

**General Correspondence
Comments on FDA's Draft Guidance**



October 30, 2006

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

**RE: Docket No. 2006D-0331
Draft Guidance for Institutional Review Boards, Clinical Investigators, and
Sponsors; Exception from Informed Consent Requirements for Emergency
Research**

Dear Sir/Madam:

Novo Nordisk Inc. appreciates the opportunity to provide comments to the above-referenced docket on the *Draft Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research*. Novo Nordisk is a pioneer in biotechnology and a world leader in diabetes care and has a leading position within areas such as hemostasis management, growth hormone therapy, and hormone therapy for women. Novo Nordisk manufactures and markets pharmaceutical products and services that make a significant difference to our patients' lives, the medical profession and society.

Novo Nordisk fully supports FDA's efforts to provide further clarification and assistance to all groups involved in development and conduct of emergency research, while at the same time continuing to ensure the protection of human subjects involved in this research. Therefore, we believe that the recently published draft guidance is a positive step. However, the revised draft guidance leaves room for interpretation and therefore we are requesting that FDA address the following questions and comments. Additionally, we are attaching an abstract of comments presented at the October 11, 2006 FDA Public Meeting by Novo Nordisk representative Dr. Richard Weiskopf, Executive Scientific Advisor, Vice President.

Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540
609-987-5800 phone
www.novonordisk-us.com

1. Section II STUDY DESIGN Prospect of Direct Benefit (page 3):

- a) General comment: The exception from informed consent only applies to patients with a life-threatening medical condition. FDA, from an ethical standpoint, has determined that the average person would agree to participate in a clinical study if it could save their life. Thus the patient needs to be in a life-threatening situation in which they are unable to give consent. This ties in with the prospect of direct benefit to the subject, implying that the benefit will either be to save the patient's life (decrease mortality) or improve their functional outcome (reduce morbidity). FDA has not assumed that patients would agree to have their decision rights denied for lesser potential outcomes.
- b) FDA should consider including not only 'preclinical studies' as demonstrating direct benefit to subjects but also recognize and include that clinical experience is appropriate here as well. The study protocol could be used to summarize how clinical experience with the investigational drug has demonstrated direct benefit to subjects e.g. summarize current literature. Inclusion of clinical experience would also ensure that the language in the guidance is more consistent with the 21 CFR 50.24 regulations.
- c) We welcome FDA broadening the requirements to include trials that have morbidity endpoints 'if subjects are at risk of death from the condition and severe morbidity that is closely associated with mortality is being evaluated.' However, we do not believe that the example of patients with stroke or stroke outcome is applicable here as morbidity is sometimes not associated with mortality e.g. blindness, spinal injury/paralysis are not associated with mortality but can be severely debilitating conditions. The Agency should provide more specific and applicable examples of morbidity endpoints useful to sponsors when designing protocols for this type of research.
- d) Given the nature of emergency research, where development does not necessarily follow traditional paths, limiting subjects' participation in such studies because 'appropriate animal and other preclinical studies support the potential for the intervention to provide a direct benefit' may not take into account whether these types of studies are feasible or an appropriate (validated) animal model exists.

2. Section II STUDY DESIGN Practicability (page 4):

- a) Given the provision of the guidance and regulations, patients will either have an LAR or be enrolled by the waiver community consent process. This mixed consent should not be interpreted necessarily as resulting in different study populations. The guidance should make this very clear.
- b) We appreciate that the guidance now provides the concept of research being 'unduly delayed'. For the guidance to be useful for the intended audience, the Agency should include a definition of unduly delayed. We understand that if patients can only be enrolled with an LAR available to consent within the treatment window, this would delay completion of a study. From a drug development perspective, a period of 3 years delay is

reasonable to authorize the exception from informed consent. Prolonged studies do not accommodate changes in treatment practices over time.

3. Section II STUDY DESIGN Study Design (page 4):

- a) The guidance states that the study design should be adequate to the task of evaluating whether the investigational drug has the hypothesized effect. This could be interpreted that the study must be powered to provide a conclusive result, thus limiting the exception from informed consent to phase 3 studies, as shorter duration studies are not powered to be conclusive. The FDA should consider providing examples of circumstances when phase 2 studies could qualify for the exception from informed consent even when followed by a phase 3 study.

4. Section III THERAPEUTIC WINDOW Therapeutic Window Rationale (page 5):

- a) FDA should clearly define what would be considered a reasonable range of a window of therapeutic effect. Even with a specified treatment window patients treated earlier may have a better response than those treated at the outer limits of the treatment window. Therefore an attempt to contact an LAR should not prevent patients being enrolled in these studies.

5. Section III THERAPEUTIC WINDOW Contact of Family Members (page 6):

- a) The guidance recognizes that even under an exception from informed consent, it may be possible to obtain consent from a legally authorized representative. However, it seems that an interpretation could be, that if subjects with LAR consent, then it would appear that the study would not qualify at all. This point in the guidance document should be easily interpretable by sponsors and FDA reviewers.

6. Section VIII COMMUNITY CONSULTATION AND PUBLIC DISCLOSURE General (page 12)

- a) Under the current guidance, the process for community consultation is left solely to the IRB to determine. This does not allow for a standard process and can vary from site to site and of course, state to state. While each disease state is different, FDA should provide examples of definitive processes for community consultation that can be adopted for use for US sites.

7. Section IX CONTACT OF LEGALLY AUTHORIZED REPRESENTATIVES OR FAMILY MEMBERS AFTER ADMINISTRATION OF THE TEST ARTICLE When (page 21)

- a) The guidance states that an LAR or family member should be contacted at the earliest feasible opportunity, and that the LAR or family member can remove the patient from the study at any time without penalty. The preamble to the original 1996 emergency research

regulation discussed whether a patient's data should be redacted from the database upon withdrawal, and the FDA response was that all data collected up to the time of withdrawal should remain in the evaluable database. No patient would be forced to undergo additional procedures or data collection post withdrawal. However, the patient's previously collected data (under a recognized community consent process) can provide relevant information for review by the health authorities. This is not universally acknowledged, and therefore if it is still applicable, it should be stated in the guidance document.

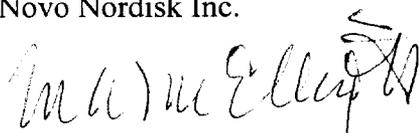
8. GENERAL COMMENT/QUESTION

- a) How will FDA handle exception from informed consent in multinational trials conducted under a US IND? While within the US, the regulations require community consultation and public disclosure, etc. to be coordinated by institutional IRBs. Non-US Ethics Committees will not likely operate to these provisions and would work under their local requirements to comply with the Declaration of Helsinki. Please describe the considerations for multinational protocols in which the US sites under the IND would comply with 21 CFR 50.24, whereas sites outside the US would comply with local legislation.

In summary, Novo Nordisk supports FDA's efforts to provide further clarification and assistance to all groups involved in development and conduct of emergency research and looks forward to the Agency's consideration of our comments.

Sincerely,

Novo Nordisk Inc.



Mary Ann McElligott, Ph.D.

Associate Vice President, Regulatory Affairs