

September 20, 2006



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

**RE: Docket No. 2006D-0331:  
Conduct of Emergency Clinical Research; Public Hearing**

Dear Sir/Madam:

Novo Nordisk thanks the FDA for providing a revision of their draft guidance, and the opportunity to provide comments and would like to make an oral presentation during the October 11, 2006 public hearing on Conduct of Emergency Clinical Research. Novo Nordisk's position will be presented by:

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**Abstract of Presentation for October 11, 2006 Public Meeting**

Novo Nordisk has an exceedingly strong ethical culture. We recognize the appropriate strong ethic of informed consent for medical treatment, and the even stronger ethic for informed consent for subjects participating in research in the U.S. Novo Nordisk is aware of the improprieties that have occurred in the past in the conduct of human research both within and external to the United States. Responses to some of these immoral transgressions committed in the name of research led to the Nuremburg Code, the Declaration of Helsinki, the Belmont Report, and a multitude of regulations in many countries, such as 21 CFR part 50. We further recognize that the FDA is the guardian of public health with respect to drugs, biologics, and medical devices and that embedded in this responsibility is the necessity of achieving a sometimes difficult balance of permitting research aimed at improving the human condition, while at the same time seeking to minimize the risks to those exposed to the as yet unproven pharmaceutical or device. This balance is generally more difficult to achieve in circumstances of medical emergencies. Similarly, planning for and conducting trials in this environment can be exceedingly challenging. Novo Nordisk has conducted several clinical trials in emergency medical conditions (intracerebral hemorrhage, ICH; traumatic

brain injury, TBI; and severe trauma). We very much appreciate the FDA's expanded clarification in the current Draft Guidance, and we wish to provide our thoughts, based on our practical experience in 6 completed phase II trials, and 3 ongoing phase III trials in these emergency medical conditions, and our extensive discussions and interactions with experts in these fields.

Novo Nordisk fully supports the need for a DMC, and independent IRB with concurrence of a licensed physician, efforts to contact legally authorized representatives and family members, obtaining informed consent where possible, community consultation and disclosure of plans before initiation of research and results following the conclusion of the research. Nevertheless, we have comments regarding some interpretive issues that affect trials in both efficacy and safety of the drugs/ biologics/ devices to be tested.

### **1. August 29, 2006 Federal Register pp 51143-51146, FDA Question 1 and 2b:**

21 CFR 50.24 (a) (1) and (3) state that a criterion for exception to informed consent is that "human subjects are in a life-threatening situation..." and participation in the research holds out the prospect of direct benefit to the subjects...". The current Draft Guidance (2006) indicates "trials that have morbidity endpoints, rather than mortality endpoints can meet the requirements ... if subjects are at risk of death from the condition and severe morbidity that is closely associated with mortality is being evaluated." The addition of morbidities as end-points is necessary and welcomed. To not permit end-points other than mortality is to negate the value of any therapeutic that does not decrease mortality. We believe that is too narrow an interpretation, with the potential for denying patients therapies that might be of other substantial benefit. However, we do not think that the current revision moves sufficiently far from the sole mortality end-point. Insisting on a close association of morbidity with mortality has some difficulties. "Close association" is not defined, leaving room for substantial differences of interpretation, making both contemplation and design of studies problematic, and in practical terms may do little to enhance research programs in this under-researched field. Thus, we think that reduction of substantial morbidity alone (without it necessarily being in "close association with mortality") should be sufficient as an end-point. Additionally, we firmly believe that substantial direct benefit can accrue to the participant with end-points that differ from mortality or severe morbidity. For example, providing hemostasis following severe trauma could be of benefit in a variety of other ways: for example, decreasing the long-term immunocompromise associated with transfusion (although it would not be possible to evaluate the long-term benefits with a randomized, blinded trial); conservation of blood components (including platelets, for which there are regular regional shortages, and there may be insufficient platelets to treat the patient and / or treating a trauma patient appropriately sometimes precludes providing adequate treatment of others requiring platelets), enabling better surgical vision and better correction of the underlying pathology; physiologic stabilization of the patient, allowing for transportation from a community hospital to a trauma center - it has been documented that care of traumatic injury at the latter improves mortality).

Although provision of hemostasis may improve mortality or severe morbidity, neither are closely related to the mechanism of action of a hemostatic agent. The treatment of bleeding is to stop the bleeding. Requiring an end-point so distant from the physiologic action is not realistic.

**2. August 29, 2006 Federal Register pp 51143-51146, FDA Question 2c:**

We welcome the FDA's guidance regarding "practicability." Almost definitionally, in the defined life-threatening situations, with the possibility of providing direct benefit to the subject, almost any delay in therapy (should it prove effective) will result in a decrease of efficacy. Here, too, "unduly delayed" allows for substantial interpretive differences. For example, hematoma volume following intracerebral hemorrhage (ICH; hemorrhagic stroke) increases during the first three or four hours following the initial hemorrhage, with neurologic outcome strongly related to the ultimate size of the hematoma. Thus, any delay of a therapy providing hemostasis for this condition, decreases the efficacy of that therapy, and thus the "direct benefit" to a subject participant. Withholding an effective agent for the 45 - 60 minutes required to obtain a properly informed consent will result in patients in the trial having inferior outcomes to those treated post-licensure in clinical practice, and in the worst case, could result in the failure to reach a positive trial outcome for a devastating disorder with no other effective treatment.

Similarly, issues related to "practicability" impact trials in trauma. Trials designed to detect significant reduction of either morbidity or mortality following severe trauma require a sufficiently large sample size, that despite world-wide enrolment in many trauma centers, the trials will be so lengthy as to threaten the practicality of the trial, and the meaning of the results, as medical care would likely change during the lengthy duration of the trial. For example, reduction of mortality following major trauma from 30% to 25 % (a reduction of this magnitude would be applauded by most traumatologists as highly medically significant) would require nearly 2600 patients for 80% power and more than 3400 patients for 90% power). These are unrealistic in terms of numbers of such patients to be enrolled if those unable to provide full informed consent can not be included. For example, our current clinical program in trauma, being conducted throughout the world, including the U.S., at more than 100 trauma centers, is expected to require approximately 4 to 5 years to enroll 1500 patients. Enlarging this trial to 2600 or 3400 patients would require approximately 7 to 9 years or 9 or 11 years, respectively. It is our thought that trials of such exaggerated duration not only tear at the meaning of "practical," but such an "undue delay" could produce results of uncertain meaning owing to the trial's duration. As a matter of public health policy, the FDA might consider these issues as being the major reason for the extremely limited number of substantial trials in this field.

**3. August 29, 2006 Federal Register pp 51143-51146, FDA Question 3:**

We welcome the recognition that those unfortunate patients unable to give consent owing to their disorder are highly likely to have a more severe form of the disorder than those capable of providing consent.

We have serious doubt that data from those less severely afflicted can, with any reasonable assurance, be extrapolated to those with the more severe form of the disorder. We believe that this may apply not only to data regarding efficacy, but to that related to safety as well. An issue of concern to us, is that following approval of such a therapeutic, physicians are highly likely to use it for those patients with the more severe form of the disorder (e.g. unconscious trauma patients), in whom safety would not have been established. For example, what might the effects of the more profound shock and / or tissue damage be on the safety of the therapeutic to be tested? Should not the answer be known before, rather than after approval?

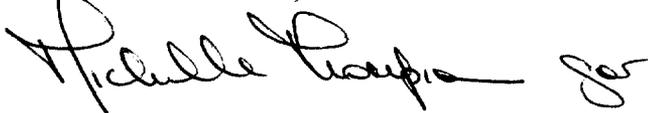
**4. August 29, 2006 Federal Register pp 51143-51146, FDA Question 2b:**

We suggest that appropriate consideration in interpretation of 21 CFR 50.24 (a) (3) (ii) be given in those proposed trials in clinical, life-threatening situations where adequate pre-clinical models do not exist.

In summary, of course, we are completely in accord with the requirement for informed consent, where possible. As does the FDA, we, too, recognize that for the public good (and potential benefit to the trial subjects), for the treatment of emergency disorders, under some circumstances, an exception is required. We believe that less limiting study end-points should be permitted; that in evaluating requests for exception to informed consent substantial consideration be given to the (in)ability to extrapolate not only efficacy, but also safety of pharmaceuticals when administered to those more severely affected (and, thus, unable to give informed consent); and that the requirement for pre-clinical studies be rephrased to take into consideration those conditions where adequate pre-clinical models are not available.

Sincerely,

Novo Nordisk Inc.,

A handwritten signature in black ink, appearing to read "Mary Ann McElligott". The signature is fluid and cursive, with a long horizontal stroke at the end.

Mary Ann McElligott, Ph.D.  
Associate Vice President,  
Regulatory Affairs