and separate from other protocols conducted under 21 CFR 312.
 - b. **Comment:** FDA noted the minimal data collection in open-label safety studies as an issue. For this reason and others noted above, FDA may consider such studies as treatment INDs, which implies a requirement for additional data collection, and monitoring. The amount of information collected needs to be commensurate with knowledge of the drug and balanced to ensure this does not become a burden that effectively reduces access.
Recommendation: As FDA develops training and education on the expanded access provisions, the level of monitoring and data collection should be addressed in a manner that promotes equitable access with emphasis on patient safety while minimizing burden on investigators and sponsors. Lilly believes the collection of information should be focused on including elements such as drug start and stop dates, dose, patient treatment outcome, and significant adverse events. If the collection of adverse events can use standardized reporting forms (e.g., MedWatch), this may promote consistent collection of reliable information.

6. 312.315 (Intermediate-size patient populations) and 312.320 (Treatment IND or treatment protocol)

Comment: The proposed rule does not provide specific criteria regarding the amount of evidence needed to support expanded access requests. We appreciate the difficulty in prospectively defining specific criteria given the intent to ensure patient safety yet allow broader investigator participation and access to investigational new drugs in earlier stages of development. The lack of standard criteria for efficacy and safety data places a burden on sponsors and the investigators. The proposed rule does not address the significant liability issues for sponsors and investigators. FDA's approval of the protocol does not remove this as an issue of concern. Providing earlier access to investigational drugs for which limited information is available needs to be balanced against the need to protect the safety of patients. Traditionally, early phases of investigation (Phase 1 and Phase 2) are conducted at institutions that have additional training and specialization in development of drugs, and include sponsor assessment of the sites capabilities to conduct such studies. Referral of patients to investigators with these capabilities should be encouraged.

Recommendation: In general, the final rule should state that expanded access programs should not commence until evidence of a drug's efficacy and safety is demonstrated in clinical trials that will be submitted for regulatory review and approval. This will usually be availability of data from Phase 3 studies but may include Phase 2 studies that support registration. Expanded access for individual patients should usually require similar evidence of safety and efficacy but may be used to provide continuity of care for a patient that appeared to benefit from the drug during participation in an earlier clinical trial.

7. In the FDA discussion of the proposed benefits (page 75160) and elsewhere in the preamble, FDA references section 561(c) of the act, which allows notification of appropriate organizations or persons about the availability of expanded access treatment INDs or treatment protocols to address concerns raised regarding awareness of availability of such programs by physicians and patients. FDA also refers in general to requirements to comply with other provisions as required by 21 CFR 312.

Comment: It is not clear whether notification of appropriate organizations applies to the additional expanded access category "intermediate-size expanded access protocols." Additionally, the FDA does not clarify the sponsor requirements for such notifications (e.g., posting to the Clinical Trials Data Bank). The ability of sponsors to communicate notification of such programs is also not addressed.

Recommendations:

- a. Lilly suggests clarification of FDA's intent to notify organizations of the availability of intermediate-size expanded access protocols.
- b. The sponsor requirements for submission to the Clinical Trials Data Bank for each category of expanded access should be specifically addressed.
- c. Lilly suggests that further guidance on the ability of the sponsor to proactively disseminate information on the availability of a treatment IND is needed, to ensure consistent and clear application of 21 CFR 312.7 (a) "Promotion of an investigational new drug."