Proposed Rules

Federal Register
Vol. 71, No. 167
Tuesday, August 29, 2006

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 50

[Docket No. 2006D–0331]

Conduct of Emergency Clinical Research; Public Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public hearing; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public hearing on emergency research conducted without informed consent under FDA's emergency research rule. The public hearing announced in this document is part of FDA's Human Subject Protection and Bioresearch Monitoring Initiative. We are particularly interested in hearing the views of individuals and groups who have encountered challenges in the conduct of emergency research in the absence of informed consent, including patient advocacy groups, individuals who have participated in clinical studies, institutional review board members (IRBs), sponsors, clinical investigators, medical societies, ethicists, and other interested parties. We are seeking input on a number of specific questions regarding aspects of emergency research and additional human subject protections. Elsewhere in this issue of the **Federal Register**, we are also issuing a draft guidance entitled ''Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors; Exception from Informed Consent Requirements for Emergency Research.'' We will consider comments received on this draft guidance together with comments and suggestions received at the hearing to determine whether the current framework is adequate for the ethical conduct of emergency research, or whether modifications would be appropriate.

DATES: The public hearing will be held on October 11, 2006, from 8 a.m. to 6 p.m. However, depending upon the level of public participation, the meeting may end early. Submit written or electronic comments by November 27, 2006. The administrative record of the hearing will remain open for 45 days following the hearing.

ADDRESSES: The public hearing will be held at the University System of Maryland Shady Grove Center, 9630 Gudelsky Dr., Rockville, MD 20850.

Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm*.

See section I. of the **SUPPLEMENTARY INFORMATION** section for information on how to participate in the meeting.

FOR FURTHER INFORMATION CONTACT: Terrie L. Crescenzi, Office of the Commissioner (HF–18), Food and Drug Administration, 5600 Fishers Lane, rm. 14B–45, Rockville, MD 20857, 301–827–7864, FAX: 301–443–9718, *terrie.crescenzi@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. How to Participate in the Meeting

All individuals wishing to make a presentation at the hearing must indicate their intent, the question to be addressed, and also provide an abstract of the presentation by September 20, 2006. Submit written or electronic comments by November 27, 2006, at the Division of Dockets Management (see **ADDRESSES**).

The procedures governing the hearing are found in part 15 (21 CFR part 15). If you wish to make an oral presentation during the hearing, you must state your intention on your submission to the docket (see **ADDRESSES**). To present, submit your name, title, business affiliation, address, telephone number, fax number, and e-mail address. FDA has identified questions and subject matter of special interest in section V of this document. You should also identify by number each question you wish to address in your presentation, although presentations do not have to be limited to those questions. FDA will do its best to accommodate requests to speak. Individuals and organizations with common interests are urged to consolidate or coordinate their presentations, and to request time for a joint presentation. FDA may require joint presentations by persons with common interests. FDA will determine the amount of time allotted to each presenter and the approximate time that each oral presentation is scheduled to begin. FDA will prepare the hearing schedule indicating which persons will be making oral presentations and the time allotted to each person, which will be filed with the Division of Dockets Management (see **ADDRESSES**) and mailed or telephoned before the hearing to each participant. Persons making oral presentations should arrive early to be sure that they are present to make their presentation in case the schedule advances. Individuals who are not present when called upon will likely lose their ability to make their oral presentation. However, the administrative record of the hearing will remain open for 45 days following the hearing and individuals may submit written comments to the docket as described in section VII of this document. Presenters should submit two copies of each presentation given. All participants are encouraged to attend the entire hearing.

If you need special accommodations due to a disability, please contact Terrie L. Crescenzi (see **FOR FURTHER INFORMATION CONTACT**).

II. Background

On October 2, 1996, FDA issued a final rule providing a narrow exception from the requirement of obtaining and documenting informed consent from each human subject prior to initiation of a clinical investigation. The intent of the regulation was to facilitate certain emergency research while ensuring adequate protection of human subjects (61 FR 51498, October 2, 1996). In the decade following issuance of the regulation, we have received approximately 60 requests to conduct a clinical investigation under § 50.24 (21 CFR 50.24) with an exception from the informed consent requirements. Now that we have received a sizeable number of requests, we have reviewed our experience with emergency clinical research under the 1996 regulatory framework. We have heard informally from some individuals that the additional safeguards in § 50.24 are either insufficient or too poorly defined to protect subjects; others have said that

the safeguards in the regulation are too onerous and interfere with important research; still others have said that the regulation contains the appropriate safeguards, but that further guidance is needed. In addition, some have asserted that important emergency research is not being carried out for a variety of reasons. These reasons include the difficulties inherent in emergency research trial designs, and the challenges and cost of applying specific aspects of § 50.24.

III. Purpose and Scope of the Hearing

The purpose of this hearing is to provide patient advocacy groups, individuals who have participated in clinical studies, IRBs, sponsors, clinical investigators, medical societies, ethicists, and other interested parties with an opportunity to discuss their experiences and concerns in the conduct of emergency research without informed consent under § 50.24, and to determine whether the current framework is adequate for the ethical conduct of emergency research or needs modification. The hearing will give us the opportunity to hear these parties' concerns related to the challenges of conducting scientifically rigorous emergency research while maintaining human subject protections and their suggestions for improving the process. We hope to obtain information that will help in developing strategies to address the identified challenges.

IV. Summary of Regulatory Requirements for Emergency Research

The regulation at § 50.24(a) describes the following criteria that must be met for a clinical investigation to be eligible for an exception from the informed consent requirements. The responsible IRB must find and document the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(a) The subjects will not be able to give their informed consent as a result of their medical condition;

(b) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(c) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(a) Subjects are facing a life-threatening situation that necessitates intervention;

(b) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(c) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the exception from informed consent.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with § 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with § 50.25(a)(7)(v).

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(a) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(b) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits:

(c) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(d) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(e) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

V. Issues for Discussion

At this part 15 hearing, we will be specifically inviting comments on the questions discussed in sections V.A and V.B of this document.

A. Scientific Aspects of Emergency Research and Human Subject Protection

In studies conducted under Investigational New Drug (IND) or Investigational Device Exemption (IDE) applications without an exception from the informed consent requirements, the products tested need not show particular promise of being superior to existing treatments in order for a clinical investigation to proceed. This is acceptable because the subject has the opportunity to make an informed decision and choose whether to participate in the clinical investigation. In the special case where a clinical investigation is permitted to proceed with an exception from the informed consent requirements, however, the regulation demands that participation hold out the prospect of direct benefit

for participants, as suggested by animal data, other preclinical studies, and related evidence. We recognize that it can be difficult to determine whether a new treatment holds out enough of a prospect of direct benefit to allow a clinical investigation to go forward and to determine whether available treatment is ''unproven or unsatisfactory''.

Therefore, FDA would like interested parties to address the following questions:

(1) Are the criteria for allowing studies conducted under § 50.24 adequate to protect human subjects and to promote scientifically rigorous research? Are any additional criteria warranted?

(2) Are the following criteria easily understood and, if not, how can they be clarified?

(a) ''Available treatments are unsatisfactory or unproven'' (§ 50.24(a)(1))

(b) ''Prospect of direct benefit'' (§ 50.24(a)(3))

(c) ''Practicably'' (§ 50.24(a)(4))

(3) Are there other criteria in the regulation, besides those identified in criteria (2)(a) through (c), that need to be clarified?

(4) Are there challenges that have not been explicitly addressed in the regulation in designing scientifically rigorous and ethically sound emergency research protocols (e.g., pediatric protocols)? If there are such challenges, should they be addressed and how?

B. Additional Human Subject Protections

Recognizing that emergency research presents unique human subject protection and ethical challenges, § 50.24 requires that additional human subject protections be provided. In particular, in order to ensure that emergency research is conducted with respect for the human subjects as discussed in the Belmont Report,[1] FDA recognizes that it is important to inform and consult with the communities involved (which include the communities where the clinical investigation will be conducted and from which the subjects will be drawn). Therefore, § 50.24 contains a number of additional human subject protections, several of which are specifically designed to provide relevant information to the involved communities. Such additional protections include: (1) Community consultation, (2) public disclosure prior to initiation of the clinical investigation of plans for the investigation and its risks and expected benefits, and (3) public disclosure following completion of the clinical investigation of information to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.

Community Consultation

The regulation (§ 50.24 (a)(7)(i)) requires consultation with representatives of the communities described previously, but provides few details about how to do this or what would constitute adequate consultation. We are aware that community consultation poses challenges and therefore invite comments on the following questions.

(5) What are the costs, benefits, and feasibility of community consultation as currently required under § 50.24?

(6) What aspects of community consultation as currently practiced are effective mechanisms for human subject protection? Are there additional practices that could enhance human subject protection?

(7) Are there elements of community consultation, both procedural and substantive, that should, at a minimum, be required (e.g., types of information presented, number and types of meetings or interactions, number of people reached)?

(8) Would opt-out mechanisms (e.g., advanced directives, jewelry similar to medical alert bracelet/necklace, and driver's license indicators) to identify individuals who do not wish to be included as subjects in particular emergency research studies provide a necessary protection for human subjects? If so, are they feasible?

(9) Who should use the information obtained from the community consultation process and how should they use it? Should the regulation be more specific on this point, and if so, what should it provide?

(10) Are there others besides the IRB (e.g., sponsors, clinical investigators, community leaders, advisory committees, ethicists) who should play a role in determining the adequacy of the plan for community consultation and the material to be publicly disclosed?

(11) The community consultation process typically includes meetings and discussions about the study with the community.

(a) Should the regulation require documentation of meeting activities and discussions in sufficient detail to show the information that was disclosed and the community reaction to the clinical investigation? If so, who should be responsible for such documentation (e.g., clinical investigator, sponsor)?

(b) The regulations (see 21 CFR 312.54(a) and 812.47(a)) currently require the sponsor to submit the information publicly disclosed prior to study initiation and after completion to FDA Docket Number 1995S–0158 (formerly 95S–0158). Should the regulation also require that documentation of community consultation activities be submitted to FDA, for example by being placed in the public docket? If so, who should be responsible for doing this?

(c) Should this information also be available elsewhere such as on *clinicaltrials.gov*?[2]

Public Disclosure Prior to Initiation

The regulation requires public disclosure, before the study begins, of plans for the investigation and its risks and expected benefits (§ 50.24(a)(7)(ii)) as an important protection for human subjects. We ask for comments on the following questions regarding such public disclosure.

(12) Are there certain types of information (e.g., adverse event reports, study protocol, informed consent document) that should, at a minimum, be publicly disclosed to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn?

(13) Should the full protocol, or other information such as the investigator's brochure, for emergency research be available (e.g., through FDA's public docket, *clinicaltrials.gov*) to the general public before initiation of the clinical investigation? If so, should protocols or other information be available for all emergency research or only for certain emergency research?

Public Disclosure Following Completion

The regulation requires public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including demographic characteristics of the research population and the study results (§ 50.24(a)(7)(iii)).

(14) Is there information regarding study results that, at a minimum, should always be disclosed after the clinical investigation is completed? If so, what is that information?

(15) How can this disclosure best be accomplished? Who should be responsible for this disclosure?

[1] The Belmont Report—Ethical Principles and Guidelines for the Protection of Human Subjects of Research, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (44 FR 23192, April 18, 1979).

[2] (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

(16) When should a clinical investigation be considered ''completed?'' How soon after a clinical investigation is completed should the results be disclosed?

(17) How can we assure timely disclosure of study results after completion of a study?

Public Discussion of Emergency Research

Currently, all emergency research protocols are subject to IRB review and community consultation. FDA has received some suggestions that it may be important, at least in some cases, to have additional public discussion, such as during an open meeting of an advisory committee or other expert panel. We invite comment on the following questions. Is there a need for such additional review and public discussion? If so, what criteria would be used to determine which protocols should be subject to this additional review and discussion?

(18) What type of venue would be best for this additional review and public discussion?

(19) What information should be included in this review?

Additional Challenges

(20) Are there any additional challenges to the conduct of emergency research that have not been identified in the preceding questions?

(21) If so, what are they and how should they be addressed?

VI. Notice of Hearing Under 21 CFR Part 15

The Acting Commissioner of Food and Drugs (the Acting Commissioner) is announcing that the public hearing will be held in accordance with part 15. The hearing will be conducted by a presiding officer, who will be accompanied by FDA senior management from the Office of the Commissioner, the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, the Office of Policy, and the Office of Human Research Protection.

Persons who wish to participate in the part 15 hearing must file a written or electronic submission with the Division of Dockets Management (see **ADDRESSES** and **DATES**). To ensure timely handling, any outer envelope should be clearly marked with the docket number found in brackets in the heading of this document, along with the statement ''Emergency Research.'' Requests to make a presentation should contain the potential presenter'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 discussion questions identified by number that will be addressed).

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 (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.

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

VII. 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 for 45 days following the hearing. Persons who wish to provide additional materials for consideration should file these materials with the Division of Dockets Management (see **ADDRESSES**). You should annotate and organize your comments to identify the specific questions identified by number to which they refer (see section V of this document). Two paper copies of any mailed comments are to be submitted, except that individuals may submit one paper copy. Comments are to be identified with the docket number at the heading of this document. Received comments may be seen in Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday.

VIII. Transcripts

The hearing will be transcribed as stipulated in § 15.30(b). Transcripts of the hearing will be available for review at the Division of Dockets Management (see **ADDRESSES**) and on the Internet at *http://www.fda.gov/ohrms/dockets* approximately 21 days after the hearing. You may place orders for copies of the transcript at the meeting or through the Freedom of Information Office (HFI–35), Food and Drug Administration, 5600 Fishers Lane, rm. 6–30, Rockville, MD 20857, at a cost of 10 cents per page.

Dated: August 18, 2006.

Jeffrey Shuren,

Associate Commissioner for Policy.

[FR Doc. E6–14264 Filed 8–25–06; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 1978N–0065 (formerly Docket No. 78N–0065)]

RIN 0910–AF53

Skin Bleaching Drug Products For Over-the-Counter Human Use; Proposed Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; withdrawal of previous proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would establish that over-the-counter (OTC) skin bleaching drug products are not generally recognized as safe and effective (GRASE) and are misbranded. FDA is also withdrawing the previous proposed rule on skin bleaching drug products for OTC human use, which was issued in the form of a tentative final monograph (TFM). FDA is issuing this proposed rule after considering new data and information on the safety of hydroquinone, the only active ingredient that had been proposed for inclusion in a monograph for these products. This proposal is part of FDA's ongoing review of OTC drug products. Further, upon issuance of a final rule, FDA intends to consider all skin bleaching drug products, whether currently marketed on a prescription or OTC basis, to be new drugs requiring an approved new drug application (NDA) for continued marketing.

DATES: Submit written or electronic comments by December 27, 2006; submit written or electronic comments on FDA's economic impact determination by December 27, 2006. The September 3, 1982, proposed rule (47 FR 39108) is withdrawn as of August 29, 2006. See section IX for the proposed effective date of any final rule that may publish based on this proposal.