Form ADV for fiscal year ends beginning on December 31, 2010, and to existing clients within 60 days of filing the annual updating amendment. Most registered advisers have fiscal years ending on December 31 and must, as a result, file an annual updating amendment by March 31, 2011.[3] Absent an extension of the compliance date, these advisers would be required to deliver their first brochure supplements to new and prospective clients no later than March 31, 2011 and to existing clients no later than May 31, 2011.

We have received correspondence from the Securities Industry and Financial Markets Association ("SIFMA"), requesting that we delay the compliance date for at least an additional four months, until July 31, 2011, solely with respect to requirements regarding delivery of the brochure supplement.[4] SIFMA asserts that preparing and disseminating brochures with respect to thousands of supervised persons to tens of thousands of clients presents its members with substantial logistical challenges in meeting the compliance date. It asserts that its members need additional time to design, test and implement systems and controls that will assure that each client receives an accurate brochure supplement with respect to the supervised person who provides advice to that client.

Based on the concerns expressed in the correspondence, and in light of similar concerns that have been expressed by other investment advisers to our staff, we are persuaded that a limited extension of the compliance date for the delivery of brochure supplements for existing registered advisers is appropriate.[5] We have based this decision on the information SIFMA has provided and our experience in overseeing the industry. In addition, to provide consistent treatment for newly registering advisers, we are also persuaded that the limited extension of the compliance date for the delivery of brochure supplements is appropriate for these advisers as well. We are not extending the compliance date for the filing and delivery of the brochure required by Part 2A of Form ADV and related rules under the Advisers Act, which is required for newly registering investment advisers beginning on January 1, 2011, and for existing registered advisers when they file their annual updating amendments for fiscal years ending on and after December 31, 2010.

Accordingly, the Commission believes it is appropriate to modify and extend the compliance date for brochure supplements for the following investment advisers:[6]

Existing Registered Investment Advisers. All investment advisers registered with the Commission as of December 31, 2010, and having a fiscal year ending on December 31, 2010 through April 30, 2011, have until July 31, 2011, to begin delivering brochure supplements to *new and prospective clients.* These advisers have until September 30, 2011 to deliver brochure supplements to *existing clients.* The compliance dates for delivering brochure supplements for existing registered investment advisers with fiscal years ending after April 30, 2011 remain unchanged.

Newly-registered Investment Advisers. All newly registered investment advisers filing their applications for registration from January 1, 2011 through April 30, 2011, have until May 1, 2011 to begin delivering brochure supplements to *new and prospective clients.* These advisers have until July 1, 2011 to deliver brochure supplements to *existing clients.* The compliance dates for delivering brochure supplements for newly-registered investment advisers filing applications for registration after April 30, 2011 remain unchanged.

The Commission finds that, for good cause and the reasons cited above, including the brief length of the extension we are granting, notice and solicitation of comment regarding the extension of the compliance date for Part 2B of Form ADV and the provisions of rule 204–3 that relate to the delivery of brochure supplements are impracticable, unnecessary, or contrary to the public interest.[7] In this regard, the Commission also notes that investment advisers need to be informed as soon as possible of the extension and its length in order to plan and adjust their implementation process accordingly.

Dated: December 28, 2010.

By the Commission.

Elizabeth M. Murphy,

Secretary.

[FR Doc. 2010–33142 Filed 1–3–11; 8:45 am]

BILLING CODE 8011–01–P

[3] Based on Investment Adviser Registration Depository data as of December 1, 2010, 92% of SEC-registered investment advisers report a December fiscal year end.

[4] Memorandum from Morgan Lewis on behalf of certain SIFMA member firms dated Dec. 16, 2010 available at *http://www.sec.gov/rules/proposed/s71000.shtml.*

[5] The North American Securities Administrators Association has recommended that the State securities authorities provide the same extension for State-registered investment advisers. However, State-registered advisers should contact the States where they are registered to confirm compliance dates.

[6] Advisers may choose to deliver brochure supplements earlier than the dates outlined in this release.

[7] *See* Section 553(b)(3)(B) of the Administrative Procedure Act (5 U.S.C. 553(b)(3)(B)) ("APA") (an agency may dispense with prior notice and comment when it finds, for good cause, that notice and comment are "impracticable, unnecessary, or contrary to the public interest"). This finding also satisfies the requirements of 5 U.S.C. 808(2), allowing the rules to become effective notwithstanding the requirement of 5 U.S.C. 801 (if a Federal agency finds that notice and public comment are "impractical, unnecessary or contrary to the public interest," a rule "shall take effect at such time as the Federal agency promulgating the rule determines"). Also, because the Regulatory Flexibility Act (5 U.S.C. 601–612) only requires agencies to prepare analyses when the Administrative Procedures Act requires general notice of rulemaking, that Act does not apply to the actions that we are taking in this release. The change to the compliance date is effective upon publication in the **Federal Register.** This date is less than 30 days after publication in the **Federal Register**, in accordance with the APA, which allows effectiveness in less than 30 days after publication for "a substantive rule which grants or recognizes an exemption or relieves a restriction." *See* 5 U.S.C. 553(d)(1).

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: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the current informed consent regulations to require that informed consent documents and processes for applicable drug (including biological products) and device clinical trials include a specific statement that clinical trial information will be entered into a databank. The databank referred to in this final rule is the clinical trial registry databank maintained by the National Institutes of Health/National Library of Medicine (NIH/NLM) which was created by statute. The submission of clinical trial information to this data bank also is required by statute. This amendment to the informed consent regulations is required by the Food and Drug Administration Amendments Act of 2007 (FDAAA) and is designed to promote transparency of clinical research to participants and patients.

DATES: *Effective date:* This rule is effective March 7, 2011.

Compliance date: The compliance date of this final rule is March 7, 2012, for clinical trials that are initiated on or after the compliance date. See section III of this document for an additional explanation of the compliance date and required implementation of this final rule.

FOR FURTHER INFORMATION CONTACT: Jarilyn Dupont, Office of Policy, Office of Commissioner, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, rm. 4248, Silver Spring, MD 20993–0002, 301–796–4830.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Introduction
II. Overview of the Final Rule
III. Compliance Date
IV. Comments on the Proposed Rule
V. Legal Authority and Enforcement
VI. Environmental Analysis
VII. Analysis of Impacts
VIII. Paperwork Reduction Act
IX. Federalism
X. References

I. Introduction

In the **Federal Register** of December 29, 2009 (74 FR 68750), FDA issued a notice of proposed rulemaking (NPRM) to amend 21 CFR 50.25, its regulations governing informed consent documents and processes. This final rule revises the current informed consent regulations to require a new element for informed consent documents and processes that will inform the potential clinical trial participant that information about applicable clinical trials has been, or will be, entered into a databank that is publicly accessible at *http://www.ClinicalTrials.gov*. (*See* section IV.F of this document for a discussion of applicable clinical trials.) The final rule adds this requirement in a new paragraph, § 50.25(c), and redesignates existing paragraphs.

This final rule is issued under section 801 of FDAAA (Pub. L. 110–85, September 27, 2007), which requires that information on an applicable clinical trial be submitted to NIH for inclusion in the clinical trial registry databank. This section also requires that the Secretary of the Department of Health and Human Services (HHS) update certain informed consent regulations to mandate that informed consent documents and processes include a statement that the required clinical trial information has been or will be submitted for inclusion in the registry databank. The current informed consent regulations do not include provisions similar to those required by FDAAA. (*See* parts 50 and 312 (21 CFR parts 50 and 312) and 21 CFR 812.2(b)(1)(iii) and 812.25(g)).

Section 801 of FDAAA amends the Public Health Service Act (the PHS Act) to require the Secretary, acting through the Director of NIH, to expand the existing clinical trial registry databank established under section 113 of the Food and Drug Administration Modernization Act (FDAMA), enacted November 21, 1997 (Pub. L. 105–115 currently codified at 42 U.S.C. 282(i)). The new provision requires the Director to ensure that the databank is made publicly available through the Internet and to expand the databank to require the submission of specified information for applicable drug clinical trials and applicable device clinical trials. (The term "drug" includes biological products regulated under section 351 of the PHS Act (42 U.S.C. 262).) The provision also requires the Secretary of HHS to ensure that the databank includes links to results information for those clinical trials that form the primary basis of an efficacy claim or are conducted after the drug involved or device involved is cleared or approved. In addition, section 801(b)(3)(A) of FDAAA states:

> NEW DRUGS AND DEVICES.—
> 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. Overview of the Final Rule

We considered all of the comments to the NPRM and the additional data and accompanying materials submitted with the comments. We also consulted with our internal experts on informed consent documents and processes as well as our internal experts in communicating health-related information to the public, clinical trial participants, and patients in evaluating the required statement.

In response to the comments, and based on our internal reconsideration of the proposed requirements in the NPRM, we have amended the specific language of the statement required to be included in informed consent documents and processes. The mandatory statement is now shorter, less complex, and more understandable for potential clinical trial participants. Specific terms that are not commonly used by lay persons, or were deemed to be misleading or confusing, have been clarified and simplified. The mandatory statement has been revised to facilitate understanding while maintaining the purpose of the statutory provision.

In response to comments expressing confusion and/or concern over the proposed placement of the new requirement as a "basic" element of informed consent under § 50.25(a), a new paragraph (c) has been added and the existing paragraphs have been redesignated. This separate new paragraph emphasizes the unique basis of the new element—required only for applicable clinical trials—as compared with existing basic elements which align with various ethics codes and apply to all clinical investigations regulated by FDA and clinical investigations that support applications for research or marketing permits for products regulated by FDA.

New paragraph § 50.25(c) interacts with all other requirements of part 50 as do the other requirements and provisions of § 50.25. Similar to other informed consent elements, it is subject to the regulations governing documentation of informed consent (§ 50.27) and Institutional Review Board (IRB) waivers (§ 56.109(c)(1) (21 CFR 56.109)). When a short form written consent document is chosen (§ 50.27(b)(2)), a short form and written summary must be provided to the clinical trial participant. All of these are considered "informed consent documents" and must contain the new statement (Ref. 1). For example, if an IRB waives the requirement for a signed written consent form under § 56.109(c)(1), and requires "the investigator to provide subjects with a written statement regarding the research," this written statement is considered a part of the documentation of ensuring the informed consent of the participant and thus, it must include the new statement (§ 56.109(d)).

III. Compliance Date

In response to comments, and after consideration of the intent and purpose of the new statutory requirement, we have determined that the compliance date of new § 50.25(c) will be 1 year after the effective date of this final rule for all informed consent documents and processes related to a clinical investigation that is initiated on or after the compliance date of this rule. In section IV.B of this document we provide, in our responses to the comments made concerning the effective date, additional explanation of the application of the compliance date to particular clinical investigations.

IV. Comments on the Proposed Rule

We received 68 comments on the NPRM. Comments were received from IRBs, academic research centers, clinical investigators, physicians, health care professional societies, trade organizations representing clinical research organizations, drug and device sponsors, blood banks, clinical research organizations, research hospitals, medical device manufacturers, nonprofit organizations for ethical research, patient advocacy organizations, health care attorneys, pharmacy and law students, and others.

To make it easier to identify comments and our responses, the word "Comment," in parentheses, will appear before each comment, and the word "Response," in parentheses, will appear before each response. We also have numbered the comments to make it easier to distinguish between comments; the numbers are for organizational purposes only and do not reflect the order in which we received the comments or any value associated with the comment. We have combined similar comments under one numbered comment.

A. General Comments

(Comment 1) We received comments that objected to adding any statement to informed consent documents about submitting information to the databank to be posted on the ClinicalTrials.gov Web site. The principal reasons given for these objections were that the additional statement: (1) Lengthens already lengthy informed consent documents, exacerbating potential participants' confusion and anxiety upon reading consent forms; (2) unnecessarily burdens or overwhelms participants because it does not provide information necessary to make an informed decision about whether to participate in a clinical trial; (3) fails to advance human subject protection in any way; and (4) will cause patients to ignore more important aspects of the consent form or other research-related forms. Other comments approved the inclusion of a statement that alerted potential participants to the clinical trials registry databank to inform them how the data are generally used and to increase awareness of the clinical trial registry.

(Response) We appreciate the concerns expressed by the comments regarding the increasing length of informed consent documents and the additional information required to be provided to potential clinical trial participants. Section 801(b)(3)(A) of FDAAA, however, requires the Secretary to update FDA's regulations to "require inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigations has been or will be submitted for inclusion in the registry data bank." Thus, while we appreciate the concerns, Congress has directed that this be implemented by FDA.

While FDA has been directed by statute to include this particular statement in informed consent documents and processes related to applicable clinical trials, there is increasing support for informing clinical trial participants about the clinical trials in which they participate and the outcome of those trials whether it is included in the informed consent document or through other efforts. The rationale for informed consent is to ensure that participants enter into the research voluntarily and with adequate information (Refs. 2, 3, and 4). Communications, other than the specific informed consent, may include informing the participant on how to obtain or access information relating to the outcomes of the research (Refs. 5 and 6). Implementing the statutory provision by including the statement in the informed consent documents and processes, as required, also advances these other goals.

We disagree with comments that the new statement does not provide any information necessary to make an informed decision about whether to participate in a clinical trial. As noted in the NPRM, alerting potential clinical trial participants to the existence of a publicly accessible databank, whether in the informed consent or during the process, can reassure them that a transparent system exists to help ensure greater accountability and responsibility of investigators (74 FR 68750 at 68752). Clinical research (as opposed to clinical practice) is not designed to deliver therapeutic benefits to individual patients, so it is possible that potential clinical trial participants would want to know the overall benefits that may accrue to society at large (Refs. 7 and 8). One of the basic elements of informed consent which investigators are required to inform participants of is "a description of any benefits to the subject or to others which may reasonably be expected from the research." (§ 50.25(a)(3)). The reference to the databank Web site allows participants to ascertain the nature, scope, and progress of a registered applicable clinical trial, thus reassuring the participant that participation in a trial contributes to the advancement of medical knowledge, an important benefit in the full disclosure of risks and benefits. Although the current statutory requirement at 42 U.S.C. 282(j), section 402(j) of the PHS Act, only requires registration at *http://www.ClinicalTrials.gov* for certain applicable clinical trials, and not all clinical trials, this limitation does not lessen the value of the information for participants.

We do not agree that the new required statement significantly increases the length of consent forms to such a degree as to increase participants' confusion and anxiety. The revised language consists of four short sentences, which will minimally impact a potential subject's reaction to a consent form. These additional sentences will not dwarf or diminish other important information in informed consent forms and documents. FDA responded to similar comments when it issued the final rule that established § 50.25 concerning the basic and additional elements of informed consent. Many of the comments suggested that there were too many elements, they were duplicative, and they would simply confuse research participants. Other comments expressed the concern that the elements would require a long, detailed consent form that would be confusing and would detract from the intended purposes of the regulation that relevant information about a study be conveyed to the human subject (46 FR 8942 at 8949, January 27, 1981). In responding to all of the comments, FDA defended the required elements, and, although minor changes were made to simplify the final rule, FDA maintained that the informed consent process involved "giving the subject all the information concerning the study that the subject would reasonably want to know." (46 FR 8942 at 8949, January 27, 1981) This same reasoning applies to the requirements of the new element in § 50.25(c). Congress has decided that clinical trial participants would reasonably want to know that applicable clinical trials will be registered and that certain results and other information will be available in a publicly accessible databank.

(Comment 2) One comment objected to the new statement as an "inefficient method of implementing the statutory mandate of FDAAA."

(Response) We disagree. The statutory mandate of FDAAA is specific. It requires FDA to update its 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." The NPRM proposed to implement the statutory

mandate by requiring the new statement in informed consent documents and processes and the final rule adopts that proposal. We believe the short required statement accomplishes the statutory mandate in the most efficient manner possible.

(Comment 3) Two comments suggested that the new statement should not be included because research involving de-identified data is exempt from human-subjects regulation since only de-identified data are submitted to *http://www.ClinicalTrials.gov.*

(Response) We believe this comment reflects a misunderstanding about the statutory requirements to register applicable clinical trials with NIH at *http://www.ClinicalTrials.gov.* The new informed consent element applies to "applicable clinical trials," which necessarily involve research on human subjects. The fact that only de-identified data derived from the applicable clinical trial will be submitted to the databank is irrelevant to the requirement to include the new statement in informed consent documents. Human subjects are still involved in the underlying "applicable clinical trial" and informed consent regulations apply to the clinical investigation. We emphasize that the new element is required by statute, and the subsequent reporting of only de-identified data to NIH in no way creates an exemption to the statutory or regulatory requirement.

B. Effective Date, Compliance Date, and Retroactivity

(Comment 4) Many comments requested clarification on the effective date of the regulation and whether it would be applied retroactively. Specifically, comments requested clarification on the following clinical trial scenarios: (1) Clinical studies that received favorable ethics committee opinion but patient recruitment has not begun before the effective date, (2) clinical studies that received favorable ethics committee opinion and patient recruitment has begun before final rule, (3) clinical studies where IRB rulings are pending or not yet submitted to IRB, (4) protocol amendment (requiring re-consent) dated within 30 days of the final rule. Other comments stated that the rule should not require re-consent of enrolled participants. One comment requested a 6-month grace period for compliance after the rule takes effect.

(Response) As discussed in section III of this document, we have decided to make the compliance date 1 year after the effective date of this final rule. This means that FDA intends to enforce this final rule, new § 50.25(c), only for informed consent documents and processes for clinical investigations that are initiated on or after the compliance date.

To address the specific examples in the comments, we generally would consider that for purposes of this final rule only, a clinical investigation has been initiated if the sponsor/investigator has had any informed consent documents for that clinical investigation cleared or approved by an IRB, a regulatory body, or other human subjects review entity. This interpretation of the initiation of the clinical trial/investigation is limited to this final rule. If the clinical investigation is a multi-site trial and informed consent documents have been cleared or approved for one or more sites before the compliance date of this final rule, but not for all sites, the clinical investigation will be considered to have initiated before the compliance date. The informed consent documents for the remaining clinical investigation sites would be considered part of the clinical investigation that initiated prior to the compliance date.

Re-consent, based solely on the new requirement, of clinical trial participants in clinical investigations that were initiated before the compliance date will not be required. If a clinical investigation is ongoing as of the final rule compliance date, the new requirement will not be applicable. We recognize that this will mean that if the informed consent documents and processes of the ongoing clinical investigation are required to be amended for any other purpose and re-consent of the already enrolled or actively participating clinical trial participants is required for that other purpose, compliance with new § 50.25(c) will not be required.

When the original informed consent regulations were issued in 1981, we chose to impose those requirements strictly prospectively—only clinical investigations that began on or after the effective date of the regulation were required to comply with new parts 50 and 56 (21 CFR part 56. (*See* 46 FR 8942 at 8945 to 8946, January 27, 1981.) In determining that those new requirements should apply only prospectively, we "balanced the cost of compliance against possible added protections to be gained by research participants, and determined that the potential cost of imposing the requirements retroactively outweighs the potential gain. The informed consent regulations that will continue to be in effect until the effective date of part 50 have assured that at least minimum standards of informed consent have been met in studies initiated before the effective date * * *" (46 FR 8942 at 8946). We believe the same principles apply in this final rule and the regulation will not be applied retroactively. There is nothing in this rule, however, that would prohibit inclusion of the statement in circumstances in which there may be re-consent for other reasons.

We are aware that many educational and governmental institutions, IRBs, and industry sponsors have created model templates for informed consent documents. These model templates generally are developed to address various situations and include mandatory provisions to ensure compliance with all regulatory requirements (Refs. 9 and 10). We anticipate that the compliance date for the final rule will permit sufficient time for this new required statement in § 50.25(c) to be added to existing model templates. While there is a benefit to including the new statement in existing informed consent documents and processes, we do not believe the benefit outweighs the difficulty, cost, and complexity of requiring revision to all existing informed consent documents.

(Comment 5) One comment requested clarification on whether the new element would require sponsors to re-consent participants enrolled in clinical trials. This comment noted FDA's 1998 Information Sheet Guidances for IRBs, Clinical Investigators, and Sponsors: Frequently Asked Questions (No. 45), advising that enrolled and actively participating subjects should be informed of a change that might relate to a subject's willingness to participate in the study.

(Response) As discussed in the Response to Comment 4, re-consent will not be required solely based on the new requirements of § 50.25(c). While the FDA's 1998 Information Sheets for IRBs, Clinical Investigators, and Sponsors: Frequently Asked Questions (No. 45) recommends that already enrolled and actively participating subjects be informed of a change that might relate to a subject's willingness to participate in the study, we are not requiring such a notification based on this new requirement. If this recommendation were to be followed by clinical investigators, we would expect that such notice, if warranted, already had occurred, as applicable clinical trials have been statutorily required to be registered with NIH at *http://www.ClinicalTrials.gov* since 2007 and results posting for certain trials has been required since 2008.

(Comment 6) One comment expressed concern that the specific language of the new element would have to be revised

after NIH issued regulations to implement changes to *ClinicalTrials.gov.* This comment recommended that FDA issue a guidance instead of a regulation because a guidance would be easier to change, if necessary, after the NIH regulations issued.

(Response) We decline to issue a guidance in lieu of a regulation. Section 801(b)(3)(A) of FDAAA makes clear that the "Secretary shall update [FDA's] regulations," not merely issue a guidance. NIH's subsequent regulations will not impact the specific language of the new element as the language of the required statement is not affected by the statutory or regulatory interpretation of an "applicable clinical trial." There is a statutory definition of "applicable clinical trial" and no matter what additional regulatory explanation of "applicable clinical trial" is provided in a future rulemaking, it will not affect or change the required statement. Changes to the definition only will impact the determination made by sponsors and investigators about their clinical trial and whether it is an "applicable clinical trial" subject to the registration requirements of 42 U.S.C. 282(j)(1)(A), section 402(j)(1)(A) of the PHS Act. That separate determination is made prior to the inclusion of the mandatory statement in informed consent documents and processes.

C. New Section 50.25(c)

In order to address some of the concerns raised by comments, and on our own initiative, we have created a new paragraph (c) in § 50.25 to include the requirements of this final rule. While this is a "required" element of informed consent documents and processes, it is only required if the clinical trial is an "applicable clinical trial" as defined in FDAAA, 42 U.S.C. 282(j)(1)(A), section 402(j)(1)(A) of the PHS Act, and any relevant regulation. Although there were comments suggesting that § 50.25(b) was the more appropriate location for the required provision, we are concerned that such placement would be confusing given the specific requirement of section 801(b)(3)(A) of FDAAA and the mandatory nature of its inclusion when an applicable clinical trial is involved. To avoid any confusion, we have created a new paragraph (c) in § 50.25 and redesignated existing paragraphs.

(Comment 7) Many comments suggested that the rule should amend § 50.25(b), "Additional Elements of Informed Consent," rather than § 50.25(a), "Basic Elements of Informed Consent." Some comments reasoned that the new statement could not be considered a "basic element" because it would not apply to all clinical trials, only applicable clinical trials. For example, a phase 1 or device feasibility study would not be considered an applicable clinical trial under the statutory definition in FDAAA. These comments further reasoned that the new statement qualified as an "additional element" because it would be required only "when appropriate" (i.e., in applicable clinical trials).

(Response) We agree with the comments that the element should not be included in § 50.25(a) since the statutory provision limits it to inclusion in informed consent documents and processes only for "applicable clinical trials." We disagree, however, that the new statement should be included as an "additional element" under § 50.25(b) as this may raise further confusion as to the mandatory nature of the requirement.

As noted in the preamble to the final rule establishing the original informed consent elements, "[t]he elements listed as 'additional' are not material to every clinical investigation." (46 FR 8942 at 8949, comments 41 and 42) This new element, however, is statutorily required, and therefore, is material to *all* applicable clinical trials. Investigators do not have the discretion to determine whether the element is "appropriate" for a particular applicable clinical trial. Therefore, we decline to include the new element in § 50.25(b) and, instead, have created a new paragraph (c).

Nothing in this preamble affects our explanation in the 1981 final rule that "when any one of those additional elements would be appropriate, § 50.25(b) *requires* that the additional information be provided to the subject." (*emphasis added*)

(Comment 8) One comment recommended that FDA accomplish its statutory mandate to inform potential participants about the databank by amending § 50.25(a) to require a statement that describes whether results or other aspects of the trial may be published. This comment suggested that posting of results on *http://www.ClinicalTrials.gov* be treated like any other publication of clinical trial results in journals or elsewhere.

(Response) We do not agree that the statement proposed by the comments would accomplish our statutory mandate, which specifies that informed consent regulations be updated to require that a statement that clinical trial information has been or will be submitted for inclusion in the registry data bank. A statement that simply alludes to the general possibility of publication does not accomplish the statutory mandate or the objectives set forth in the NPRM and this final rule: informing clinical trial participants and potential patients about the data bank; directing them to the *http://www.ClinicalTrials.gov* Web site in order to enhance the system of checks and balances for the research community and trial sponsors; assisting individuals in deciding whether to participate in a trial; and, providing patients with additional information beyond traditional publications.

(Comment 9) One comment recommended that the new element amend § 50.25(a)(5), which requires a statement describing the extent to which confidentiality of records identifying the subject will be maintained. This comment expressed concern that a wholly new provision devoted to a new basic element in § 50.25(a) would place undue emphasis on "low-risk" reporting requirements to the detriment of the other "high-risk" provisions of § 50.25(a) devoted to protecting clinical trial participants.

(Response) We agree that the new element has a unique basis and thus differs in a fundamental way from the basic consent elements in § 50.25(a) but disagree that the new element should be located in § 50.25(a)(5). Section 50.25(a)(5) requires that in seeking informed consent, investigators provide to potential participants "A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records." This statement concerning confidentiality is applicable to all aspects of the clinical trial data. The same confidentiality standards that apply to a submission of an article to a medical journal also apply to a *http://www.ClinicalTrials.gov* submission—only aggregate data are provided. Thus, creating a paragraph of § 50.25(a) which would identify only the extent to which confidentiality would be maintained with respect to submissions of data to *http://www.ClinicalTrials.gov* could be confusing and misleading.

To avoid confusion and to emphasize the unique basis for the new element, FDA has created a new paragraph (c) in § 50.25. This paragraph specifies that the new element is required for all applicable clinical trials but not for non-applicable clinical trials. Thus, § 50.25(c) is distinct from § 50.25(a), which requires basic elements for all clinical trials of FDA-regulated products whether or not they are "applicable clinical trials," and from § 50.25(b), which requires additional elements in informed consent documents and

processes "when appropriate." Furthermore, the new element merits a wholly new provision owing to its unique basis. The new element has an external informational component directed to the participant, it enhances the protection of the human subject participating in the "applicable clinical trial," and is statutorily mandated.

D. Specific Language for Informed Consent Documents and Processes

(Comment 10) Many comments objected to specific required language, as opposed to a general requirement for the content of the message with flexibility to craft the exact language. These comments stated that specific language denies institutions the flexibility to tailor the language to the local community, subject population, type of study, or, in non-U.S. trials, other countries' unique data privacy concerns. One comment stated that requiring specific language is inconsistent with other elements of informed consent, which specifies content but not language. Another comment objected to the specific language because it would require additional clarifying language about other registries.

(Response) In proposing specific language, we considered issues similar to those raised by the comments but concluded that the risk of inaccurate and confusing statements was too great to permit investigators and sponsors to craft their own statements regarding the inclusion of clinical trial information in *http://www.ClinicalTrials.gov.* The comments received in response to the NPRM support our previous conclusion that specific language needs to be provided. While we agree that the proposed language should be simpler and more understandable, and has been made so in this final rule, the diverse comments showed much confusion and misunderstanding about the FDAAA statutory requirements for registration of clinical trials with NIH and the type of information required to be provided to potential clinical trial participants. Suggested revisions to simplify the language resulted in very different, and often inaccurate, messages. If each sponsor/entity were to craft their own individual statement, we are concerned that participants in different clinical trials would receive vastly different messages. Many statements could be inaccurate, confusing, or different from that intended by the statutory requirement. We want to ensure that potential clinical trial participants receive a consistent and accurate message and are directed to the specific Web site that contains the clinical trial databank. Investigators, sponsors, and IRBs are not restricted from providing additional explanation. It is essential, however, that one common message appear consistently in all informed consent documents and processes. The provision of the specific language also will make it easier for IRBs and other review entities to identify the inclusion of this statutorily required statement in their review of informed consent documents and processes and to incorporate it into any model templates.

E. Communication and Readability of Language

(Comment 11) Many comments criticized the new statement as too complex or technical for many potential clinical trial participants to understand. Some comments noted that the proposed language registered approximately 18 on the Flesch-Kincaid reading grade level (Ref. 11) Many recommended that the required new statement register at an eighth-grade reading level (8 on the Flesch-Kincaid scale). Other comments objected to undefined terms not commonly used (*e.g.,* "data bank," "registry"), phrases that were meaningful to sponsors but not trial participants (submission "at the appropriate and required time"), and words perceived as too unspecific to be informative (*e.g.,* "information," "not personally identifiable," "certain clinical trials").

(Response) We agree that the language proposed in the NPRM was too complex and may be too difficult for some potential participants to understand. We consulted with our internal experts on risk communication to identify specific problems with the proposed statement and to devise a statement that was more understandable across a greater range of reading skills (Ref. 12). We have revised the statement to include simpler language, and removed many of the terms perceived as objectionable. For example, the statement no longer contains the words "data bank" and "registry;" these are replaced by the more commonly used term "Web site." Sponsor-oriented phrases and some general words also have been removed. The revised statement registers 7.2 on the Flesch-Kincaid reading scale.

We have not further defined the term "information" in the statement. The definition depends on when data are submitted to the databank and what would be included depends on the data fields being completed. The word "information" is basic enough to encompass anything that may be required to be submitted to the databank at any point in time. The statement provides the specific Web address to the databank so that clinical trial participants may visit the Web site to see what "information" is included in a particular clinical trial record. The new statement will read as follows:

"A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

(Comment 12) Several comments expressed concern that a statement using complex language would be difficult to translate into other languages for international consent forms or for U.S. clinical trial participants whose first language is not English.

(Response) We have revised the required statement to use simpler language and do not believe that the revised statement will pose translation difficulties. See the response to Comment 18 for additional discussion on translation of the required statement.

(Comment 13) One comment objected to directing participants to a Web site that promotes therapeutic misconception. Therapeutic misconception is the common misunderstanding among clinical trial participants that the primary purpose of a clinical trial is to provide therapeutic treatment, rather than experimental research.

(Response) We disagree that *http://www.ClinicalTrials.gov* promotes therapeutic treatment as the primary focus of the clinical trials posted to the databank. The ClinicalTrials.gov Web site makes clear that clinical trials are research studies. Extensive questions and answers are provided on the Web site detailing what a clinical trial is and what participation encompasses. Regardless, the informed consent documents and process, properly administered, should dispel any misconception about the purpose of the clinical trial.

(Comment 14) Several comments stated that the reference to the ClinicalTrials.gov Web site should be omitted because: (1) It was not necessary for a subject to make an informed decision about whether to participate in the trial and (2) the Web site had no more information than the informed consent document about the trial. Other comments favored the reference to ClinicalTrials.gov, stating that this information is consistent with the goals of enhancing transparency of clinical trials, boosting public confidence in the clinical research process, and better informing potential participants.

(Response) We decline to omit the reference to *http://www.ClinicalTrials.gov* and agree the specific Web site is helpful to direct potential participants to that databank and to help them become better educated about clinical trials. The specific Web site address also eliminates the need for the participant to search the Internet for access to the databank Web site. The Web site address allows participants to more quickly take the opportunity to view the contents of the databank and review the types of information submitted to and posted on the Web site. The Web site is not intended to substitute for the information and description of the clinical trial in the consent form; however, the Web site also can provide reference to other related trials conducted before or after the clinical trial in which the participant took part. Furthermore, the Web site does have more information than the informed consent documents since the databank may eventually contain the final results of the specific clinical trial for which the participant consented—information the informed consent documents will not contain.

(Comment 15) Two comments recommended that the statement list Web sites other than *http://www.ClinicalTrials.gov* because the link could change in the future, or more common Web sites would be easier for participants to find. The comment alternatively recommended that the rule reference FDA's Web site, which should provide a link to the clinical trials databank.

(Response) We decline to replace *http://www.ClinicalTrials.gov* with another or FDA's own Web site. In response to the comments that the Web site might change, it is unlikely that this Web address will change, since it has been in use for over 10 years. If in the future it is altered, we can revise the final rule with an amendment identifying the new Web address. We think it important that clinical trial participants know specifically where to locate the clinical trial information without having to perform an Internet search. We do not see any advantage in referring potential participants to more "common" Web sites that link to *http://www.ClinicalTrials.gov* instead of a direct link. In fact, *http://www.ClinicalTrials.gov* has become quite well known and could be considered a "common" Web site itself. The Web site currently has over 50 million page views per month and 65,000 visitors daily.

(Comment 16) One comment suggested that the new statement was misleading in several ways: (1) It implies that the trial is registered only at ClinicalTrials.gov and not elsewhere, (2) it implies that results for all trials will be submitted to the databank; and (3) the statement that U.S. law requires submission of information to the databank does not take into account that some studies are voluntarily registered.

(Response) The new words have been carefully chosen to accurately represent how clinical trial data are included in the databank. First, the element states that "A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. law." The new element is required only in informed consent documents and processes related to applicable clinical trials, so this statement is true. The new statement should not be included in informed consent documents or processes for clinical trials that are not applicable clinical trials because, as the regulation makes clear, only applicable clinical trials are subject to the requirement. Second, we have chosen to say "will be available" to generalize the statement for early-phase participants (when the trial has not been registered yet) and participants joining after the trial is registered at *http://www.ClinicalTrials.gov.* Under the statute, responsible parties for applicable clinical trials must submit relevant clinical trial information to NIH/NLM for inclusion in the registry databank no later than 21 days after the first participant is enrolled in the applicable clinical trial. We believe "will be available" reasonably applies to all participants and is simpler than saying "has been or will be submitted." Third, the revised language states that "At most, the Web site will include a summary of the results." Thus, potential participants will not expect that clinical trial results will always appear on the Web site but, if results do appear, these will be in summary form. Fourth, the statement makes no reference to non-applicable or voluntarily registered trials, and we disagree that the language misleads anyone about these other trials in any way. By stating that "this clinical trial will be available * * * as required by U.S. law," the new element in no way implies that other types of trials cannot be registered. The new language also does not imply that all clinical trials must be registered; it only refers to the clinical trial in which the participant is taking part.

(Comment 17) Several comments suggested that the regulation also should require an alternate statement for non-applicable, voluntarily registered clinical trials that they will not be included in the databank. These comments suggested that such a statement would be necessary for potential participants to make an informed decision about whether to participate in the trial.

(Response) We decline to include an alternate statement for non-applicable, voluntarily registered clinical trials, some of which may be registered in the databank. Potential participants will have no expectation that a non-applicable clinical trial will be registered, since an informed consent document for a non-applicable clinical trial is not required to include the new statement. If an investigator, sponsor, or IRB feels that a potential participant would want to know about the existence of a registry databank for trials other than the one the participant is contemplating or for non-applicable clinical trials, nothing in this regulation would prevent an investigator, sponsor, or IRB from informing potential participants of such information in an appropriate manner.

(Comment 18) One comment requested that FDA provide translations into other languages frequently encountered in the United States. This comment also recommended that if FDA would not provide such translations, then FDA should state in the regulation that the text may be freely translated into other languages.

(Response) Under § 50.20, the informed consent document should be in language understandable to the subject (or legally authorized representative). When the potential participants are non-English speaking or the clinical investigator or the IRB anticipates that the consent interviews will be conducted in a language other than English, the IRB should require a translated consent document to be prepared and assure that the translation is accurate. As required by § 50.27, a copy of the consent document must be given to each subject. In the case of non-English speaking participants, this would be the translated document. While a translator may be helpful in facilitating conversation with a non-English speaking subject, routine ad hoc translation of the consent document should not be substituted for a written translation. This is explained in more detail in our guidance documents/information sheets concerning informed consent (Ref. 13). The statement can be translated into languages other than English for potential clinical trial participants. FDA will not provide translations of the statement.

(Comment 19) One comment recommended that the words "federal law" be replaced with a reference to U.S. law, since "federal law" might cause

confusion in multinational clinical trials.

(Response) We agree and the revised statement indicates that the clinical trial description on *http://www.ClinicalTrials.gov* is required by "U.S. law."

F. Applicable Clinical Trials

(Comment 20) Several comments requested clarification on whether certain types of clinical trials, such as investigational device trials considered to be non-interventional, would be considered "applicable clinical trials." Several bloodbank organizations specifically inquired about clinical studies done by blood centers under investigational new drug applications (INDs) to validate new blood screening tests.

(Response) We decline to provide a more detailed definition of "applicable clinical trial," as it is not necessary for the purposes of this final rule. Section 801(a)(1) of FDAAA contains a statutory definition of this term (section 402(j)(1)(A) of the PHS Act). NIH/NLM also has elaborated on the meaning of "applicable clinical trial" at *http://prsinfo.clinicaltrials.gov/fdaaa.html* and at *http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf* (Ref. 14), which represents NIH's current thinking on the definitions. It is possible these definitions will be expanded upon in rulemaking by NIH. It is the responsibility of the sponsors and investigators to determine if their clinical trial meets the definition of an applicable clinical trial and to ensure compliance with the most current applicable statutory and regulatory requirements.

(Comment 21) Several comments recommended that the new statement not be required in the informed consent forms for clinical trials conducted outside of the United States, even if done in support of U.S. regulatory approval or conducted under an FDA IND. These comments stated that the new element should be required only when the clinical trials are conducted in the United States. These comments reasoned that: (1) Institutions and patients in other countries may object to or be offended by U.S.-centric language, (2) 21 other countries and regions already have in place or are in the process of implementing their own clinical trial registries, (3) foreign governments may prefer references to their own countries' registries, and (4) foreign IRBs and ethics committees may have their own informed consent requirements that conflict with the new statement.

(Response) We disagree. The new informed consent statement applies to all "applicable clinical trials" as defined in section 801(a)(1) of FDAAA. FDAAA does not limit "applicable clinical trials" to only those conducted in the United States; it also includes clinical trials that are not conducted in the United States that are subject to FDA's jurisdiction. Thus, informed consent documents and processes of all "applicable clinical trials," including those conducted in foreign countries, must include this new statement regarding the inclusion of information in the clinical trial databank. Congress did not provide an exemption from this requirement for applicable clinical trials conducted in foreign countries.

(Comment 22) One comment requested clarification on whether the new element is required only when a trial is conducted under a U.S. IND or is otherwise subject to FDA regulation at the time the research participant is enrolled. This comment focused in particular on data from non-U.S. trials that were not conducted under a U.S. IND or subject to FDA regulation at the time of inception but were later submitted in support of a new drug application (NDA).

(Response) Yes, the new requirement, § 50.25(c), applies only when a trial is conducted under a U.S. IND or is otherwise subject to FDA regulation.

(Comment 23) Several comments expressed concern that the new element would conflict with or cause confusion about other countries' registries or informed consent practices. One comment suggested that the new statement might conflict with the informed consent practices of IRBs and ethics committees residing outside the United States, and that foreign governments may not want references to a U.S. database in the informed consent forms for multinational trials being conducted in their countries. This comment recommended that the new element apply to informed consent documents used only at U.S. clinical trial sites and not for clinical trials at foreign sites even if the clinical trial was conducted under an FDA IND.

(Response) See the response to Comment 21.

(Comment 24) One comment suggested that U.S. participants in international clinical trials be informed that information about the trial also may be available in the registries of other countries. This comment further suggested including the statement "Information about this trial may also be available on the Internet in the clinical trial registries of other countries."

(Response) We decline to require a statement alerting potential participants of information about clinical trial registries of other countries. If other countries require the inclusion of such a statement, we would not object. FDA is only requiring a reference to the NIH/NLM databank as it has been directed to do by Congress. Nothing in this final rule prevents investigators, sponsors, or IRBs from advising potential participants that information about the clinical trial may be found in other countries' registries.

(Comment 25) One comment praised the Agency's decision to apply the ClinicalTrials.gov reporting requirements to drug and device trials. Another comment acknowledged the Agency's authority to issue a regulation applying the statutory requirement to device trials but requested that FDA use its discretion to not exercise that authority until Congress explicitly indicated that drug and device trials should be treated the same.

(Response) FDA has decided to require that all applicable clinical trials (including applicable device clinical trials) include the new required statement for the reasons stated in the NPRM: To maintain consistency of informed consent requirements for all applicable clinical trials, to simplify informed consent requirements for clinical trials involving both drugs and devices, to offer all potential participants the same information that could affect their decisions to enter a clinical trial, and to efficiently implement the statutory mandate. Our legal authority to issue this regulation and require it to be applied to applicable device clinical trials is further described in section V of this document.

G. Other Miscellaneous Comments

(Comment 26) One comment stated that "the sharing of de-identified data falls under the category of exempt research or is not considered human subject research at all, and it is common for IRBs, following the regulations, to allow the research to go forward with a waiver of the consent requirement." The comment apparently suggests that the new element can be or should be waived.

(Response) Similar to other provisions required by § 50.25, the new element is waiveable only under the exceptions specified in §§ 50.23 and 50.24 for waiver of informed consent. Some clinical trials (those that are conducted or supported by HHS) are also governed by 45 CFR part 46, which permits an IRB to waive the requirement for one or more elements of informed consent. It

should be noted for purposes of clarification that under 45 CFR 46.102(f) research using de-identified data would not be considered research on a human subject and, thus, the waiver of the informed consent requirement would not be applicable.

As a general matter, clinical research that both involves FDA-regulated products and is conducted or supported by HHS must meet the requirements of both sets of regulations. If such clinical trials are also applicable clinical trials under FDAAA, the new element must be included in the informed consent documents and process for these trials unless waived under part 50, regardless of whether an IRB determines that one or more of the elements is waiveable under 45 CFR part 46.

In some instances, review of records containing de-identified data may be exempt from IRB review because such record review does not qualify as human subject research. This is not always the case under FDA regulations and there are some circumstances in which the use of de-identified data requires IRB review. See §§ 56.101 and 56.103 and "Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff: Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens That Are Not Individually Identifiable." (Ref. 15). The definition of an "applicable clinical trial," however, necessarily involves human subjects; thus an applicable clinical trial must comply with human subject regulations. The use of the new statement would not be implicated in research that does not qualify as human subject research under the definition of applicable clinical trial (Ref. 14).

It is also true that de-identified data (stripped of the 18 specified identifiers) fall outside of the Health Insurance Portability and Accountability Act of 1996 (Pub. L. 104–191) (HIPAA) privacy regulations and thus are not considered individually identifiable health information. As a consequence, clinical investigators need not obtain a subject's authorization to release de-identified data in a HIPAA authorization form, which is often included in a research consent form and accompanies an informed consent form. Regardless of whether an IRB determines that the information concerning submission of aggregate results to ClinicalTrials.gov does not need to be included in a HIPAA authorization form, the new element is still required by statute to be included in the informed consent documents and processes for applicable clinical trials.

(Comment 27) One comment suggested that the new element be included in an information sheet separate from the informed consent document, where the sheet explained the ClinicalTrials.gov Web site in simple terms.

(Response) FDAAA requires that the new element be included "in the informed consent documents and processes," not in an information sheet that is separate from an informed consent document. There is nothing in this final rule, however, that prevents an investigator, sponsor, or IRB from providing additional information in an information sheet further explaining ClinicalTrials.gov as part of the informed consent process.

(Comment 28) Many comments voiced a variety of opinions on the issue that no personally identifiable information is submitted to the databank or shown on the Web site. Several comments supported including such a statement to that effect in the required statement. Several comments requested that FDA include additional language in the new element to clarify any potential confidentiality issues posed by the databank. These comments suggested including: (1) Assurance that participants' names and identities will not be posted on ClinicalTrials.gov, will not be made available to employers, and will not be discoverable in court proceedings; (2) a statement that it is probable that participants' information will be re-identified; (3) a lay person description of data submitted to ClinicalTrials.gov and the Basic Element Results Definitions; and (4) an expanded description of the clinical trial registry and databank. Other comments recognized that no personal information about participants is submitted to ClinicalTrials.gov, so there are no privacy or confidentiality issues. Still another comment stated that its consent documents already contain language that non-identifiable information may be made public in scientific journals, presentations, and, if applicable, submitted to a government data bank/registry.

(Response) We have revised the new statement in the final rule so that it is clear that the Web site does not include information that can identify the clinical trial participant. We believe the new statement will provide reassurance to potential participants. The only results information submitted to the databank and posted on the Web site are aggregate statistics, such as those that typically appear in medical journals and product package inserts. No individual-level data are submitted to the databank. A review of the data fields on *http://www.ClinicalTrials.gov* for which data are required to be submitted by the sponsor/investigator confirms that there is no individual information, only aggregate, overall data (Ref. 16). Furthermore, § 50.25(a)(5) requires informed consent documents to explain the extent, if any, to which confidentiality of clinical trial data and the records of the clinical trial participant will be maintained. Nothing in this rule prohibits an investigator, sponsor, or IRB from including further explanation on the nature and confidentiality of information submitted to ClinicalTrials.gov in the informed consent form or process or a HIPAA authorization form.

(Comment 29) One comment suggested that the new statement should be inserted into the section of the consent document that invites the potential or enrolled participant to ask questions of the individual conducting the informed consent process. Such placement, according to the comment, would facilitate communication and encourage participants to ask questions.

(Response) The final rule does not require that the new statement be located in any particular section of the consent form. Investigators, sponsors, and IRBs have the flexibility to place the new statement in the consent form where they believe best serves participants' interests.

(Comment 30) One comment requested that the new statement include a phrase indicating that the information would be submitted to ClinicalTrials.gov "if required by law." The comment requested this change to eliminate the need for separate templates for studies that require registry in the databank and those that do not. Anticipated benefits were stated to be simplified documentation; reduced review time by sponsors, investigators, and IRBs; and reduced likelihood of using the incorrect consent template for a particular clinical study. Other comments apparently read the NPRM to require the statement in consent forms for all clinical trials and objected to the inclusion of the statement for trials that did not require registry in the databank.

(Response) We do not agree that it is necessary to include an additional phrase that would allow for a universal consent template. Sponsors and investigators already have to determine if a clinical trial is an applicable clinical trial in order to comply with the requirements of 42 U.S.C. 282(j), section 402(j) of the PHS Act. Adding the required statement to informed consent documents and processes will occur after that determination has been made

by the sponsor or investigator. Furthermore, because the mandatory statement requires specific language, it should not be burdensome for reviewers to determine whether the statement is included in the informed consent documents.

(Comment 31) Two comments expressed concern that the required new element would create an inconsistency between regulations governing applicable clinical trials of FDA-regulated products (part 50) and regulations governing clinical trials funded or supported by HHS (45 CFR part 46). The comments perceived the new element as contrary to FDA's objective to harmonize regulations of human-subject protection.

(Response) FDA does not agree that the required element would create an inconsistency or lack of harmony between the regulations on human subjects in the two sets of regulations. The new element merely entails an additional requirement for applicable clinical trials of FDA-regulated products in accordance with a statutory mandate, whether or not the trial is supported or funded by HHS. The new element does not conflict with any existing regulations under 45 CFR part 46.

(Comment 32) There were several comments that questioned the estimates contained in the preliminary Analysis of Impacts including the estimated time to explain the required statement if a potential participant asked questions.

(Response) These comments are addressed fully in section VII of this document.

V. Legal Authority and Enforcement

Section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(i)(4) requires drug manufacturers to "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. Section 520(g)(3)(D) of the FD&C Act (21 U.S.C. 360j(g)(3)(D) contains a similar requirement for medical device manufacturers. Sections 505(i) and 520(g) of the FD&C Act also authorize the Secretary to issue regulations for the protection of human subjects in clinical investigations. Additionally, section 701(a) of the FD&C Act (21 U.S.C. 371(a)) confers general authority to the Secretary to issue regulations for the efficient enforcement of the FD&C Act.

Section 801(b)(3)A) of FDAAA amends section 505(i)(4) of the FD&C 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 FD&C Act can be found at parts 312 and 50. Part 312 sets forth regulations governing drug IND applications, while part 50 includes 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 and medical devices. Section 801(b)(3)(A) of FDAAA does not amend section 520(g) of the FD&C Act; however, in instances where the regulations have been amended to address human subject protection, FDA has not made distinctions between clinical investigations for drugs and medical devices.

For example, FDA created a uniform system of human subject protection when it initially amended its regulations governing human subject protection in 1981 (46 FR 8942). 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 registry databank for informed consent documents and processes for only applicable clinical drug trials but not applicable clinical device trials would create a disparity in FDA's policy on human subject protection. This disparity could result in confusion among those who conduct such clinical trials over what is required in informed consent documents and processes, especially in the cases of applicable clinical trials involving both a drug and device or for investigators conducting applicable clinical trials of both types of regulated products.

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 applicable drug clinical trials conducted under section 505(i) of the FD&C Act, under its general authority to issue regulations for the efficient enforcement of the FD&C Act (section 701(a) of the FD&C Act), FDA is requiring all applicable clinical trials, including applicable device clinical trials, to include this new statement in informed consent documents and processes. Requiring an additional statement regarding the inclusion of clinical trial information in the registry databank to 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 applicable clinical drug and device trials and implement the congressional purpose reflected in FDAAA, we will apply the same standards regarding elements of informed consent to applicable clinical drug and device trials by amending § 50.25 to include a new paragraph (c) which requires a statement about the registry databank in informed consent discussions and documents for all applicable clinical trials under section 801 of FDAAA.

The Agency has several options available for enforcing the new informed consent requirement. The authority to issue regulations for the protection of human subjects is accompanied by the authority to impose penalties for violations of such regulations. Specifically, section 301(e) of the FD&C Act (21 U.S.C. 331(e)) makes the "failure to establish or maintain any record, or make any report, required under section * * * 505(i) * * *" and the "failure or refusal to comply with any requirement prescribed under section * * * 520(g)" prohibited acts. The FD&C Act and implementing regulations allow FDA to seek administrative, civil, and criminal penalties for violations of section 301 of the FD&C Act. 21 U.S.C. § 303(a); §§ 312.44(b)(1)(ix), 312.70(a), 812.30(b)(4), 812.119(a), 56. 121(b).

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

A. Introduction

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 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 final 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 final rule is expected to impose costs of about $3 per clinical trial participant or $611 to $1,061 per trial protocol, the Agency certifies that it 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 $135 million, using the most current (2009) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

B. The Final Rule

On December 29, 2009, FDA published a proposed rule that would require that the informed consent documents for applicable drug and device clinical trials include a statement that applicable clinical trial information has been or will be submitted to the NIH/NLM for inclusion in the statutorily required clinical trial databank. As it pertains to applicable drug clinical trials, the final rule would implement a requirement of FDAAA. As discussed previously in this preamble, FDA also requires that the same statement be included in the informed consent documents for applicable device clinical trials.

The proposed rule included an analysis of impacts as required by Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). FDA received many public comments concerning its estimated costs and benefits for the proposed rule. As a result of the review and consideration of these and other comments to the proposed rule, FDA has made changes to both the codified final rule and its analysis of impacts section.

C. Need for the Final Rule

The need for this rule arises from section 801(b)(3)(A) of FDAAA. It requires that the current regulations for informed consent documents and process be amended to include a statement that clinical trial information from the clinical investigation has been or will be submitted to the NIH/NLM clinical trial registry databank. FDA has decided that revising the general informed consent section is the appropriate course by which to fulfill the requirements of the statute, and will provide the pertinent information and protection for clinical trial participants.

D. Public Comments Concerning Impacts Analysis

Several comments objected to the inclusion of the informed consent statement for various reasons. Some believed the statement would cause confusion or anxiety to the participants. Others believed it would distract the participants from focusing on the substantive issues concerning the study that would affect one's decision to participate in the study. Some comments stated that the overall effect would be a reduced participation rate for prospective participants. No estimates of the size of this reduced participation rate were submitted. Additional comments questioned whether any relevant or valuable information could be acquired from an informed consent statement that takes less than 1 minute to read and discuss, resulting in less benefit to the participant than the administrative costs to the investigator.

FDA acknowledges that additional time will be required to read and, if necessary, discuss the statement that FDAAA mandates be included in the informed consent documents and process. FDA does not agree, however, that the benefit of the statement to the participant is directly related to the time it takes to read and discuss the statement. Further, FDA maintains that the benefits of the informed consent statement would be difficult to estimate with any certainty, making a meaningful comparison of benefits to costs impractical. FDA also has revised the statement to make it shorter and easier to understand by deleting those terms that could be expected to cause anxiety and confusion. FDA believes that in doing so it has reduced the theoretical possibility that the statement would cause some participants to abandon the study as much as possible while still fulfilling the FDAAA mandate.

E. Benefits of the Final Rule

FDA published a qualitative explanation of the expected benefits to clinical trial participants in its 2009 proposed rule. FDA received some public comments that agreed with the expected benefits. Others disagreed, criticizing the proposed rule for not educating the public at large about the clinical trial registry databank. Some proposed that FDA undertake a public education campaign to broaden awareness of the clinical trial registry databank. That policy option, however laudable, was not included in the FDAAA mandate concerning updating FDA's regulations concerning informed consent documents and process. While an educational campaign is not the subject of this rulemaking, there will be other opportunities for improving awareness of the NIH clinical trials databank. The comments as a whole did not contain any arguments that convinced FDA that it should amend its initial explanation of benefits. As a result, FDA restates the expected benefits for this final rule.

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. By helping to create a system of checks and balances through which participants, patients, and health care providers are encouraged to check whether information about a trial of interest is registered in the databank, it also would provide greater accountability of clinical trial investigators for outcomes and adverse events, thereby raising 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, but believes that the overall effect of the rule on public health would be positive.

F. Costs of the Final Rule

FDA estimated the total costs of the proposed rule to both industry and the

clinical trial participant population to range from $688,000 to $2,398,000 annually. This equated to $98 to $342 per trial protocol, or about $0.48 to $0.96 per clinical trial participant. These costs included labor costs for both the investigator and the trial participant, as well as document preparation costs and paper materials costs. The cost of government oversight was not expected to be significant. For the most part, the public comments on the proposed rule did not address the structure of the cost analysis (except IRB review costs). FDA retains much of the cost analysis of the proposed rule for the final rule.

1. Labor Costs

The costs of the final 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.

We have revised the final cost estimate to account for the administrative costs for companies involved in pharmaceutical, biologic, and medical device research and manufacturing, and administrative costs for IRB oversight. These additional labor costs are due to the administrative review of the rule and the determination of compliance responsibilities. All companies involved in this would incur some labor costs, regardless of the frequency with which they undertake clinical trials. Census data from 2002 list 5,666 companies in the seven North American Industrial Classification System (NAICS) categories that would be subject to this rule. FDA estimates that each could expend about 2 hours to review the final rule and determine any changes it needs to make to its internal administrative policies due to this rule. The pharmaceutical and medicine manufacturing category of the NAICS lists the hourly wage for a manager in this category at about $54. A 35 percent adjustment to this figure for employee benefits results in total hourly compensation costs of about $73. A one-time 2 hour review for each company would result in compliance costs of almost $147 per company, and a total of about $830,000 for the industry. This equates to an annualized cost (over 5 years at a 7 percent discount rate) of about $202,000 for the entire industry. These estimates may overstate true compliance costs for review of the rule since those companies that rarely sponsor clinical trials on even an occasional basis may not expend as much labor as those who do so more frequently.

For the proposed rule, FDA estimated that it receives about 7,000 clinical trial protocol submissions annually for applicable clinical trials that would be subject to this final rule, with the vast majority of the submissions to the FDA's Center for Drug Evaluation and Research (CDER). The public comments did not address the size of this estimate. However, further analysis of the data upon which the estimates were made shows that up to 30 percent of the CDER protocols may be for phase 1 clinical trials which would not be subject to the final rule. FDA has adjusted the estimated number of CDER trial protocols accordingly, which results in a reduction of the total trial protocols estimate to 5,146. FDA estimates of average numbers of participants per clinical trial vary greatly across FDA Centers, from single-patient INDs to vaccine trials with over 25,000 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, biotech, and medical device products may range from about 200 to 360.[1] FDA did not receive any comments on this estimate of the average number of participants per clinical trial, and retains it for the analysis of the final rule.

Compliance with the rule would require that the informed consent documents contain the required statement concerning the clinical trial's 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. As discussed previously in this preamble, FDA received many comments concerning the language used in the statement, as well as the length of time necessary to read and, if necessary, discuss this statement with the medical professional administering the study. Due to these comments, FDA has both simplified the language used in the statement, and reduced the length of the statement by about 50 percent. Additionally, FDA has revised its estimate of the average number of minutes that a clinical trial participant would require to read and discuss the statement from a range of 30 seconds to 1 minute used in the analysis of the proposed rule to 3 minutes for the analysis of the final rule.

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 $2.09 million to $3.76 million (see Table 1 of this document). This estimate is the result of $40.54 per hour times 3 minutes per participant times 200 to 360 participants per trial times 5,146 protocols per year. The cost to the sponsor per prospective participant is estimated at $2.03 and the cost per trial protocol is estimated to range from $405 to $730.

TABLE 1—COSTS OF INFORMED CONSENT PROPOSED RULE

Cost factor	Annual cost
Labor Cost—Administrative Review of Rule [1]	$202,000
Labor Cost—Clinical Trial Administrator	2,086,000–3,755,000
Labor Cost—Clinical Trial Participant	801,000–1,442,000
Labor Cost—IRB Review	29,000
Document Preparation Cost	17,000
Paper Cost	7,000–12,000

[1] *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 three clinical phases, which would tend to overstate the average size of participants. This upper bound is calculated at 360 participants per trial protocol.

TABLE 1—COSTS OF INFORMED CONSENT PROPOSED RULE—Continued

Cost factor	Annual cost
Total Costs	3,143,000–5,458,000

[1] This is a one-time cost of $830,000 annualized over 5 years at 7 percent.

Some clinical trial participants are compensated for their participation in trials. Whether an individual participant receives compensation or not, 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 of $0.78 for the 3 minutes to read and, if necessary, discuss the proposed informed consent statement. On an annual basis over the 5,146 clinical trials, this would amount to about $0.80 million to $1.44 million.

Comments to the proposed rule included a criticism that FDA had failed to account for the costs to IRB for its oversight role of the new statement. FDA agrees that the new informed consent statement will require an additional amount of oversight from IRBs. FDA has added to its cost elements a labor cost for the effort of the IRBs to determine that the statement has been added to the model templates for informed consent documents. Although IRBs can have many members, in practice, only one or two members may be involved in reviewing the study documents on behalf of the IRB for inclusion of all the necessary informed consent statements. FDA estimates the additional review of the entirety of consent forms and documents to determine that the new statement is appropriately included could take an additional 3 minutes of administrative effort for each of the 5,146 protocols. FDA bases its cost estimate on the mean hourly pay rate for physicians, adjusted 35 percent for benefits, of $113.[2] Using these factors, FDA estimates that an additional $29,000 in labor costs will be incurred due to this final rule.

The cost of incorporating 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 mentioned previously, $40.54 per hour, the additional annual costs to write the statement for the 5,146 annual protocols would total to about $17,000. 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 $7,000 to $12,000 annually.

2. Total Industry Costs

The total costs of the final rule to both industry and the clinical trial participant population are estimated to range from $3.14 million to $5.46 million annually. This equates to $611 to $1,061 per trial protocol, or about $2.95 to $3.05 per clinical trial participant.

3. Costs to Government

FDA did not receive any comments on its estimate of the impacts of the proposed rule on government costs, and retains its conclusions for the final rule. The costs to government for oversight of this rule would be extremely low as 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.

4. Alternatives to the Final Rule

FDAAA specifically requires that the regulations concerning informed consent documents include a statement that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank. It did not provide FDA with discretion concerning the inclusion of a statement for applicable drug clinical trials. For the reasons stated previously in this document, FDA has decided to require the revised, shorter statement be included in the informed consent documents for medical device trials as well. If the final 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 $207,000 to $615,000 per year. If FDA had not revised the informed consent statement to make it both shorter and easier to understand, the compliance costs would have been larger than those estimated in this analysis.

5. 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. The companies that would be affected are classified in seven separate 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—Opthalmic 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 (the 2007 Census data on the size distributions were not yet available; using 2002 data for the calculations overstates the likely effects on small businesses). 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 sponsoring 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 $611 to $1,061. Some firms will direct

[2] U.S. Department of Labor, Bureau of Labor Statistics, May 2009 National Occupational Employment and Wage Estimates United States, p. 8.

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 $6,110 to $10,610 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, 0.43 percent of the annual value of shipments. For establishments with 50 or more employees, the compliance costs would represent 0.11 percent 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 0.23 percent or less of the value of shipments even with 50 applicable clinical trials administered annually. Because of the small costs that would be incurred relative both to the total cost of a clinical trial and the revenues of an individual sponsor of a product undergoing a clinical trial, the Agency certifies that the final 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 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 requirement to include a statement in informed consent documents and processes on submission of information to the clinical trial data bank 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. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the final 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 final 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.

X. References

The following references have been placed on display in the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857 and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. We have verified the Web site addresses, but we are not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.

1. Food and Drug Administration, "Protection of Human Subjects; Informed Consent Final Rule" (46 FR 8942, January 27, 1981). "FDA recognizes that the documentation of informed consent represents only one part of the entire consent process. The consent form itself is merely an aid to assure that a required minimum of information is provided to the subject and that the subject consents. The entire informed consent process involves giving the subject all the information concerning the study that the subject would reasonably want to know; assuring that the subject has comprehended this information; and finally, obtaining the subject's consent to participate." 46 FR 8942 at 8945. Available at: *http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm113818.htm*, accessed August 9, 2010.

2. 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." Part A: Boundaries Between Practice & Research, April 18, 1979, available at: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm, accessed August 9, 2010.

3. National Research Act, Title II (Pub. L. 93–348, July 12, 1974).

4. 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), available at: *http://www.loc.gov/rr/frd/Military_Law/pdf/NT_war-criminals_Vol-II.pdf,* accessed August 9, 2010.

5. Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (2002), Guideline 5, No. 7 states that the informed consent process include information that subjects, after completion of the study, will be provided with general research results and any findings relating to their particular health status. Guideline 5, No. 11 states that the subject be informed of "the expected benefits of the research to the community or to society at large.", available at: *http://www.cioms.ch/publications/layout_guide2002.pdf,* accessed August 9, 2010.

6. World Medical Association, *Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects,* 59th WMA General Assembly, Seoul, October 2008, Section C.33 states that: "At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it. * * *", available at: *http://www.wma.net/en/30publications/10policies/b3/17c.pdf*, accessed August 9, 2010.

7. Sim, I., A. Chan, A. Gülmezoglu, "Clinical Trial Registration: Transparency is the Watchword," *The Lancet,* Vol. 367, Issue 9523, p. 1631, May 2006.

8. 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/update_may05.html*, accessed October 4, 2010.

9. Several examples of model templates can be found at:

a. Mayo Clinic, Institutional Review Board, IRB Consent Form Template, available at: *http://mayoresearch.mayo.edu/mayo/research/irb/upload/irb10294.pdf* accessed July 7, 2010;

b. Stanford University Research Compliance Office, Human Subjects Research, "Stanford University Consent (includes HIPAA), available at: *http://humansubjects.stanford.edu/consents/SUSampCons_CA_privacy.doc,* accessed July 7, 2010;

c. Duke University School of Medicine, Institutional Review Board, "Sample Consent," available at: *http://irb.duhs.duke.edu/wysiwyg/downloads/Consent_Template_-_Long_Form_102_01-02-09_JW.doc,* accessed July 7, 2010;

d. University of Michigan Medical School, Informed Consent & Assent Templates, "Informed Consent Template (Standard) Version 3–29–10," available at: *http://med.umich.edu/irbmed/ict.htm,* accessed July 7, 2010;

e. University of Texas at Austin, Office of Research Support, "Consent Form 1—For Greater Than Minimal Risk Studies," available at: *http://www.utexas.edu/research/rsc/humansubjects/forms/consent_form_1.doc,* accessed on July 7, 2010;

f. Children's Hospital Boston, Office of Clinical Investigation, "English Informed Consent Template," available at: *http://www.childrenshospital.org/cfapps/research/data_admin/Site2206/Documents/Consent_Template.doc,* accessed July 8, 2010;

g. Partners Human Research Committee, Consent Forms, "Drug Trial Consent Form Template," available at: *http://healthcare.partners.org/phsirb/irbforms/Consent_Templates_and_Instructions/PHS_Research_Consent_Form_Adult_Surrogate_Drug_2.2010.doc,* accessed July 8, 2010;

h. Walter Reed Army Medical Center, NCA Templates, "Informed Consent Form." Available at: *http://www.wramc.army.mil/Patients/healthcare/dci/protocols/nca templates/INFORMED%20CONSENT%20FORM%20(ICF)/WRNMMC_ClinicalTrials ICF.doc,* accessed July 8, 2010;

i. American College of Radiology Imaging Network, Protocol Development & Regulatory Resources, "Informed Consent Template & Checklist," available at: *http://www.acrin.org/Portals/0/Administration/Regulatory/ICF_Template.doc,* accessed July 8, 2010;

j. National Cancer Institute, "Simplification of Informed Consent Documents," available at: *http://www.cancer.gov/clinicaltrials/education/simplification-of-informed-consent-docs/allpages*, accessed July 7, 2010.

10. Institutional Review Board: Management and Function (edited by Bankert, E. A. and R. J. Amdur), 2d Ed., 2006 (Chapter 6–1, *The Institutional Review Board's Role in Editing Consent Documents,* Pensha, R. L., pp. 199–201 and Chapter 6–2, *The Consent Documents,* Brown, A., pp 202–204).

11. Flesch-Kincaid Reading Scale Information, Rudolf Flesch, "A New Readability Yardstick," *Journal of Applied Psychology,* vol. 32, pp. 221–233, 1948.

12. FDA, Office of Planning, Risk Communication Staff, ANALYSIS NOTE: Note No. 2010–001, July 30, 2010.

13. FDA: A Guide to Informed Consent—Information Sheet, available at: *http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm#nonenglish*, accessed August 8, 2010.

14. NIH: ClinicalTrials.gov: Protocol Registration System: PRS and U.S. Public Law 110–85: "Applicable Clinical Trials," available at: *http://prsinfo.clinicaltrials.gov/fdaaa.html* and *http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf*, accessed August 8, 2010.

15. "Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff: Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens That Are Not Individually Identifiable," available at: *http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078384.htm*, accessed August 8, 2010.

16. NIH: ClinicalTrials.gov "Basic Results Data Element Definitions (DRAFT)," available at: *http://prsinfo.clinicaltrials.gov/results_definitions.html,* accessed August 8, 2010.

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, 21 CFR part 50 is 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 redesignating paragraphs (c) and (d) as paragraphs (d) and (e), and by adding new paragraph (c) to read as follows:

§ 50.25 Elements of informed consent.

* * * * *

(c) When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial 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. The statement is: "A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

* * * * *

Dated: December 28, 2010.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2010–33193 Filed 1–3–11; 8:45 am]

BILLING CODE 4160–01–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 239 and 258

[EPA–R10–RCRA–2010–0953; FRL–9247–6]

Alaska: Adequacy of Alaska Municipal Solid Waste Landfill Permit Program

AGENCY: Environmental Protection Agency (EPA).

ACTION: Direct final rule.

SUMMARY: This action approves a modification to Alaska's approved Municipal Solid Waste Landfill (MSWLF) permit program. The approved modification allows the State to issue Research, Development, and Demonstration (RD&D) permits to owners and operators of MSWLFs in accordance with its State law. On March 22, 2004, EPA issued final regulations allowing RD&D permits to be issued to certain MSWLFs by approved States. On September 7, 2010, the State of Alaska submitted an application to EPA Region 10 seeking Federal approval of its RD&D requirements. After thorough review, EPA Region 10 has determined that Alaska's RD&D permit requirements are adequate through this direct final action.

DATES: This direct final rule will become effective March 7, 2011 without further notice unless EPA receives adverse comments on or before February 3, 2011. If adverse comments are received, EPA will publish a timely withdrawal of this direct final rule in the **Federal Register** informing the public that the rule will not take effect. EPA will then review the comments and then will publish a final rule in the **Federal Register** responding to the comments and affirming or revising its initial decision.

ADDRESSES: Submit your comments, identified by Docket ID No. EPA–R10–RCRA–2010–0953, by one of the following methods:

- *http://www.regulations.gov:* Follow the on-line instructions for submitting comments.
- *E-mail: calabro.domenic@epa.gov.*
- *Fax:* (206) 553–8509, to the attention of Domenic Calabro.
- *Mail:* Domenic Calabro, Office of Air, Waste and Toxics, U.S. EPA, Region 10, 1200 Sixth Avenue, Suite 900, Mailstop: AWT–122, Seattle, WA 98101.
- *Hand Delivery or Courier:* Deliver your comments to Domenic Calabro, Office of Air, Waste and Toxics, U.S. EPA, Region 10, 1200 Sixth Avenue, Suite 900, Mailstop: AWT–122, Seattle, WA 98101. Such deliveries are only accepted during the Office's normal hours of operation.

Instructions: Identify your comments as relating to Docket ID No. EPA–R10–RCRA–2010–0953. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at *http://www.regulations.gov*, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or claimed to be other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through *http://www.regulations.gov* or e-mail. The *http://www.regulations.gov* Web site is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through *http://www.regulations.gov*, your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any