DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

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TO: Philip Budashewitz
Policy Coordinator, Office of the Executive Secretariat, OS

FROM: Deputy Director for Management, NIH

SUBJECT: FDA Proposed Rules: (1) Determination that Informed Consent is Not Feasible; Revocation of Interim Final Rule; and (2) New Drug and Biological Drug Products; Evidence Needed to Demonstrate Efficacy of New Drugs and Biological Drug Products for Use Against Lethal or Permanently Disabling Toxic Substances when Efficacy Studies in Humans Ethically Cannot be Conducted

Thank you for the opportunity to comment on the two FDA proposed rules: (1) Determination that Informed Consent is not Feasible; Revocation of Interim Final Rule [Docket No. 90N-0302]; and (2) Evidence Needed to Demonstrate Efficacy of New Drugs and Biological Drug Products for Use Against Lethal or Permanently Disabling Toxic Substances when Efficacy Studies in Humans Ethically Cannot be Conducted [Docket No. 98N-0237].

The National Institutes of Health (NIH) concurs with FDA's proposed rule [Docket No. 90N-0302], as written. NIH also concurs with FDA's proposed rule [Docket No. 98N-0237], as written, however, FDA should consider the following issues in developing its final rule:

- *Section III. Introduction to the Rule*, Page 9 (last sentence) states, "FDA believes that approval should not be withheld for a product that is intended to, and is being widely used to, ameliorate or prevent the lethal or permanently...". The meaning of this statement is unclear. Nowhere else in the document is mention made of "that is intended to, and is being widely used...". Consultation with FDA clarified that this statement refers to products that remain in a perpetual IND state, and are widely used as an IND because efficacy trials in humans cannot ethically be conducted; this situation is common with products used by the DOD. In developing the final rule, FDA should consider clarifying this statement.

- In developing its final rule, FDA should consider whether IRB review, or some other form of ethical and scientific review, might be needed for INDs proposing that efficacy be determined through only animal studies, and/or before approving new drugs for which human efficacy has been established from only animal studies. Since such studies would not involve human subjects, they would be exempt from FDA's IRB review requirements. Requiring ethical and scientific review, however, might be advisable. For instance,

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reliance on animal studies to demonstrate human efficacy would be permitted only when it would be unethical to conduct efficacy studies in humans; however, FDA's proposal does not identify who would be responsible for determining whether human efficacy studies would be unethical. This determination may not always be unequivocal, however. IRBs or perhaps some other ethical/scientific review body, might be most appropriate to make such a decision. It is noted on page 14 of the proposed rule that, "The agency also intends **in most cases** to consult on applications to market such products with an advisory committee, supplemented with appropriate expert consultants, in meetings open to the public in order to receive expert advice on whether a particular set of animal data support efficacy of a product under this rule." While most applications may be reviewed by an FDA advisory committee, given the sensitive nature of these studies and products, consideration needs to be given as to whether external consultation should be required– prior to the conduct of the animal efficacy trial and/or as part of FDA's approval process.

- In addition, in developing its final rule, FDA should consider whether the following condition for FDA approval is adequate: "information be provided to patients and potential patients...[and that] patient labeling will explain that the drug's approval was based on efficacy studies conducted in animals alone...". Consideration should be given as to whether such labeling will be sufficient or meaningful–especially since the drugs' most common use will likely be related to military combat. It seems that the DOD could require its military members to take such drugs approved by FDA on the basis of efficacy studies conducted on animals alone; therefore, the following questions arise: is labeling sufficient?; should methods, in addition to drug labeling, be required to convey that the efficacy of the drug was tested in animals only? This issue is of particular concern since the DOD stated in their comments to the FDA's request for comments in the July 31, 1997, Federal Register, that "To the extent the conduct of military operations includes **requirements** to take drugs or vaccines when indicated by the best evidence of safety and efficacy, the degree of peril posed, and the absence of satisfactory alternative therapy..., this is **subsumed** by the obligation freely accepted–legally, ethically, and practically–by every military member [emphasis added]."

Please contact Jerry Moore, NIH Regulations Officer, at 301-496-4607 if you have any questions concerning this matter.

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