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Issued in Seattle, Washington, on December 16, 2009.

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[FR Doc. E9-30796 Filed 12-28-09; 8:45 am]

BILLING CODE 4910-13-P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### 21 CFR Part 50

[Docket No. FDA-2009-N-0592]

RIN No. 0910-AG32

#### Informed Consent Elements

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule; opportunity for public comment.

**SUMMARY:** The Food and Drug Administration (FDA or agency) is issuing a proposed rule that, if finalized, would amend the informed consent regulations to require that the informed consent documents and processes for applicable drug, biologic, and device clinical investigations include a statement that clinical trial information for such clinical investigations has been or will be submitted to the National Institutes of Health/National Library of Medicine (NIH/NLM) for inclusion in the clinical trial registry databank. The Food and Drug Administration Amendments Act of 2007 (FDAAA) requires that FDA update its informed consent regulations to require that the informed consent documents and processes for certain clinical investigations include a statement that clinical trial information for such investigations has been or will be submitted for inclusion in the clinical trial registry databank.

**DATES:** Submit written or electronic comments on the proposed rule by March 1, 2010.

**ADDRESSES:** You may submit comments, identified by Docket No. FDA-2009-N-0592 and/or RIN number 0910-AG32, by any of the following methods.

#### *Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

#### *Written Submissions*

Submit written submissions in the following ways:

- FAX: 301-827-6870.
- Mail/Hand delivery/Courier (for paper, disk, or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

*Instructions:* All submissions received must include the agency name and docket number and Regulatory Information Number (RIN) for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

*Docket:* For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Jarilyn Dupont, Office of Policy, Office of Commissioner, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, rm. 4305, Silver Spring, MD 20993-0002, 301-796-4830.

#### **SUPPLEMENTARY INFORMATION:**

##### **I. Introduction**

FDAAA was enacted on September 27, 2007. Section 801 of FDAAA amends the Public Health Service (PHS) Act to require the Secretary of the Department of Health and Human Services (HHS), acting through the Director of NIH, to expand the clinical trial registry databank established under section 113 of the 1997 Food and Drug Administration Modernization Act (FDAMA) (Public Law 105-115, currently codified at 42 U.S.C. 282(i)) and to ensure that the databank is made publicly available through the Internet. Section 801 provides for the expansion of the registry databank through requiring investigators and sponsors to submit certain information about any applicable clinical trial to NIH/NLM for inclusion in the clinical trial registry databank. Section 801's requirements apply to applicable device clinical trials or applicable drug clinical trials, as defined in the statute. Under FDAAA, applicable drug clinical trials include clinical trials for biological products regulated under section 351 of the PHS

Act (42 U.S.C. 262). Section 801 also requires the Secretary to ensure that the databank includes links to results information for those clinical investigations that form the primary basis of an efficacy claim or are conducted after the drug involved is approved or after the device involved is cleared or approved.

Section 801(b)(3)(A) of FDAAA also amends section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)) to require that the Secretary update FDA's informed consent regulations to require that informed consent documents and processes for the clinical investigations in question include a statement that clinical trial information has been or will be submitted to this registry databank. The current informed consent regulations do not include provisions addressing the clinical trial registry databank. (See part 50 (21 CFR part 50); part 312 (21 CFR part 312); and 21 CFR 812.2(b)(1)(iii) and 812.25(g).) Specifically, section 801(b)(3)(A) of FDAAA states:

NEW DRUGS AND DEVICES.—

(A) INVESTIGATIONAL NEW DRUGS.—

Section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) is amended in paragraph (4), by adding at the end the following: The Secretary shall update such regulations to require inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigation has been or will be submitted for inclusion in the registry data bank pursuant to subsection (j) of section 402 of the Public Health Service Act.

##### **II. Background**

FDA has various regulations that govern the conduct of clinical investigations. The informed consent regulations provide protection to subjects in clinical investigations conducted under FDA's jurisdiction. (See part 50.) These informed consent regulations are based on ethics codes such as the Nuremberg Code (Ref. 1), the Declaration of Helsinki (Ref. 2), the National Research Act (Ref. 3), and the Belmont Report (Ref. 4); these codes embody the basic ethical principles relevant to the protection of human research subjects. (See 60 FR 49086, September 21, 1995, and 44 FR 47713, August 14, 1979, for a detailed discussion of the ethical basis for the agency's regulations governing human subject protection.) These principles identify standards to protect participants from unethical practices, allow subjects to have equal access to, opportunity to participate in, and the ability to withdraw from clinical trials voluntarily, educate participants so they make autonomous decisions, and

require disclosure of the risks and benefits of participating in clinical research, with the goal of maximizing the benefit of clinical trial research and minimizing and protecting participants from harm.

Section 113 of FDAMA required the Secretary, acting through the Director of NIH, to establish, maintain, and operate a databank of information on clinical trials for experimental treatments for serious or life-threatening diseases or conditions conducted under FDA's investigational new drug (IND) regulations (42 U.S.C. 282(i)(1)(A)). This databank is known as *www.ClinicalTrials.gov*. Section 113 of FDAMA required that the clinical trials databank contain: (1) Information about Federally- and privately-funded clinical trials for experimental treatments (drug and biological products) for serious or life-threatening diseases and conditions, (2) a description of the purpose of each experimental drug, (3) participant eligibility criteria, (4) a description of the location of clinical trial sites, and (5) a point of contact for those wanting to enroll in the trial (42 U.S.C. 282(i)(3)(A)). FDAMA also required that information provided through the clinical trials databank be in a form that can be readily understood by the public. *Id.* FDAMA was a response to efforts by patient advocacy groups and others toward obtaining greater access to clinical trials.

After consulting with FDA and others, NIH, through NLM, developed the clinical trial registry databank. The first version of the registry databank was made available to the public on February 29, 2000, on the Internet. At that time, the registry databank included primarily NIH-sponsored trials. In 2002, FDA published a guidance to provide recommendations for industry on submitting protocol information to the registry databank. (See "Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," (March 18, 2002) available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126838.pdf>).

In 2004, FDA published a revised draft guidance to update the earlier version to include recommendations for sponsors who would be submitting information required by the Best Pharmaceuticals for Children Act (BPCA, Public Law 107-109). (See "Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" (January 2004) available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory>

*Information/Guidances/ucm077229.pdf*.) Under the BPCA, manufacturers or sponsors of clinical investigations are required to submit to the clinical trials registry databank a description of whether and through what procedure the manufacturer or sponsor will respond to requests for protocol exception for single-patient and expanded access use of investigational drugs.

In September 2004, the members of the International Committee of Medical Journal Editors published a joint editorial aimed at promoting registration of all clinical trials. (Ref. 5) In that editorial, the members declared that they would consider an article related to a clinical trial for publication only if the clinical trial had been registered, before the enrollment of the first participant, in a publicly available database. (*Id.*; Ref. 6) This policy applies to trials that started recruiting on or after July 1, 2005. This was another step toward fostering a transparent, comprehensive, publicly available database of clinical trials.

Although Section 113 of FDAMA required that the clinical trials databank be established, it was silent on the enforcement of that requirement. Subsequent legislative proposals addressed the shortcomings of the existing clinical trial registry databank. Versions of proposed legislation required registration of *all* clinical trials conducted in the United States and reporting of such details as research outcomes, basic demographic information, sources of funding, significant adverse events, and FDA approval status, and provided for strong enforcement measures such as civil money penalties. Subsequently, Title VIII of FDAAA was enacted.

With the enactment of FDAAA, the registry requirements have been expanded and broadened to include not only trials in serious and life threatening diseases and conditions but to include any "applicable clinical trial" as defined in section 402(j)(1)(A) of the PHS Act (42 U.S.C. 282(j)(1)(A)). Although not all clinical trials meet this definition, a significant portion of clinical trials involving FDA-regulated drugs, biological products, or devices meet it. For this reason, revising the general informed consent provisions in part 50 provides the most straightforward direction for clinical investigators and the most information to clinical trial participants.

The basic elements of informed consent which also can be considered the "essential" elements, are set forth in § 50.25(a) of the human subject projection regulations. These elements

are required for all clinical investigations that are regulated by FDA or that support applications for research or marketing permits for products regulated by the agency. The statement required by section 801(b)(3)(A) of FDAAA that the information about the clinical investigation has been or will be submitted for inclusion in the clinical trial registry databank should be considered a basic, or essential, element of informed consent and should apply to all applicable clinical trials as defined in FDAAA. This statement is mandated by law under section 505(i) of the act; adding the requirement as a basic element of informed consent makes it clear that this requirement to inform subjects of the clinical trials registry databank is not discretionary. Furthermore, the required inclusion of clinical trial information in the registry databank is not limited to a small subset of clinical investigations; as such, it makes little sense to inform only a small subset of participants of applicable clinical trials about the registry databank and that the clinical trial information has been or will be submitted for inclusion in the registry databank. FDA thus proposes that this requirement be added as new § 50.25(a)(9) since it is a basic, or essential, element of informed consent, which will apply to applicable clinical trials as defined in FDAAA.

### III. Description of Proposal

The text of section 801(b)(3)(A) of FDAAA amends only section 505(i) of the act, which is the statutory provision concerning INDs. The provision does not amend or refer to section 520(g) of the act (21 U.S.C. 360j(g)), which is the statutory provision concerning investigational device exemptions. However, Title VIII of FDAAA generally applies to both drug and device clinical investigations. Human subject protection applies to all clinical trials, regardless of the type of treatment being studied, and FDA can find no justification for a scheme that would result in device trials having different or lesser requirements for human subject protection and informed consent. In addition, knowledge of existence of the clinical trial registry databank and of the fact that information about a particular clinical investigation may be included in the registry databank could affect an individual's decision to participate in a clinical trial; as such, knowledge of this information is equally important for potential participants in clinical device trials as it is for potential participants in clinical drug trials. Therefore, FDA proposes to amend the regulatory language in the general informed

consent regulations in § 50.25, which will apply to all applicable clinical trials as defined by FDAAA.

Requiring investigators to provide information regarding the possible inclusion of clinical trial information in the clinical trial registry databank in informed consent documents and processes for only clinical drug trials would create a disparity in FDA's policy on human subject protection and could result in confusion among those who conduct clinical trials over what is required in informed consent documents and processes. In addition, as stated previously, to the extent that knowledge of the fact that the clinical trial information could be included in the clinical trial registry databank could affect an individual's decision to participate in a clinical trial, this information is as important for potential participants in clinical device trials as it is for potential participants in clinical drug trials.

The existing informed consent basic, or essential, elements do not include a requirement to inform potential participants that a clinical trial they may be invited to participate in is registered, or will be registered, in the clinical trial registry databank. The proposed rule, if finalized, would require that investigators include a statement in their informed consent documents and processes that the clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank. Under § 50.27(b)(1), the informed consent must be documented by the use of a written consent document that embodies the elements of informed consent required by § 50.25. A proposed specific statement required in informed consent documents is set forth in the codified language of this proposed rule. A specific statement will help ensure that consistent information about the clinical trial databank is provided to clinical trial participants. In addition to the required language regarding the inclusion of clinical trial information in the clinical trial registry databank, the specific statement includes a descriptive explanation of the clinical trials registry that will be useful for informing clinical trial participants of the nature and purpose of the clinical trial registry databank. Investigators and Institutional Review Boards may include other information about the clinical trial registry databank in addition to the required statement in informed consent documents. The required statement, however, must be used to satisfy the requirements of this rule, if finalized.

There are several benefits to requiring investigators to include in informed

consent documents and processes for all applicable clinical trials a statement that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank. First, it would increase public awareness of the existence of the database and thereby increase transparency of clinical trials. In particular, it would enable individuals to access more detailed information about trials relevant to their medical conditions of interest. Furthermore, to the extent that information about the clinical trial registry databank would affect individuals' decisions to participate in clinical research, requiring investigators to provide such information to potential participants would foster individuals' ability to make a fully informed decision about participating in a clinical trial. Second, it would provide greater accountability and responsibility of investigators for outcomes and adverse events and improve transparency of all clinical trial outcomes information. Informing clinical trial participants and potential patients about the databank and directing them to [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) would become part of a system of checks and balances for the research community and a means of ensuring that researchers, investigators, and manufacturers or sponsors comply with their legal requirements under FDAAA. Third, it would increase public confidence in the validity of the research process. With the knowledge that the information generated by the clinical investigation is likely to be made public, and thus subject to additional scrutiny, participants can anticipate that the trial "results" could have more impact on other medical research and analysis. "Individuals voluntarily participate in trials expecting that the results will be used to improve medical knowledge in general, and not only to serve proprietary or commercial interests. These ethical obligations to the public good are in addition to the obligations to protect individual participants during a trial (e.g., informed consent), and they extend to all trials regardless of study design or trial population." (Ref. 7) Finally, it would give sponsors, physicians, and patients access to more information and thus enable them to make more educated treatment decisions. In these ways, amending the basic elements of the informed consent provision to require a statement regarding the inclusion of clinical trial information in the clinical trial registry databank would lead to better promotion and protection of public health, help foster innovation to further

the scientific process, and reduce duplicative research efforts.

#### IV. What Clinical Trials Require a Revised Informed Consent Document and Process?

The statute defines an "applicable clinical trial" in section 402(j)(1)(A)(i) of the PHS Act (42 U.S.C. 282(j)(1)(A)(i)) as follows:

(j) EXPANDED CLINICAL TRIAL REGISTRY DATA BANK.—

(1) DEFINITIONS; REQUIREMENT.—

(A) DEFINITIONS.—In this subsection: "(i) APPLICABLE CLINICAL TRIAL.—The term 'applicable clinical trial' means an applicable device clinical trial or an applicable drug clinical trial.

(ii) APPLICABLE DEVICE CLINICAL TRIAL.—The term 'applicable device clinical trial' means—

(I) a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes); and

(II) a pediatric postmarket surveillance as required under section 522 of the Federal Food, Drug, and Cosmetic Act.

(iii) APPLICABLE DRUG CLINICAL TRIAL.—

(I) IN GENERAL.—The term 'applicable drug clinical trial' means a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of this Act.

(II) CLINICAL INVESTIGATION.—For purposes of subclause (I), the term 'clinical investigation' has the meaning given that term in section 312.3 of title 21, Code of Federal Regulations (or any successor regulation).

Additional information to improve understanding of the common terminology and the applicability of the requirements used in implementing the clinical trial databank can be found at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) and the database registry Web site at [www.prsinfo.clinicaltrials.gov](http://www.prsinfo.clinicaltrials.gov).

#### V. Legal Authority

Section 505(i) of the act requires drug manufacturers or sponsors of investigations to ensure that experts using investigational drugs in clinical trials "inform any human beings to whom [investigational] drugs \* \* \* are being administered \* \* \* that such drugs are being used for investigational purposes" and obtain consent prior to administering such drugs (21 U.S.C. 355(i)). Similarly, section 520(g) of the act requires individuals applying for investigational device exemptions to ensure that informed consent will be obtained from each human subject of

proposed clinical testing involving the device (21 U.S.C. 360j(g)). Sections 505(i) and 520(g) of the act also require the Secretary to issue regulations for the protection of human subjects in clinical investigations (21 U.S.C. 355(i)(4) and 360j(g)(2)). Additionally, section 701(a) of the act (21 U.S.C. 371) confers general authority on the Secretary to issue regulations for the efficient enforcement of the act.

Section 801(b)(3)(A) of FDAAA amends section 505(i)(4) of the act by adding at the end the following:

The Secretary shall update such regulations to require inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigation has been or will be submitted for inclusion in the registry data bank pursuant to subsection (j) of section 402 of the Public Health Service Act.

The regulations implementing section 505(i) of the act can be found at parts 312 and 50. Part 312 sets forth regulations governing drug and biological product IND applications; part 50 sets forth general requirements for human subject protection in all FDA-regulated clinical investigations and clinical investigations that support applications for research or marketing permits for products regulated by FDA, including trials for drugs, biological products, and medical devices. Section 801(b)(3)(A) of FDAAA does not amend section 520(g) of the act; however, in instances where the regulations are amended to address human subject protection, FDA has not in the past made distinctions among clinical investigations for drugs, biological products, and medical devices.

FDA created a uniform system of human subject protection when it initially amended its regulations governing human subject protection in 1981 (46 FR 8942, January 27, 1981). In revising part 50, FDA aimed to: (1) Address the informed consent provision included in the device amendments; (2) create a uniform set of agency-wide informed consent standards for more effective administration of the agency's bioresearch monitoring program; (3) implement recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; and (4) harmonize FDA's rules with those of HHS (then the Department of Health, Education, and Welfare). Indeed, the preamble expressed the agency's intent to adopt a single standard that reflected the most current congressional thinking on informed consent and the important ethical principles and social policies underlying the doctrine of informed consent (46 FR 8942 at 8943).

Requiring a statement regarding the clinical trial registry databank in informed consent documents and process for only clinical investigations for drugs but not devices would create a disparity in FDA's policy on human subject protection and could result in confusion among those who conduct clinical trials over what is required in informed consent documents and processes, especially in the cases of trials involving both a drug and device or for investigators conducting trials of both types of regulated products. Furthermore, knowledge of the existence of the clinical trial registry databank and of the fact that information about a particular clinical investigation has been or will be submitted for inclusion in the registry databank could affect an individual's decision to participate in a clinical trial; as such, this knowledge is equally important for potential participants of clinical device trials as it is for potential participants of clinical drug trials.

Thus, although section 801(b)(3)(A) of FDAAA requires the statement regarding the clinical trial registry databank for informed consent documents and processes only for clinical investigations conducted under section 505(i) of the act, under its general authority, FDA proposes to require that all applicable clinical trials, including applicable medical device trials, include this new statement. This proposed rule requiring that a statement regarding the inclusion of clinical trial information in the clinical trial registry databank be included in the informed consent documents and processes for all applicable clinical trials is the most efficient method of implementing the statutory mandate. To prevent confusion that might result from different requirements for informed consent for drug and device research, FDA is proposing, by this rule, to apply the same standards regarding elements of informed consent to drug and device research. As such, FDA is proposing to amend § 50.25 to require a statement about the registry databank in informed consent documents and processes for all applicable clinical trials under section 801 of FDAAA.

## VI. Environmental Analysis

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## VII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the rule is likely to impose costs of less than \$1 per clinical trial participant, the agency proposes to certify that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$133 million, using the most current (2008) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

### A. The Proposed Rule

This rule would require that the informed consent documents and processes for applicable clinical drug trials and applicable clinical device trials as defined by section 801 of FDAAA include a statement that clinical trial information has been or will be submitted to NIH/NLM for inclusion in the clinical trial registry databank. As it pertains to applicable clinical drug trials, the rule would implement a requirement of FDAAA. As discussed previously in this preamble, FDA is also proposing to require that the same statement be included in the informed consent documents for applicable clinical device trials.

### B. Need for the Proposed Rule

FDAAA section 801(b)(3)(A) amends section 505(i) of the act to require that the Secretary update regulations for informed consent documents and process to require inclusion of a statement that clinical trial information has been or will be submitted to NIH/NLM for inclusion in the clinical trial registry databank. FDA has determined that revising the general informed consent provision is the most appropriate course by which to fulfill the requirements of the statute, in a way that will provide the pertinent information to and protection for clinical trial participants.

### C. Benefits of the Proposed Rule

As discussed in this preamble, this proposed rule would provide several benefits to clinical trial participants. The rule would increase the transparency of clinical trials by increasing participant and patient awareness of the existence of the clinical trials databank and those trials that are registered in the databank. The rule would also provide greater accountability of clinical trial investigators for outcomes and adverse events by helping to create a system of checks and balances through which participants, patients and healthcare providers are encouraged to check whether information about a trial of interest is registered in the databank. Furthermore, the rule would increase public confidence in the validity of the research process. Last of all, it would encourage physicians and patients to obtain more information in order to make more educated treatment decisions. FDA has not attempted to quantify these benefits; however, the agency believes that the overall effect of the rule on public health will be positive.

### D. Costs of the Proposed Rule

#### 1. Labor Costs

The costs of the proposed rule derive from complying with the requirement to add another statement to the informed consent documents and the additional time that medical professionals and clinical trial participants spend reading and discussing this statement.

FDA estimates that it receives about 7,000 clinical trial protocol submissions annually for applicable clinical trials that would be subject to this proposed rule, with the vast majority of the submissions going to the FDA's Center for Drug Evaluation and Research. FDA estimates of average numbers of participants per clinical trial vary greatly across FDA Centers, from single-

patient INDs to vaccine trials with over twenty-five thousand participants. Published data on average number of participants per trial, therapeutic area, suggests that the average number of participants in phase 1, 2, and 3 clinical trials of pharmaceuticals, biotechnology, and medical device products may range from about 200 to 360.<sup>1</sup> FDA uses this estimated range for the average number of participants per clinical trial, and invites public comment on the estimated average number of participants per clinical trial.

Compliance with the rule would require that investigators include in informed consent documents and processes the required statement concerning the submission of clinical trial information for inclusion in the clinical trial registry databank and provide for any additional discussion concerning this statement between participants and the medical professional administering the documents. FDA does not expect that this statement will provoke any controversy. It is expected that in most cases, after reading the proposed statement, the clinical trial participant will not choose to discuss it with the investigator. In some cases, however, it is possible that a short discussion will occur. FDA estimates that, on average, a clinical trial participant would require an additional 30 seconds to 1 minute to read and, if necessary, discuss the added statement with the medical professional administering the informed consent documents.

Registered nurses or other medical professionals with a similar level of training often administer and discuss the informed consent forms with trial participants. The average compensation for a registered nurse in 2008 was \$40.54 per hour, including a 35 percent increase to account for benefits. The increased labor cost for administering the informed consent procedures for these medical professionals in applicable clinical trials for all participants ranges from \$473,000 to \$1,704,000 (see Table 1 of this document). This estimate is the result of \$42.27 per hour, times 30 to 60 seconds per participant, times 200 to 360

participants per trial times 7,000 protocols per year. The cost to the sponsor per prospective participant would range from \$0.34 to \$0.68 and the cost per trial protocol would range from \$68 to \$243.

TABLE 1.—COSTS OF INFORMED CONSENT PROPOSED RULE

Cost Factor	Annual Cost
Labor Cost for Clinical Trial Administrator	\$473,000 to \$1,704,000
Labor Cost for Clinical Trial Participant	\$182,000 to \$654,000
Document Preparation Cost	\$17,000
Paper Cost	\$9,000 to \$18,000
Total Costs	\$688,000 to \$2,398,000

Whether or not clinical trial participants receive compensation for their participation in clinical trials, the additional time spent by all participants to read and discuss the new informed consent statement represents a social cost of the rule. Using the median U.S. wage rate of \$15.57 per hour, a clinical trial participant would be expected to incur a cost ranging from \$0.13 to \$0.26 to read and, if necessary, discuss the proposed informed consent statement concerning the inclusion of clinical trial information in the clinical trial registry databank. On an annual basis, this would amount to about \$182,000 to \$654,000 for 7,000 clinical trials.

The cost of writing the new statement into the informed consent documents is expected to be very small. The new statement would only need to be written once per protocol and is estimated to take about 5 minutes. Using the same wage rate as shown previously, \$40.54 per hour, the additional annual costs to write the statement for the 7,000 annual protocols would total about \$24,000.

The capital cost of adding the new informed consent statement would only consist of the additional paper. At a cost of about \$0.02 per page and about one-third of a page per participant, the total paper costs for this rule are estimated to range from \$9,000 to \$17,000 annually.

The total costs of the proposed rule to both industry and the clinical trial participant population are estimated to range from \$688,000 to \$2,398,000 annually. This equates to \$98 to \$342 per trial protocol, or about \$0.48 to \$0.96 per clinical trial participant.

#### 2. Costs to Government

The costs to government for oversight of this rule would be extremely low as

<sup>1</sup> Parexel's *Bio/Pharmaceutical R&D Statistical Sourcebook 2008/2009*, Parexel International Corp., copyright 2008, p. 160. The average number of participants (not weighted by therapeutic area) in phase 1, 2, and 3 clinical trials in 2006 was 27, 141, and 444, respectively. The unweighted average of these numbers is 204. As an upper bound, FDA uses the average of the numbers representing the therapeutic area with the largest average number of participants in each of the 3 clinical phases, which would tend to overstate the average size of participants. This upper bound is calculated at 360 participants per trial protocol.

a review of a sample of informed consent documents for each trial would only be increased, at most, by a few minutes per clinical trial due to the additional informed consent statement. FDA believes this cost would not be significant.

#### E. Alternatives to the Proposed Rule

FDAAA specifically requires that the regulations concerning informed consent documents include the statement that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank. It does not give FDA discretion concerning the inclusion of this language in informed consent documents and processes for applicable clinical drug trials. For the reasons stated previously in this preamble, FDA has decided to require the language be included in the informed consent documents and processes for applicable clinical medical device trials as well. If the proposed rule did not include the new informed consent statement for applicable medical device clinical trials, the annual costs of the rule would be reduced by \$36,000 to \$124,000 per year.

#### F. Regulatory Flexibility Act

##### Impacts on Small Entities

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because of the small costs that would be incurred by an individual sponsor of a product undergoing a clinical trial, the agency believes that the final rule is not likely to have a significant economic impact on a substantial number of small entities.

The companies that would be affected are classified in seven separate North American Industrial Classification System (NAICS) categories by the Census Bureau. The affected industries are NAICS 325412—Pharmaceutical Preparation; NAICS 325414—Biological Products (except diagnostic); NAICS 334510—Electromedical and Electrotherapeutic Apparatus; NAICS 339112—Surgical and Medical Instrument; NAICS 339113—Surgical Appliance and Supplies; NAICS 339114—Dental Equipment and Supplies; NAICS 339115—Ophthalmic Goods. The Small Business Administration (SBA) size standards for all these industries define small entities as those companies with less than 500 employees, except for pharmaceutical preparation, for which it defines a small entity as one with less than 750 employees. The most recent Census of

Manufacturers data that offers the level of detail for establishments at or near the employee size limits as defined by SBA is from 2002. In each of these establishment size categories, large majorities of the establishments meet the criteria as small entities. Even taking into account that many of these establishments are parts of multi-establishment corporations, significant numbers of companies would still qualify as small entities. Preliminary Census data from 2007, though less detailed, shows that significant numbers of establishments continue to have less than 100 employees across all of these categories. While FDA expects that most companies sponsoring applicable clinical trials would be larger than the average-sized company in their industry, FDA concludes that a substantial number of companies would still qualify as small entities.

The cost analysis concluded that the compliance cost of the proposed rule per trial protocol would range from \$98 to \$342. Some firms will direct multiple applicable clinical trials in the same year. For large firms that would administer the informed consent documents for 10 separate trials, the cost would range from \$980 to \$3,420 per year. Using 2002 Census data, the average value of shipments for establishments in these industries with one to four employees ranged from \$244,000 to \$824,000 according to the Census of Manufacturers. Assuming that such small operations had one applicable clinical trial administered each year, the costs of the proposed rule would represent, at most, 0.14% of the annual value of shipments. For establishments with 50 or more employees, the compliance costs would represent 0.04% or less of the value of shipments even with 10 applicable clinical trials administered annually. For establishments with 100 or more employees, the compliance costs would represent 0.08% or less of the value of shipments even with 50 applicable clinical trials administered annually. FDA concludes that this proposed rule would not have a significant economic impact on a substantial number of small entities.

#### VIII. Paperwork Reduction Act

FDA concludes that the informed consent requirement proposed in this document is not subject to review by the Office of Management and Budget because it does not constitute a “collection of information” under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Rather, the proposed requirement to include a statement in informed consent documents regarding

submission of clinical trial information to the clinical trial registry databank is a “public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public” (5 CFR 1320.3(c)(2)).

#### IX. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper 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.

#### X. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

#### XI. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**), and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but we are not responsible for any subsequent changes to the Web sites after the document publishes in the **Federal Register**.)

1. “*Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10*”, Vol. 2, pp. 181–182. Washington, DC: U.S. Government Printing Office, 1949.
2. World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, available at <http://www.wma.net/e/policy/b3.htm>; accessed on July 30, 2009.
3. National Research Act, Title II (Public Law 93–348, July 12, 1974).
4. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, “The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research,”

April 18, 1979, available at <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>, accessed July 30, 2009.

5. De Angelis C., J.M. Drazen, F.A. Frizelle, et al., "Clinical Trial Registration: A Statement From the International Committee of Medical Journal Editors," *Annals of Internal Medicine*, 2004;141:477-8, electronically published on September 8, 2004.

6. De Angelis, C., J.M. Drazen, et al., "Is This Clinical Trial Fully Registered?: A Statement From the International Committee of Medical Journal Editors," *International Committee of Medical Journal Editors*, available at [http://www.icmje.org/clin\\_trialup.htm](http://www.icmje.org/clin_trialup.htm), accessed on July 30, 2009.

7. Sim, I., A. Chan, A. Gülmezoglu, T. Evans, et al., "Clinical Trial Registration: Transparency Is the Watchword," *The Lancet*, Vol. 367, Issue 9523, pp. 1631-33, May 2006.

#### List of Subjects in 21 CFR Part 50

Human research subjects, Prisoners, Reporting and recordkeeping requirements, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 50 be amended as follows:

#### PART 50—PROTECTION OF HUMAN SUBJECTS

1. The authority citation for 21 CFR part 50 continues to read as follows:

**Authority:** 21 U.S.C. 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.

2. Section 50.25 is amended by adding paragraph (a)(9) to read as follows:

#### § 50.25 Elements of informed consent.

(a) \* \* \*  
\* \* \* \* \*

(9) For applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement, notifying the subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act: Information, that does not include personally identifiable information, concerning this clinical trial has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered clinical trials. This data bank can be accessed by you and the general public at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov). Federal law requires clinical trial information for

certain clinical trials to be submitted to the data bank.

\* \* \* \* \*

Dated: December 23, 2009.

**David Horowitz,**

*Assistant Commissioner for Policy.*

[FR Doc. E9-30751 Filed 12-28-09; 8:45 am]

**BILLING CODE 4160-01-S**

## DEPARTMENT OF STATE

### 22 CFR Part 62

[Public Notice: 6858]

#### Exchange Visitor Program—Secondary School Students

**AGENCY:** Department of State.

**ACTION:** Proposed rule; withdrawal.

**SUMMARY:** On December 23, 2009 the State Department published in the **Federal Register** a proposed rule titled Exchange Visitor Program—Secondary School Students. The Department revised existing regulations to provide greater specificity and clarity to sponsors of the Secondary School Student category with respect to the execution of sponsor oversight responsibilities under the exchange visitor program. This rule is being withdrawn because it was submitted prior to OMB completing review. The proposed rule is withdrawn in its entirety.

**DATES:** The proposed rule published at 74 FR, Number 245, December 23, 2009 is withdrawn effective December 28, 2009.

**FOR FURTHER INFORMATION CONTACT:** Michael Cheman, U.S. Department of State, Washington, DC 20547, (202) 312-9605.

#### SUPPLEMENTARY INFORMATION:

##### Background

On December 23, 2009 the State Department published a final rule at 74 FR, Number 245. The rule was intended to revise existing regulations to provide greater specificity and clarity to sponsors of the Secondary School Student category with respect to the execution of sponsor oversight responsibilities under the exchange visitor program.

##### Reason for Withdrawal

This rule is being withdrawn because it was submitted prior to OMB completing review. The proposed rule is withdrawn in its entirety. Accordingly, the Department withdraws the rule "Exchange Visitor Program—Secondary School Students", RIN 1400-AC56. This

Proposed Rule was submitted on Friday, 18 December and was published Wednesday, 23 December, 2009 in Volume 74, Number 245 on pages 68200-68208.

Withdrawal of the rule does not preclude the Department from issuing another rule on the subject matter in the future or committing the agency to any future course of action.

Issued in Washington, DC, on December 23, 2009.

Dated: December 20, 2009.

**Thelma Furlong,**

*Director, Office of Directives Management, Department of State.*

[FR Doc. E9-30837 Filed 12-28-09; 8:45 am]

**BILLING CODE 4710-24-P**

## DEPARTMENT OF LABOR

### Occupational Safety and Health Administration

#### 29 CFR Parts 1910, 1915, and 1926

[Docket No. OSHA-H022K-2006-0062 (formerly OSHA Docket No. H022K)]

RIN 1218-AC20

#### Hazard Communication

**AGENCY:** Occupational Safety and Health Administration (OSHA), Department of Labor.

**ACTION:** Proposed rule; notice of informal public hearings.

**SUMMARY:** OSHA is scheduling informal public hearings on its proposal to revise the Hazard Communication Standard. OSHA anticipates receiving several hearing requests, and this document describes the procedures the public must use to participate in the hearings.

**DATES:** *Informal public hearing.* The hearing will begin at 9:30 a.m., local time, on the following dates:

- March 2, 2010, in Washington, DC;
  - March 31, 2010, in Pittsburgh, PA;
- and

- April 13, 2010, in Los Angeles, CA.

If necessary, the hearing will continue at the same time on subsequent days at each location.

*Notice of intention to appear at the hearing.* Interested persons who intend to present testimony or question witnesses at any of these locations must submit (transmit, send, postmark, deliver) a notice of their intention to do so by January 18, 2010.

*Hearing testimony and documentary evidence.* Interested persons who request more than 10 minutes to present testimony or who intend to submit documentary evidence at the hearing