

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 81N-0279]

Institutional Review Boards; Request for Information

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is seeking comments on the advisability of, and possible mechanisms for reducing its involvement in the review of early phase clinical investigations in a way that would facilitate the drug approval process but not lessen human subject protection. As part of this appraisal, FDA is interested in obtaining information from Institutional Review Boards (IRB's) about their willingness to assume additional review responsibilities over certain clinical investigations conducted under an investigational new drug exemption (IND). FDA is interested in obtaining views from IRB's and others to supplement information already obtained in the process of promulgating the current IRB regulations. This information will permit FDA to consider the feasibility of later activities which might lead to increasing IRB responsibilities in the drug approval process without changing the standards of human subject protection to which the agency now adheres. This document is a request for information, not a proposed regulation.

DATE: Written comments by November 10, 1981.

ADDRESS: Written comments should be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Halyna P. Breslawec, Office of Health Affairs (HFY-2), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20057. 301-443-1382.

SUPPLEMENTARY INFORMATION: FDA is reviewing the human drug approval process and attempting, as part of that review, to find ways in which the time required for approval can be shortened without endangering the public health. Changes that have been suggested and discussed both inside and outside the agency involve revising regulations to reduce the agency's direct involvement in the review and approval of early stages of clinical investigations. One strategy being explored to accomplish this is to give to local review committees

(Institutional Review Boards (IRB's)) exclusive review responsibility for certain drug investigations. Before considering this option in more detail, FDA is asking for public comments and suggestions on the feasibility and wisdom of such a change. Earlier FDA proposals relating to IRB's and review of mechanisms utilizing expanded IRB functions have provided some information on this topic.

Clinical testing of previously untested drugs usually consists of three separate phases. Initial testing in humans (Phase I) begins with short-term studies in a small number of normal subjects or patients to test the properties of the drug and levels of toxicity, metabolism, and when appropriate, pharmacologic effects. After basic information about the drug is obtained, larger, more detailed studies in patients (Phase II) are performed to evaluate the effectiveness of the drug and to obtain information about the drug's relative safety. Finally, more extensive testing is performed on patients (Phase III) to systematically assess the drug's safety and effectiveness.

Current regulations governing the clinical investigation of drugs provide for review of proposed human studies both by FDA and by local IRB's. Under current regulations, before human testing may begin, the sponsor of an investigation must submit a Notice of Claimed Investigational Exemption for a New Drug (IND) to FDA containing complete information about the drug, its composition, its source, the method of manufacturing, and how the drug is intended to be used. The IND must also contain the results of prior investigations with the drug, including the results of animal studies showing that the drug is reasonably safe for human testing, and the proposed protocols or plans for the tests. In addition to the submission of data, the sponsor must also make a number of commitments intended to ensure that the proposed investigation will be conducted in accordance with applicable regulations. Thus, the sponsor must make a commitment that an IRB will be responsible for the initial and continuing review and approval of the proposed clinical investigation. The sponsor must also provide assurance that the investigators will report to the IRB all changes in the investigation that may involve risks to the human subject and that the investigators will not make any changes in the research without IRB approval. The agency has 30 days from receipt of the IND to notify a sponsor that an IND is deficient. If the sponsor is

not notified of any deficiencies in 30 days, human testing may begin.

Current and Potential Approaches

During the last several years FDA has been exploring possible revisions to the IND regulations to improve the efficiency of the investigational drug review process and to reduce the burden associated with early stage clinical investigations, i.e., Phases I and II. Several models designed to "deregulate" the new drug approval process have been suggested.

The agency notes that for certain kinds of clinical investigations, local review boards or functionally equivalent bodies now carry out all or part of FDA's normal review functions. For example, and IND is not required when a radioactive tag is used during the course of a research project intended to obtain information regarding basic human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic or diagnostic purposes to carry out a clinical trial (21 CFR 361.1). Instead, there are alternative requirements for these studies including dose limits, research committee review, and reporting. FDA believes that, based upon the absence of a known safety problem apart from the potential hazard of radiation exposure, and upon the experience of the Nuclear Regulatory Commission with peer review of research studies conducted under its auspices, IRB approval and monitoring of such studies is acceptable.

Certain studies are exempted from FDA review on the basis of the degree of risk to human subjects. The recently finalized investigational device exemption (IDE) regulations (21 CFR Part 812) are structured so that on investigation of a device other than a significant risk device is considered to have an approved IDE if certain minimum requirements are met, including IRD review and approval of the study, prior submission of an IDE to FDA is not required. These regulations were implemented under the Medical Device Amendments of 1976 (Pub. L. 94-295).

Several other alternatives for reducing FDA review functions have been suggested. One of these would be maintaining the current system of dual review by FDA and IRB's but confining FDA's discretion to stop an investigation to a narrowly defined safety standard. Another alternative was suggested in a petition submitted to FDA by the Pharmaceutical Manufacturers Association on November 30, 1983. This petition proposed delegating review of early phase clinical investigations to

IRB's. (Copies of the petition may be obtained from the Dockets Management Branch.) These and other alternatives have been discussed in a variety of forums, dealing with the reform of the drug investigation regulatory process, both inside and outside the agency. One such forum includes discussion of comments on the proposed IRB regulations (see preamble to the final regulations (46FR 8958; January 27, 1981)). The agency currently is assessing the merits and feasibility of various alternatives.

Request for Specific Information

In looking at the merit of alternative review schemes, FDA will carefully evaluate its experience with review of radiopharmaceuticals and nonsignificant risk devices. In addition, the agency recognizes the comments which previously have been received on the responsibility of IRB's and these will be considered along with the information received in response to this notice. At the same time, FDA believes that to make an accurate assessment of the potential merits of the various deregulatory models it must have a better gauge of the perceptions of IRB members and others, particularly those representing institutions where such

research is conducted, of the feasibility of the alternative review procedures. In particular, FDA would like to determine whether IRB's have the resources and are willing to assume additional responsibilities for the conduct of the early phases of clinical investigations. FDA is soliciting views on the following:

1. The willingness of IRB's to assume additional responsibilities and authorities for reviewing, approving, and monitoring early phases of drug testing (Phase I or Phase I/Phase II).

2. The capability of IRB's to assess the scientific merit and general safety of clinical studies to a greater extent than is now required. The ability of IRB's to obtain the views of experts (IRB members or not) in relevant disciplines (e.g., toxicology and clinical pharmacology) as needed to review adequately clinical studies.

3. Problems to IRB's, such as resources, time commitments, funds, and liability, which might be associated with additional responsibilities. The extent to which these problems could or could not be overcome.

4. The advisability of delegating only limited additional authorities to IRB's, while requiring FDA review in specific situations: for example, high risk studies

or studies involving specific drug categories.

5. The effect of increased IRB responsibilities with concomitant decreased FDA involvement on expediting the drug approval process.

Although FDA is particularly interested in comments from IRB's, their chairpersons and members, comments from institutions, sponsors, clinical investigators, and other interested individuals or groups are welcome.

Interested persons may, on or before November 10, 1981, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this notice. Two copies of any comments should be submitted, except that individuals may submit one copy. Comments should be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 6, 1981.

Arthur Hull Hayes, Jr.,
Commissioner of Food and Drugs

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