Office for Human Research Protections (OHRP)
Department of Health and Human Services (HHS)

Applicability of 45 CFR part 46 to Clinical Investigations Conducted Under FDA's Interim Final Rule at 21 CFR 50.23(e)

Date: June 7, 2006

Scope: This document addresses how to determine whether the HHS regulations at 45 CFR part 46 are applicable to the activities covered by the Food and Drug Administration's (FDA's) interim final rule, "Medical Devices; Exception From General Requirements for Informed Consent" (21 CFR 50.23(e)).[1] Specifically, the document provides guidance on the following:

(1) The determination of when institutions conducting activities covered by 21 CFR 50.23(e) would be engaged in non-exempt human subjects research. Specifically, the document:

- Clarifies that institutions whose employees or agents use an investigational device only to (1) identify a potentially life-threatening chemical, biological, radiological, or nuclear agent, (2) facilitate the treatment of individuals exposed to such an agent, and/or (3) report test results to a public health authority ***would not*** be engaged in human subjects research under 45 CFR part 46.

- Clarifies that institutions whose employees or agents obtain or analyze identifiable private information derived from an investigational in vitro diagnostic device in order to evaluate the safety and effectiveness of the in vitro diagnostic device ***would*** be engaged in human subjects research under 45 CFR part 46.

(2) The requirements for obtaining or waiving informed consent under 45 CFR 46.116.

---

1 Note that this guidance only applies to clinical investigations that are conducted or supported by HHS. If the clinical investigation is being conducted or supported by one of the other 14 Federal departments or agencies that has adopted the Federal Policy for the Protection of Human Subjects (the "Common Rule"), the institution should contact appropriate officials at the department or agency conducting or supporting the clinical investigation for guidance on implementing the Common Rule or other applicable federal regulations.

- Clarifies OHRP's expectation that IRBs often will find that informed consent ***may be waived*** under 45 CFR 46.116(d) for the research activities involving the analysis of identifiable private information obtained through clinical investigation covered by 21 CFR 50.23(e).

Target Audience: Institutional review boards (IRBs), investigators, sponsors and funding agencies that may be responsible for review or oversight of human subjects research conducted or supported by HHS.

Regulatory Background:

HHS Regulations (45 CFR part 46)

The HHS regulations at 45 CFR part 46 apply to research activities involving human subjects conducted or supported by HHS, unless the activities qualify for exemption under 45 CFR 46.101(b).

HHS regulations define *research* at 45 CFR 46.102(d) as follows:

> *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

HHS regulations define *human subject* at 45 CFR 46.102(f) as follows:

> *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains
>
> (1) data through intervention or interaction with the individual, or
>
> (2) identifiable private information.
>
> *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

OHRP recommends that the process for determining whether the HHS regulations apply should address the following three questions in order:

(1) Does the activity involve *research* under 45 CFR 46.102(d)? (If yes, proceed to the second question.)(2) Does the activity involve *human subjects* under 45 CFR 46.102(f)? (If yes, proceed to the third question.)

(3) Is the activity *exempt* under 45 CFR 46.101(b)?

If the answer to the first two questions is "yes", and the answer to the third question is "no", then the HHS regulations apply; otherwise, the HHS regulations do not apply. To view a chart regarding this decision-making process, see OHRP's "Human Subject Regulations Decision Charts" at [http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm].

If it is determined that the activity involves non-exempt human subjects research, the next question is whether an institution is "engaged." OHRP's guidance on "Engagement of Institutions in Research" is available at http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm.

Institutions that are engaged in non-exempt human subjects research that is conducted or supported by HHS are required by 45 CFR part 46 to:

(1) Hold or obtain an applicable OHRP-approved Federalwide Assurance of compliance (45 CFR 46.103(a)); and

(2) Certify to the HHS agency conducting or supporting the research that the application or proposal for research has been reviewed and approved by an IRB designated in the FWA, and will be subject to continuing review by the IRB (45 CFR 46.103(b) and (f)).

Finally, HHS regulations at 45 CFR 46.116 describe the general requirements for informed consent for non-exempt human subjects research conducted or supported by HHS. HHS regulations at 45 CFR 46.116(d) permit an IRB to *waive* the requirements to obtain informed consent if the IRB finds and documents that:

(1) the research involves no more than minimal risk to the subjects;

(2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) the research could not practicably be carried out without the waiver of alteration; and

(4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

FDA's Interim Final Rule (21 CFR 50.23(e))

Under FDA's regulations, informed consent must be obtained before an investigational in vitro diagnostic device may be used, unless an exception under part 50 (21 CFR part 50) applies. IRB-review and approval is also required unless an exception under part 56 (21 CFR part 56) applies. Through the interim final rule (21 CFR 50.23(e)), FDA has created a new exception from the general requirements for informed consent to respond to chemical, biological, radiological, or nuclear terrorism or other potential public health emergencies. The exception applies when investigational in vitro diagnostic devices are used and the investigator is unable to obtain timely informed consent from subjects (or their legally authorized representatives) whose specimens are being tested. The new limited exception is applicable only when it is not feasible to obtain informed consent because, at the time the specimen is collected, it may not be known that an investigational device would need to be used on that specimen, and delay in diagnosis could be life-threatening to the subject.

Guidance:

The activities covered by 21 CFR 50.23(e) may include the analysis of identifiable private information to evaluate the safety and effectiveness of the investigational in vitro diagnostic device being used under this provision of FDA's regulations. Such data analysis activities generally will also be human subjects research as defined by the Department of Health and Human Services (HHS) regulations for the protection of human subjects at 45 CFR 46.102(d) and 46.102(f). If an institution is engaged in non-exempt human subjects research that is conducted or supported by HHS, an OHRP-approved assurance of compliance is required by HHS regulations at 45 CFR 46.103(a). Depending on the nature and purpose of their activities, some of the institutions (e.g., institutions operating public health laboratories) involved in investigations covered by 21 CFR 50.23(e) may not be considered engaged in human subjects research under 45 CFR part 46. This is further explained below.

As described by FDA, 21 CFR 50.23(e) envisions that the clinical investigators will include laboratory personnel, who would typically be employed by a public health laboratory that would have been prospectively identified by the sponsor of the investigation (e.g., CDC) to use the investigational device in certain public health emergencies to (1) identify a potentially life-threatening chemical, biological, radiological, or nuclear agent, (2) facilitate the treatment of individuals exposed to such an agent, and/or (3) report test results to a public health authority as appropriate. Under the HHS regulations at 45 CFR part 46, ***OHRP would not consider an institution operating such a laboratory to be engaged in human subjects research, if the activities of the laboratory's personnel were limited to the three activities identified above***. ***Therefore, 45 CFR part 46 would not apply to such uses of an investigational device.***

However, if the laboratory personnel were also involved in the analysis of the identifiable private information derived from the investigational in vitro diagnostic device in order to

evaluate the safety and effectiveness of the in vitro diagnostic device, then the institution operating the laboratory would be engaged in human subjects research, thus triggering the requirement for an OHRP-approved assurance of compliance whenever the research is conducted or supported by HHS and is not otherwise exempt under HHS regulations at 45 CFR 46.101(b).

It is also OHRP's understanding that FDA envisions that the sponsor of investigations covered by 21 CFR 50.23(e) would generally obtain identifiable private information from public health laboratories or other entities using the test to assess the ability of the investigational device to correctly identify the chemical, biological, radiological, or nuclear agent that may have caused, or may cause, human disease or injury. Under the HHS regulations, OHRP generally would consider sponsors who conduct such activities to be engaged in human subjects research, thus triggering the requirement for an OHRP-approved assurance of compliance whenever the research is conducted or supported by HHS and is not otherwise exempt.

Non-exempt human subjects research that is covered by 45 CFR part 46 must be reviewed prospectively by an IRB, and must be conducted with the informed consent of the research subject(s) (or the subject's legally authorized representative) unless the requirement for obtaining informed consent has been waived appropriately by an IRB under 45 CFR 46.116. For research that is covered by both the exception from the general requirements of informed consent under 21 CFR 50.23(e) and by 45 CFR part 46, OHRP expects that IRBs often will find that informed consent may be waived under 45 CFR 46.116(d) for the research activities involving the analysis of identifiable private information obtained through use of the investigational device. As described earlier, in order for an IRB to waive the requirements to obtain informed consent under the HHS human subject protection regulations the IRB must find and document that:

> (1) the research involves no more than minimal risk to the subjects;
>
> (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;
>
> (3) the research could not practicably be carried out without the waiver or alteration; and
>
> (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation. 45 CFR 46.116(d).

Conversely, if the IRB finds that informed consent ***for the data analysis activities*** may not be appropriately waived under 45 CFR 46.116(d), research that is covered by both 45 CFR part 46 and the exception from the general requirements of informed consent under 21 CFR 50.23(e), must be conducted with the informed consent of the research subject(s) as required by 45 CFR 46.116. In addition, informed consent for such studies must be documented to the extent required by 45 CFR 46.117. OHRP notes that when the requirements of these two regulations conflict, it is the stricter of the two that governs

unless waived by the department or agency. Therefore, 45 CFR part 46 would govern instead of 21 CFR 50.23(e) if both regulations were to apply to the research involving the data analysis activities.

If you have specific questions about how to apply this guidance, please contact OHRP by phone at (866) 477-4777 (toll-free within the U.S.), (240) 453-6900, or by e-mail at ohrp@hhs.gov.