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Part VIII

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 50, 312, and 812
Protection of Human Subjects; Informed Consent Verification; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 50, 312, and 812

[Docket No. 95N-0359]

Protection of Human Subjects; Informed Consent Verification

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its current informed consent regulations to require that the consent form signed by the subject or the subject's legally authorized representative, be dated by the subject or the subject's legally authorized representative at the time consent is given. FDA is also amending its regulation on case histories to clarify what adequate case histories include and to clarify that the case histories must document that informed consent was obtained prior to participation in a study. FDA is taking this action in response to problems the agency has had on occasion verifying that informed consent was obtained from a research subject prior to participation in a study because the consent document was not dated and other verification was not contained in the individual's case history documentation. The agency believes that by explicitly requiring that the consent form be dated at the time it is signed and requiring the case history to document that consent was obtained prior to participation in a study, the agency will be able to help ensure that informed consent was, in fact, obtained prior to entry into the study as required by FDA regulations.

DATES: The regulation is effective December 5, 1996.

FOR FURTHER INFORMATION CONTACT: Gary L. Chadwick, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-1685.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of December 22, 1995 (60 FR 66530), FDA proposed to amend FDA's current informed consent regulations to require that the written consent form signed by the subject or the subject's legally authorized representative, be dated by the subject or the subject's legally authorized representative at the time consent is given. FDA also proposed to amend its regulation on case histories to clarify what adequate case histories include.

Interested persons were given until March 21, 1996, to comment on the proposed rule. The agency received a total of eight comments: One from a patient advocacy group, three from pharmaceutical companies, one from a medical device company, and three from private individuals. All of these comments supported the proposal to amend the agency's informed consent regulations to require that consent forms be dated by the subject or subject's legally authorized representative at the time consent is given. One comment expressed support for the agency's proposal to clarify the meaning of adequate case histories; the remaining comments were silent on this issue. Several of these comments recommended additional changes to the informed consent regulations. These comments and FDA's responses are discussed below.

II. Comments

1. One comment suggested that the agency should require not only the date, but also the time, that the consent form was signed in order to be able to verify that consent was obtained prior to a subject's entry into a study. This comment expressed concern by the potential 24-hour window created by requiring the date and not the time for research subjects who sign the consent form on the day that they begin their participation in the study. The comment suggested that this 24-hour window should be closed to ensure that investigators fulfill their responsibilities and to enable the agency to verify that consent is obtained prior to entry into the study. The comment provided the following three additional reasons for requiring the time of day that the consent form is signed: (1) The role of informed consent in clinical investigations is to help ensure voluntary decisionmaking about enrollment in a study, (2) documentation of the timing of the signature helps to provide evidence of when consent was obtained in relation to when the investigational intervention commenced, and (3) the interest of historians and scholars in knowing whether the research was conducted in accordance with societal standards related to the conduct of research.

The agency has considered this comment and whether the regulation should be modified to permit verification that consent was obtained prior to a subject's entry into a study when both consent is obtained and participation in a study occur on the same day. The agency agrees that when, for example, the consent form is signed on the same day that the subject begins participation in the study, it may not be able to verify from a dated consent form that consent was obtained prior to an individual's participation in the research; therefore, other documentation may be needed. However, the agency does not think that it is appropriate to require the time of signature to be included on every consent form in order to permit this verification.

FDA notes that adding the time of day to the consent form may not provide the additional assurance suggested by the comment. The investigational new drug application and investigational device exemption regulations (parts 312 and 812 (21 CFR parts 312 and 812)) do not require the time of day to be recorded in the individual's case history for each research intervention. In practice, the time of day is generally not recorded in case histories, except when time-sensitive procedures are carried out. Therefore, recording the time of day on the consent form may not establish that the form was signed before participation in the study. Rather than requiring the time of day to accomplish the agency's verification goal, the agency has modified §§ 312.62(b) and 812.140(a)(3)(i) to allow flexibility in approaches to providing verification. These sections now state "The case history for each individual shall document that informed consent was obtained prior to participation in the study." This case history documentation may be contained in the case report form; in the individual's medical record, e.g., in progress notes of the physician, on the individual's hospital chart, in the nurse's notes; on the consent form; in a combination of these documents; or elsewhere in the individual's case history. The documentation may consist of, e.g., a chronological record of the sequence of events that establishes that informed consent was obtained prior to a procedure required by the clinical investigation, or the time that consent was obtained and the time of the first study-related procedure performed on the individual.

The agency notes that 21 CFR 56.109(c) provides for an exception from the requirement for written documentation of informed consent and that part 50 (21 CFR part 50) provides for certain limited exceptions to the requirement for obtaining informed consent. This rule does not change those regulatory provisions.

2. Another comment recommended that the agency conduct a comprehensive review of the informed consent process, noting that a "flaw in the system has been the failure of IRBs

to insist that the consent form be drafted in lay language" and that such a review would disclose other problems. This comment went on to note that during FDA inspections, the comment was unaware of FDA challenging the content of consent forms.

This comment does not request a change in the regulations. The agency already requires consent documents to describe, in language that is understandable to subjects, all relevant information about the study.

Under the agency's Bioresearch Monitoring Program, FDA conducts onsite inspections of institutional review boards (IRB's) and clinical investigators. During the IRB inspections, IRB members and/or administrators are interviewed regarding procedures and then IRB records are inspected to verify compliance with parts 50 and 56. During these inspections, copies of informed consent forms approved by the IRB are collected and reviewed by agency components. Under FDA's clinical investigator compliance program, FDA conducts study-specific inspections and audits of investigators conducting clinical trials of FDA-regulated products. These inspections also include an evaluation of whether the informed consent document conforms to FDA regulations (part 50). Through these inspections, the agency is able to assess whether there are common problems with these documents such as their failure to include all the required elements of informed consent specified in § 50.25 and their failure to explain technical/scientific language. FDA provides information to IRB's and investigators to address these issues. (See the "FDA Information Sheets for Institutional Review Boards and Clinical Investigators" reprinted March 1996, pages 52–53. Copies are available from Gary L. Chadwick, Office of Health Affairs (address above) or on the World Wide Web (http://www.fda.gov/oc/oha/informed.html).)

To improve the quality of consent forms, following an inspection where deficiencies are found, FDA explains its regulatory requirements as well as deficiencies found in consent forms to clinical investigators and IRB's in post-inspection letters. FDA also carries out a wide variety of educational efforts in the area of human subject protection; a part of these educational efforts is focused on issues associated with informed consent. By making clinical investigators and IRB's aware of FDA regulatory requirements and problems related to informed consent and human subject protection, FDA thinks that the consent process and the protections provided to research subjects will be improved.

3. One comment recommended that the requirement that the consent form be dated at the time the form is signed not be retrospectively applied to research subjects entered into a study prior to the effective date of the final rule.

The agency agrees with this comment and does not intend to retrospectively apply this rule to research subjects entered into a study prior to its effective date. Thus, this final rule applies to research subjects entered into studies on or after the effective date of this regulation.

4. Another comment recommended that § 50.27(b)(2) be amended to require that "short forms and summaries" be dated at the time that they are signed.

The agency does not think that § 50.27(b)(2) needs to be revised. The provision set forth in § 50.27(a) requiring that a written consent form be dated at the time of consent applies both to a written consent document that embodies the elements of informed consent (§ 50.27(b)(1)) as well as to a "short form" written consent document (stating that the elements of informed consent required by § 50.25 have been presented orally to the subject or the subject's legally authorized representative (§ 50.27(b)(2))). Thus, the agency is not revising § 50.27(b)(2).

5. One comment was received on the clarifying amendment of what constitutes adequate case history records. The comment supported the amendment; however, the agency believes that the respondent misunderstood the agency's intention. The comment suggested that the proposed change to § 312.62(b) would allow case report forms to be collected earlier by the sponsor because investigators would not need to transcribe information onto a case report form if that information were contained in the subject's medical records.

This comment misinterpreted the clarifying amendment to § 312.62(b). The revisions to this section were to clarify that adequate case history records include the case report forms and supporting data, including, e.g., signed and dated consent forms and medical records. The purpose of the case report form is to provide sufficient information for the sponsor to evaluate the use of the product in an individual subject; thus, the case report form may need to duplicate information contained in the subject's medical record. If the case report form is made a permanent part of the subject's medical record, then the medical record may not need to contain information that is contained in that case report form. In most instances, the agency thinks that information is typically entered into the subject's medical record first; then, it is entered onto the case report form for transmittal to the research sponsor.

6. On the agency's own initiative, it has made technical changes to the conforming amendments at §§ 312.53, 312.62, and 812.140(a)(3). In § 312.53(c)(1)(vi)(*d*), "patients" has been changed to "potential subjects" to clarify that an individual who participates in a research study may be either a healthy individual or a patient. In addition, the agency has deleted the phrase "or any persons used as controls" because "subject" is defined as a recipient of an investigational new drug or as a control. (See § 312.3(b).) In § 312.62(b), "treated with the investigational drug" has been changed to "administered the investigational drug" to clarify that the administration of an investigational drug may not constitute treatment. In § 312.62(b), examples have been added to describe the variety of documents that are considered to be part of an individual's medical record. These documents include, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Section 812.140(a)(3) has been amended to clarify what constitutes adequate case history records and to provide examples of the variety of documents that are considered to be part of an individual's medical record; this clarification is consistent with the language contained in § 312.62(b).

III. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) 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.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). 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 consistent with the regulatory philosophy and

principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. This rule simply adds a requirement that consent forms be dated at the time that they are signed and that the individual's case history documents that consent was obtained prior to participation in a study in order to permit the agency to verify that informed consent is obtained prior to an individual's entry into a research study. Because the majority of consent forms are currently dated at the time that they are signed and the majority of case histories currently contain this verifying information, the Commissioner of Food and Drugs certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

V. Paperwork Reduction Act of 1995

This final rule contains no additional information collection requirements which are subject to review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (Pub. L. 104–13).

List of Subjects

21 CFR Part 50

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

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 812

Health records, Medical devices, Medical research, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic 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: Secs. 201, 406, 408, 409, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371, 379e, 381); secs. 215, 301, 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b–263n).

2. Section 50.27 is amended by revising paragraph (a) to read as follows:

§ 50.27 Documentation of informed consent.

(a) Except as provided in § 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

* * * * *

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

3. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

4. Section 312.53 is amended by revising paragraph (c)(1)(vi)(*d*) to read as follows:

§ 312.53 Selecting investigators and monitors.

* * * * *

(c) * * *

(1) * * *

(vi) * * *

(*d*) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

* * * * *

5. Section 312.62 is amended by revising paragraph (b) to read as follows:

§ 312.62 Investigator recordkeeping and record retention.

* * * * *

(b) *Case histories.* An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

* * * * *

PART 812—INVESTIGATIONAL DEVICE EXEMPTIONS

6. The authority citation for 21 CFR part 812 continues to read as follows:

Authority: Secs. 301, 501, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701, 702, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331, 351, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371, 372, 374, 379e, 381); secs. 215, 301, 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263b–263n).

7. Section 812.140 is amended by revising the introductory text of paragraph (a)(3) and adding a new sentence to the end of paragraph (a)(3) to read as follows:

§ 812.140 Records.

(a) * * *

(3) Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:

(i) * * * The case history for each individual shall document that informed consent was obtained prior to participation in the study.

* * * * *

Dated: October 28, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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