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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2005N–0038]

Reporting of Adverse Events to Institutional Review Boards; Public Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public hearing; request for comment.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public hearing to consider the process by which institutional review boards (IRBs) obtain and review information on adverse events that occur during the conduct of clinical investigations. FDA is increasingly aware of concerns within the IRB community that the process is burdensome, inefficient, and not as effective as it should be in providing IRBs the information they need to ensure that the rights and welfare of human subjects are protected during the course of a clinical study. The purpose of the hearing is to solicit information and views from interested persons on issues and concerns regarding the submission of adverse events to and their review by IRBs. FDA is seeking general information about the nature of the problem and possible solutions, responses to specific questions (see section III of this document), and any other pertinent information stakeholders would like to share.

Date and Time: The public hearing will be held on March 21, 2005, from 9 a.m. to 5 p.m. Submit written or electronic notices of participation by 4:30 p.m. on March 4, 2005. Submit written and electronic comments by April 21, 2005.

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Location: The public hearing will be held at the Advisors and Consultants Staff Conference Room, 5630 Fishers Lane, Rockville, MD 20857.

Addresses: Written or electronic notices of participation should be submitted to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, e-mail: *FDADockets@oc.fda.gov*; or on the Internet at *http://www.accessdata.fda.gov/scripts/oc/dockets/meetings/meetingdocket.cfm*. Written or electronic comments should be submitted to *http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm* or to the Division of Dockets Management (see *Addresses* above).

Contacts: Nancy L. Stanisic, Center for Drug Evaluation and Research (HFD–1), Food and Drug Administration, 5600 Fishers Lane, rm. 9–64, Rockville, MD 20857, 301–827–1660, FAX: 301–443–9718, e-mail: *stanisicn@cder.fda.gov*.

For Registration and/or to participate in the meeting: Because of limited seating, we recommend that persons interested in attending the meeting register at *http://www.accessdata.fda.gov/scripts/oc/dockets/meetings/meetingdocket.cfm*. Registration will be accepted on a first-come, first-served basis.

The procedures governing the hearing are found in part 15 (21 CFR part 15). If you wish to make an oral presentation during the open public comment period of the hearing, you must state your intention on your registration form (see *Addresses*). To participate, submit your name, title, business affiliation, address, telephone, fax number, and e-mail address. You should also submit a written statement at the time of registration for each discussion question you wish to address, the names and addresses of all individuals that plan to

participate, and the approximate time requested to make your presentation. Individuals who have registered to make an oral presentation will be notified of the scheduled time for their presentation prior to the hearing. Depending on the number of presentations, FDA may need to limit the time allotted for each presentation. Presentations will be limited to the questions and subject matter identified in section III of this document. Presenters should submit two copies of each presentation given. All participants are encouraged to attend the entire day.

If you need special accommodations due to a disability, please inform the registration contact person when you register.

SUPPLEMENTARY INFORMATION:

I. Background

Clinical investigations regulated by FDA under sections 505(i) (drugs and biologics) and 520(g) (medical devices) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i) and 360j(g)) must be reviewed and approved by an IRB in a manner consistent with the requirements of 21 CFR part 50 and part 56 (21 CFR part 56). To approve a proposed clinical investigation, IRBs must determine, among other things, that the risks to subjects are minimized; the risks are reasonable in relation to anticipated benefits (if any); the selection of subjects is equitable; and the informed consent process is adequate for the anticipated study population and appropriately documented (see § 56.111).

After their initial review and approval of a clinical study, IRBs are required to conduct continuing review of the study at intervals appropriate to the degree of risk presented by a study (at least annually) (§ 56.109(f)). IRBs are required to follow written procedures for continuing review of research and for

determining which studies require review more often than annually (§ 56.108(a)), and must maintain records of continuing review activities (§ 56.115(a)(3)).

Under existing regulations for drugs and biologics, investigators are required to promptly report to an IRB all unanticipated problems involving risk to human subjects or others (§ 312.66 (21 CFR 312.66)). Under this reporting requirement, IRBs receive many reports of adverse events from clinical investigators. Under existing regulations for medical devices, IRBs receive information about unanticipated adverse device effects from investigators and sponsors. Investigators are required to submit to the IRB and the sponsor a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, and in no event later than 10 days after the investigator learns of the effect (§ 812.150(a)(1) (21 CFR 812.150(a)(1))), and sponsors are required to report the results of an evaluation of a reported effect to reviewing IRBs and investigators within 10 working days after the sponsor receives notice of the effect (§ 812.50(b)(1)). In addition, IRBs are required to follow written procedures to ensure that there is prompt reporting to the IRB, appropriate institutional officials, and FDA of any unanticipated problems involving risks to human subjects or others (§ 56.108(b)).

The regulations describing IRB responsibilities in part 56 and the regulations describing sponsor and investigator responsibilities in parts 312 and 812, were implemented at a time when most clinical studies were conducted at a single site or a small number of sites. In the intervening years, the number of multicenter studies has grown substantially. There are many more studies with very large numbers of study sites, including trials with both

foreign and domestic sites. FDA is increasingly aware of significant concerns and confusion within the IRB community about the way IRBs obtain and review adverse event information during the course of a clinical study, particularly in the context of a large multicenter study.

A. Volume of Adverse Event Reports

The rapid growth in the number of clinical research programs in recent years has led to a situation in which many IRBs receive large volumes of information, including a multitude of individual adverse event reports. In a recent letter, the Department of Health and Human Services Secretary's Advisory Committee on Human Research Protections (SACHRP letter) noted that some institutions are receiving in excess of 12,000 adverse event reports per year.[1] The clinical significance and relevance of reported events can vary considerably. FDA is aware that IRBs receive reports of events that range from serious to relatively minor, and that in some cases both anticipated and unanticipated events are reported. FDA is also aware that IRBs receive adverse event reports from other studies using the same drug, but not necessarily under the same conditions (e.g., different doses, durations of therapy, diseases, or subpopulations).

The prevalence of large, multicenter trials further contributes to the volume of adverse event reports to IRBs. Sponsors of investigations of drugs and biological products are required to notify all participating investigators of any adverse experience associated with the use of a drug that is both serious and unexpected and any finding from tests in laboratory animals that suggests a significant risk for human subjects (§ 312.32(c)(1)). Investigators typically

[1]July 8, 2004, letter from Ernest D. Prentice, Chair of SACHRP to The Honorable Tommy Thompson, Secretary of Health and Human Services concerning SACHRP recommendations to improve human research protections.

forward copies of such reports to their IRBs, and also forward additional sponsor reports that do not meet these criteria. Thus an IRB for a single study site commonly receives reports of adverse events and other information from all study sites.

B. Quality of Adverse Events Information

Another significant concern is that individual adverse event reports submitted to IRBs are often not sufficiently informative to permit IRBs to assess the implications of reported events for study subjects. The SACHRP letter concluded that adverse event reports "seldom contain adequate information."

Considerable variation exists among reports in the amount of detail and quality of information provided. For example, in blinded studies, reports might not disclose the treatment the subject received (i.e., whether the subject received the study drug, an active control, or placebo). In addition, it may be difficult for IRBs to review and interpret the significance of large volumes of individual adverse event reports received in isolation (unaggregated and unanalyzed) at sporadic intervals over the course of study.

II. Purpose and Scope of the Hearing

This hearing is intended to provide the IRB community, sponsors, investigators, data monitoring committees, individuals who have participated in clinical studies, and other interested parties an opportunity to discuss their experiences and concerns about the process by which IRBs obtain and review information about adverse events, and to share their ideas about how the process might be improved to best meet the purposes of IRB review—to protect human subjects. FDA is not seeking comment on how to interpret the existing regulations in parts 56, 312, and 812 requiring the reporting of "unanticipated problems involving risk to human subjects or others" at this time. Instead,

given the role of IRB's, FDA is asking what information about adverse events is necessary or useful for IRBs to consider in how to best protect human subjects, and is asking what the best process is for submitting such information. FDA hopes to obtain information that will help it develop strategies, such as guidance or a change to the regulations, to address the identified concerns.

III. Issues for Discussion

FDA is interested in hearing about the experiences of IRBs, investigators, sponsors, data monitoring committee, individuals who have participated in clinical studies, and other affected parties concerning the reporting of adverse events to IRBs and how IRBs evaluate such reports.

In the conduct of a clinical trial, the following parties have responsibilities related to identifying, evaluating, reporting, and analyzing adverse events:

- Clinical investigators

Clinical investigators have the responsibility of identifying adverse events associated with a drug, biologic, or device, evaluating and documenting the occurrence of such events, and making required safety reports. For drug and biologics trials, the investigator must report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, a drug (§ 312.64(b)) or biologic. The investigator must also report to the IRB all unanticipated problems involving risk to human subjects (§ 312.66). In a multicenter trial, the investigator at a site may also serve as a conduit to the site IRB for reports of serious, unexpected adverse events occurring at other study sites because he or she received reports of such events from the sponsor (§ 312.32(c)). For medical device trials, the investigator must report to the

sponsor and reviewing IRB any unanticipated adverse device effects occurring during an investigation § 812.150(b)(1).

• Sponsors

Trial or study sponsors are required to monitor their trials and provide required safety reports (§ 312.32). Sponsors of drug or biologics trials must report to FDA and clinical investigators any adverse experience associated with the use of the drug that is both serious and unexpected or any finding from tests in laboratory animals that suggests a significant risk for human subjects (§ 312.32). Sponsors are also required to submit to FDA annual reports, a component of which contains summary information about adverse events (§ 312.33). Sponsors of medical device trials are required to report the results of evaluations unanticipated adverse device effects to FDA and all reviewing IRBs (§ 812.150(b)(1)).

• FDA

FDA reviews safety reports, and annual reports of adverse events to determine whether there is new information that affects its original evaluation of the reasonableness of the risk to study subjects.

• Data Monitoring Committee (DMC)

In large phase 3 trials, there may also be a DMC (sometimes referred to as a data and safety monitoring board or DSMB) that conducts periodic review of accumulating data from an ongoing trial to assess whether the study continues to be safe and scientifically valid. DMCs report their analyses to the sponsor or an independent steering committee set up by the sponsor.

• IRBs

IRBs are responsible for performing a continuing review of ongoing research at appropriate intervals (at least annually) (§ 56.109(f)). IRBs must have written procedures to ensure prompt reporting to the IRB, appropriate

institutional officials, and FDA of any unanticipated problems involving risk to human subjects or others (§ 56.108(b)).

FDA would like to understand better how the IRB's responsibility with respect to adverse events fits with the roles of these other parties and how the process for reporting adverse events to IRBs can be improved to better enable IRBs to meet their obligation to protect the rights and welfare of human subjects. FDA would like interested parties to address the following issues and questions:

1. The role of IRBs in the review of adverse event information from ongoing clinical trials.

Given the number of parties with responsibilities related to adverse events that occur during the course of a clinical trial, what role should IRBs play in the review of adverse events information from an ongoing clinical trial? How does that role differ from the current role of IRBs? Should IRB responsibilities for multi-site trials differ from those for single-site trials? If so, how should they differ?

2. The types of adverse events about which IRBs should receive information.

Based on your view of the role of IRBs in the review of adverse event information from ongoing clinical trials, what types of adverse events should an IRB receive information about, and what types of information need not be provided to IRBs? For example, should IRBs generally receive information only about adverse events that are both serious and unexpected? Are there circumstances under which IRBs should receive information about adverse events that are not both serious and unexpected (e.g., if the information would provide a basis for changing the protocol, informed consent, or investigator's

brochure)? In a multicenter study, should the criteria for reporting adverse events to an IRB differ, depending on whether the adverse events occur at the IRB's site or at another site?

3. Approaches to providing adverse events information to IRBs.

There seems to be a general consensus in the IRB community that adverse event reports submitted individually and sporadically throughout the course of a study without any type of interpretation are ordinarily not informative to permit IRBs to assess the implications of reported events for study subjects (see, e.g., the SACHRP letter, NIH Regulatory Burden v. Human Subjects Protection—Workgroups Report, available at *http://grants2.nih.gov/grants/policy/regulatoryburden/humansubjectsprotection.htm*, which states that data that are neither aggregated nor interpreted do "not provide useful information to allow the IRB to make an informed judgment on the appropriate action to be taken, if any."). What can be done to provide IRBs adverse event information that will enable them to better assess the implications of reported events for study subjects? For example, if prior to submission to an IRB, adverse event reports were consolidated or aggregated and the information analyzed and/or summarized, would that improve an IRB's ability to make useful determinations based on the adverse event information it receives? If so, what kinds of information should be included in consolidated reports? And when should consolidated reports be provided to IRBs (e.g., at specified intervals, only when there is a change to the protocol, informed consent, or investigator's brochure due to adverse events experience)? Who should provide such reports? Should the approach to providing IRB's adverse event reports be the same for drugs and devices?

IV. Notice of Hearing Under Part 15

The Commissioner of FDA is announcing that the public hearing will be held in accordance with part 15. The hearing will have a presiding officer, who will be accompanied by senior management from the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, and the agency's Good Clinical Practice Program.

Persons who wish to participate in the part 15 hearing must file a written or electronic notice of participation with the Division of Dockets Management (see *Addresses*). To ensure timely handling, any outer envelope should be clearly marked with the docket number listed in brackets in the heading of this document along with the statement "IRB-Adverse Event Reporting." Groups should submit two written copies. The notice of participation should contain the person's name, address, telephone number, affiliation, if any; the sponsor of the presentation (e.g., the organization paying travel expenses or fees), if any; a brief summary of the presentation (including the specific discussion questions that will be addressed); and the approximate amount of time requested for the presentation. The agency requests that interested persons and groups having similar interests consolidate their comments and present them through a single representative. After reviewing the notices of participation and accompanying information, FDA will schedule each appearance and notify each participant by telephone of the time allotted to the person and the approximate time the person's oral presentation is scheduled to begin. If time permits, FDA may allow interested persons attending the hearing who did not submit a written or electronic notice of participation in advance to make an oral presentation at the conclusion of the

hearing. The hearing schedule will be available at the hearing. After the hearing, the hearing schedule will be placed on file in the Division of Dockets Management under the docket number listed in brackets in the heading of this document.

Under § 15.30(f), the hearing is informal, and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members may question any person during or at the conclusion of each presentation.

Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (part 10, subpart C (21 CFR part 10, subpart C)). Under § 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants.

Any persons requiring special accommodations to attend the hearing should contact Nancy L. Stanisic (see *Contacts*).

To the extent that the conditions for the hearing, as described in this notice, conflict with any provisions set out in part 15, this notice acts as a waiver of those provisions as specified in § 15.30(h).

V. Request for Comments

Interested persons may submit to the Division of Dockets Management (see *Addresses*) written or electronic notices of participation and comments for consideration at the hearing. To permit time for all interested persons to submit data, information, or views on this subject, the administrative record of the hearing will remain open following the hearing. Persons who wish to provide additional materials for consideration should file these materials with the Division of Dockets Management. You should annotate and organize your

comments to identify the specific questions to which they refer (see section III of this document). Two copies of any mailed comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday. Transcripts of the hearing also will be available for review at the Division of Dockets Management.

VI. Transcripts

The hearing will be transcribed as stipulated in § 15.30(b). The transcript of the hearing will be available 30 days after the hearing on the Internet at *http://www.fda.gov/ohrms/dockets*, and orders for copies of the transcript can be placed at the meeting or through the Freedom of Information Staff (HFI–35), Food and Drug Administration, 5600 Fishers Lane, rm. 12A–16, Rockville, MD 20857, at a cost of 10 cents per page.

Dated: 2/2/05

February 2, 2005.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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