

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 50

RIN 0910-AC25

[Docket No. 2003N-0355]

Medical Devices; Exception From General Requirements for Informed
Consent

AGENCY: Food and Drug Administration, HHS.

ACTION: Interim final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing this interim final rule to amend its regulations to establish a new exception from the general requirements for informed consent, to permit the use of investigational in vitro diagnostic devices to identify chemical, biological, radiological, or nuclear agents without informed consent in certain circumstances. The agency is taking this action because it is concerned that, during a potential terrorism event or other potential public health emergency, delaying the testing of specimens to obtain informed consent may threaten the life of the subject. In many instances, there may also be others who have been exposed to, or who may be at risk of exposure to, a dangerous chemical, biological, radiological, or nuclear agent, thus necessitating identification of the agent as soon as possible. FDA is creating this exception to help ensure that individuals who may have been exposed to a chemical, biological, radiological, or nuclear agent are able to benefit from the timely use of the most appropriate diagnostic devices, including those that are investigational.

dwb

Display Date	<i>6-6-06</i>
Publication Date	<i>6-7-06</i>
Officer	<i>Joelle</i>

DATES: This rule is effective [*insert date of publication in the Federal Register*]. Submit written or electronic comments by [*insert date 60 days after date of publication in the Federal Register*].

ADDRESSES: Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Claudia M. Gaffey, Center for Devices and Radiological Health (HFZ-440), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 240-276-0496, ext. 109.

SUPPLEMENTARY INFORMATION:

I. Background

U.S. Federal, State, and local authorities have developed and are refining a comprehensive public health plan to prepare for, and respond to, the threat of terrorism and other potential public health emergencies. A critical element in responding to such emergencies is the ability to correctly and quickly identify the chemical, biological, radiological, or nuclear agents that may have caused, or may cause, human disease or injury. The devices included within the scope of this rule are those for the detection of agents that have the potential to be used in acts of chemical, biological, radiological, or nuclear terrorism, or that can lead to other potential public health emergencies.

Examples of these agents include *Bacillus anthracis* (anthrax); *Yersinia pestis* (plague); ricin (a lethal chemical agent); and cobalt-60, a radiological material that could be used to build a dirty bomb. Although it is not possible to provide an all inclusive list of etiological agents that would be identified under conditions that meet the criteria described in this rule, critical biologic agents

such as Category A Diseases/Agents (available at <http://www.bt.cdc.gov/agent/agentlist-category.asp>) or specific chemical agents (<http://www.bt.cdc.gov/chemical/>) that are used by the federal government for regulatory and emergency planning purposes, may serve as examples of the types of agents within the scope of this rule. Select agents as defined in 42 CFR 73.1, that would suggest a terrorism event or other public health emergency, may be considered as other examples. Most in vitro diagnostic devices used to identify such agents have been developed (and more are under development) by the Centers for Disease Control and Prevention (CDC), and the Department of Defense (DOD). Some nongovernment entities are also developing such in vitro diagnostic devices. In most instances, these are the only devices available to provide timely diagnostic information on the identity of these agents, although they may not yet have been approved or cleared by FDA.

Many of these devices have not yet been approved or cleared by FDA because clinical studies involving devices used for the identification of such agents frequently cannot be conducted. Studies may not be possible because natural exposure to these agents is rare or never occurs, and there may not be enough exposed subjects to enroll in a study. Studies also may not be possible because it is not ethical to expose healthy human volunteers to a life-threatening toxic substance or organism to determine the ability of the unapproved diagnostic device to correctly identify the agent. While these unapproved devices may not have been evaluated on specimens collected from human subjects, testing (procedural) validation and other analytical studies generally have been conducted (or are being conducted) by the sponsors.

Some of these devices may be under clinical investigation, while others may not have reached that stage of development. For purposes of this rule we

are considering the term "investigational device" to include those devices being evaluated in a clinical investigation as well as those that are undergoing preclinical and/or analytical evaluation.

Given all of these facts, the agency believes that the use of these investigational diagnostic devices in limited circumstances is justified when the devices are needed to identify the causative agent in a potential public health emergency and thereby enable authorities to promptly provide appropriate care to those exposed, and to provide preventive therapies (if available) to others in the affected geographic region(s).

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. Institutional review board (IRB) review and approval is also required, unless an exception under part 56 (21 CFR Part 56) applies. Under the IRB regulations investigations may be reviewed by an IRB through a joint review process, reliance upon the review of another qualified IRB (e.g., at the research site, a central IRB, an independent or commercial IRB), or similar arrangements. (See 21 CFR 56.114.) Therefore, absent an applicable exception, investigational in vitro diagnostic devices used to identify chemical, biological, radiological, or nuclear agents in human specimens may only be used after obtaining informed consent from each subject whose specimen is tested, and with IRB review and approval.

If a terrorism event (such as dissemination of *B. anthracis* spores in the mail system in 2001) or other potential public health emergency occurs (such as the multistate outbreak of monkeypox in persons exposed to pet prairie dogs in 2003), the timely identification of the etiological agent may be critical to the lives of the affected subjects as well as to the general population who may

also have been exposed. The risk to subjects and others exposed could be life-threatening, and difficult to assess and address without the use of these investigational devices. Identification of the agent could be delayed significantly or precluded while the investigator seeks to obtain informed consent. Also, in some cases, storing the specimen while awaiting consent could have an adverse effect on the specimen and compromise the test results. The consequences of delay could be catastrophic for subjects and for public health in general.

Consider the following possible scenario in which a terrorist event is not suspected until a public health laboratory cultures an unusual or rare organism. When a patient presents to a health care facility with symptoms suggesting a systemic microbial infection, blood and other specimens are typically collected to determine the identity of the causative organism. The clinical laboratory would determine that the specimens contain an unusual organism that cannot be identified by the tests available in that laboratory. Because many clinical laboratories do not have the capability or resources to identify unusual organisms or those to which humans are rarely exposed naturally, the organism (culture isolate) or collected specimen would be referred to a public health laboratory. The public health laboratory would use in vitro diagnostic devices, including those that are investigational, to try to identify the cultured organism or detect its presence directly in the specimen.

In this scenario, the referring laboratory would not have obtained informed consent when the specimen was collected because the person directing that the specimen be collected would not have known at the time that the infecting organism could be reliably identified only by using an investigational device. To obtain informed consent would require a number of steps and introduce

unacceptable delays. The public health laboratory would have to contact the referring laboratory that collected the specimen or the physician who ordered the cultures in order to locate the subject (or the subject's legally authorized representative). Once located, the subject or the subject's legally authorized representative would need to be contacted, provided the informed consent information, and given the opportunity to ask questions and sign the informed consent document. The referring laboratory or health care facility would then have to notify the public health laboratory that informed consent had been obtained. Only at that point could testing be performed.

The scenario described in the previous paragraph is one example and is not the only set of circumstances in which this exception to informed consent might apply. The new exception would also apply if the event were not terrorism-related but was another type of potential public health emergency, such as sporadic outbreaks resulting from the spread of an emerging infectious agent that has the potential to cause a life-threatening situation, as in the case of Severe Acute Respiratory Syndrome (SARS) or the potential for a pandemic influenza virus strain. This rule would not apply in a situation which is not life-threatening or where there is a cleared or approved available alternative method of diagnosis that provides an equal or greater likelihood of saving the life of the subject, such as the in vitro diagnostic devices for identifying agents causing certain known sexually transmitted diseases such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, human papillomavirus, human immunodeficiency virus, etc. The emergency nature of the event may or may not be suspected at the time the specimen is collected, and the laboratory involved may or may not be a public health laboratory. Finally, even if the nature of the event is suspected, the person collecting the specimen may not

know the investigational status of the in vitro diagnostic device and thus would not know that informed consent should be obtained from the patient. These variables are examples and are not meant to be the exclusive circumstances in which this rule might apply. The exception has been constructed in somewhat general terms because we can not anticipate the circumstances of every emergency involving a chemical, biological, radiological, or nuclear agent that may occur.

The process for obtaining informed consent in the scenarios described previously would introduce dangerous delays or could compromise the effectiveness of the testing. This process would delay not only the diagnosis and possibly lifesaving treatment of the subject, but would also delay recognition of a terrorism event or other public health emergency, with serious public health consequences.

To avoid potentially dangerous delays in using investigational in vitro diagnostic devices to identify these agents, FDA is creating a new limited exception, within the restrictions of section 520(g)(3)(D) of the act (21 U.S.C. 360j(g)(3)(D)), from the requirement of informed consent. The exception applies to investigational in vitro diagnostic tests used to identify agents, when a specimen is collected without the recognition that an investigational test will have to be used.

II. Current Exceptions From the General Requirements for Informed Consent

Two exceptions from the general requirements for informed consent are described in § 50.23. Section 50.23(a) provides that informed consent shall be deemed feasible unless, before use of the test article, both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following: The human subject is confronted by a

life-threatening situation necessitating the use of the test article; informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject; time is not sufficient to obtain consent from the subject's legally authorized representative; and there is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject. An inability to communicate in the context of § 50.23(a) means that the subject is in a coma or unconscious. (See 46 FR 8942 at 8946, January 27, 1981). Section 50.23(d) states that, under 10 U.S.C. 1107(f), the President may waive the prior informed consent requirement for the administration of an investigational new drug to armed forces personnel in connection with the personnel's participation in a particular military operation. The waiver is based on a finding by the President that obtaining consent is not feasible, is contrary to the best interests of the military personnel, or is not in the interests of national security (64 FR 54180, October 5, 1999). Currently FDA is re-examining this regulation in light of the recent amendment of 10 U.S.C. 1107 by the Ronald W. Reagan National Defense Authorization Act for Fiscal Year 2005 which changed the criteria that may be used by the President for waiving informed consent.

In addition, § 50.24 provides an exception from the informed consent requirements for emergency research. Section 50.24 is intended to permit the study of potential improvements in the treatment of life-threatening conditions where current treatment is unproven or unsatisfactory, in order to improve interventions and patient outcomes. The exception applies to limited research activities involving human subjects who are in need of emergency medical intervention, but cannot give informed consent because of their medical

condition. (See 61 FR 51498 at 51499, October 2, 1996.) Section 50.24 is intended to be used in circumstances that are different than those described in this rule, i.e., planned clinical research of a specific investigational article that will be studied in a specific class of patients.

The situation described in this document does not meet the requirements of the current exceptions from the general requirements for informed consent in § 50.23. It does not satisfy the requirements of § 50.23(a) because the subject may be physically able to provide informed consent. It does not satisfy the requirements of § 50.23(d) because that exception applies only to administration of investigational drugs to military personnel by DOD. In addition, Section 50.24 is generally not applicable because, in the situations addressed in that section, subjects are not able to consent because of their medical condition. In contrast, in the situations addressed in this document, it is not the condition of the subject that prevents the subject from giving informed consent, but rather the fact that, by the time it is known that the laboratory needs to use an investigational device to identify the etiological agent, the subject is physically separated from the specimen, and there is not enough time to locate the subject or the subject's legally authorized representative and obtain informed consent.

III. Revisions

FDA is creating a new exception from the general requirements for informed consent to address situations associated with preparing for, and responding 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.

This exception is contingent on several determinations that must be made before using the investigational device, and later certified in writing, by both the investigator and, if time permits, by a physician who is not otherwise participating in the clinical investigation. These determinations are:

- The human subject is confronted with a life-threatening situation necessitating the use of the investigational in vitro diagnostic device;
- Informed consent cannot be obtained from the subject because:
 1. There was no reasonable way for the person directing that the specimen be collected to know at the time the specimen was collected, that there would be a need to use the investigational device on that specimen and;
 2. Time is not sufficient to obtain consent from the subject without risking the life of the subject;
 - Time is not sufficient to obtain consent from the subject's legally authorized representative; and
 - There is no available alternative approved or cleared method of diagnosis to identify the chemical, biological, radiological, or nuclear agent that provides an equal or greater likelihood of saving the life of the subject.

Under this interim final rule, the investigator has 5 working days after using the investigational device to submit to the IRB these determinations as well as the review and evaluation of an independent licensed physician. However, if, in the opinion of the investigator, there is not sufficient time to obtain the determination of an independent licensed physician in advance of

using the investigational device, the independent physician is required to review and evaluate the determinations of the investigator and the investigator is required to submit this documentation to the IRB within 5 working days after using the device.

Until the investigational in vitro diagnostic device is used, it will not be known whether there has been actual exposure to a chemical, biological, radiological, or nuclear agent and whether that agent is life-threatening. Nonetheless, FDA believes the possibility of such exposure itself represents a life-threatening situation for the subject because, until the investigational in vitro diagnostic device is used, it is unknown to what agent, if any, the subject has been exposed or how the subject should be treated.

FDA expects that in accordance with routine clinical practice, the investigator will provide the test results obtained using the investigational in vitro diagnostic device to the subject's health care provider and that the results will be used in the clinical management of the human subject. It is possible that, in certain circumstances, the test results will also be reported to the appropriate public health authorities. This reporting will occur when appropriate and/or required by State or Federal law. Under the regulation, at the time the result of the test is reported (whether to the subject's health care provider and/or to the appropriate public health officials), the investigator is required to disclose the investigational status of the device used to perform the diagnostic test.

The investigator is also responsible for providing the IRB with the information required in § 50.25, the elements of informed consent, and the procedures that will be used to provide this information to each subject or

to the subject's legally authorized representative. Section 50.25(a) requires that the following information be provided to each subject:

- A statement that the study involves research and an explanation of its purposes and the expected duration of the subject's participation;
- A description of the procedures to be followed, and identification of any procedures which are experimental;
- A description of any reasonably foreseeable risks or discomforts to the subject;
- A description of any benefits to the subject or others which may be reasonably expected from the research;
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
- A statement of the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that FDA may inspect the records;
- For more than minimal risk research, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained; and
- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

Section 50.25(b) requires this additional information when it is appropriate:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- Any additional costs to the subject that may result from participation in the research;
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation; and
- The approximate number of subjects involved in the study. This information will be provided at the time the test results are sent to the subject's health care provider and to public health authorities, if public health reporting is required by Federal, State, or local law.

In this rule, we are requiring investigators to provide all information described in § 50.25 except the information in § 50.25(a)(8) concerning voluntary participation. Normally under the regulations subjects voluntarily agree to participate in research before the research begins. In the circumstances covered by this rule, an individual provides a specimen for diagnostic testing without the knowledge of either the patient or the physician that an investigational in vitro diagnostic (IVD) will be necessary. When the investigational IVD is used at a setting remote from the patient and treating physician in this case, it is not practicable (because of the time and distance involved to contact the patient or the patient's legally authorized representative) to obtain consent for the use of the device. Under this rule, by the time the patient is informed that an investigational device has been used to test his/her specimen, the investigation is already underway, and the

time at which a subject would normally consent to voluntary participation has past. Therefore, the investigator is not responsible for providing the information described in § 50.25(a)(8) concerning voluntary participation. In addition, subjects or their legally authorized representatives will not be entitled to withdraw previously collected data from the research database, because it is critical that FDA obtain and have available for review all data on the investigational in vitro diagnostic device's use in order to determine whether it is safe and effective. As a result, it is the responsibility of the IRB to ensure the adequacy of the information required in § 50.25 (except for the requirements under § 50.25(a)(8)) concerning voluntary participation) and to ensure that procedures for providing this information to the subject or the subject's legally authorized representative are in place. The IRB is responsible for this even if an exception under § 56.104(c) exists under which the emergency use of the test article would be reported to the IRB within 5 working days. We recognize that, in this situation, the IRB may be delayed in assuring that these procedures are in place.

IV. Applicability of 45 CFR Part 46 and Other Legal Requirements

According to the Office for Human Research Protection (OHRP) in the Department of Health and Human Services (HHS), some of the activities described in this rule may also constitute non-exempt human subjects research within the meaning of 45 CFR part 46. In particular, the use of the investigational in vitro diagnostic device on individually identifiable human specimens as described in this rule would not be human subjects research under 45 CFR part 46, while the analysis of the individually identifiable data obtained from the use of the investigational device to determine the safety and effectiveness of the device would be considered human subject research under

45 CFR part 46. If the analysis of individually identifiable data involves non-exempt human subjects research that is conducted or supported by HHS, the institution conducting the analysis must obtain an OHRP-approved assurance. In addition, this means that this research activity, if not exempt, i.e., the analysis of the individually identifiable data, must be reviewed prospectively by an IRB and must be conducted with the informed consent of the subjects unless waived. OHRP expects that IRBs will often find that informed consent may be waived under 45 CFR 46.116(d) for the analysis of the individually identifiable data obtained through the use of the investigational device. OHRP is issuing guidance regarding this issue simultaneously with the publication of this interim final rule which can be found at <http://www.hhs.gov/ohrp/policy/index.html>. Those interested in seeking additional information concerning the application of the regulations at 45 CFR part 46 should contact OHRP. We note that research conducted or supported by another department or agency may be subject to other laws and regulations. Sponsors should check to see if they are complying with all applicable requirements.

V. Legal Authority

FDA believes the statutory authority provided in section 520(g)(3)(D) of the act permits this limited exception to obtaining informed consent for the use of investigational in vitro diagnostic devices to identify chemical, biological, radiological, or nuclear agents in potential terrorism events or other potential public health emergencies. Section 520(g)(3)(D) of the act specifically states when an exception from informed consent is permissible. Under section 520(g)(3)(D) of the act, informed consent is required unless the investigator determines the following in writing: (1) There exists a life threatening situation involving the human subject of such testing which necessitates the use of such

device; (2) it is not feasible to obtain informed consent from the subject; and (3) there is not sufficient time to obtain such consent from the subject's legally authorized representative. Further, a licensed physician uninvolved in the testing must agree with this three-part determination in advance of using the device unless use of the device is required to save the life of the human subject of such testing, and there is not sufficient time to obtain such concurrence.

As noted earlier, FDA believes that, if the presence of an agent is suspected, there exists a life-threatening situation for the subjects whose specimens have been sent to laboratories. Until the laboratory identifies the agent to which the subject has been exposed or by which the subject has been infected, specific treatment cannot be provided. However, this limited exception applies only if it is also not feasible to obtain informed consent because there is an inability to communicate, in a timely manner, with the subject or the subject's legally authorized representative, and there was no reasonable way to know, at the time the specimen was collected, that there would be a need to use the investigational device on that specimen. In such a situation, the act would permit a limited exception to obtaining informed consent.

In accordance with section 521 of the act (21 U.S.C. 360k), state or local requirements that are different from, or in addition to, the requirements in this rule are expressly preempted. This rule establishes a new exception from the general requirements for informed consent, to permit the use of investigational in vitro diagnostic devices to identify chemical, biological, radiological, or nuclear agents without informed consent in certain circumstances. Consequently, State and local laws that require that informed consent be obtained in those situations are preempted.

VI. Issuance of an Interim Final Rule and Effective Date

FDA is proceeding without notice and comment rulemaking because the Nation needs to have this regulation in place immediately to be prepared to deal effectively with a terrorism event or other potential public health emergency. Under the provisions of the Administrative Procedure Act at 5 U.S.C. 553(b)(B), FDA finds for good cause that prior notice and comment on this rule are impracticable and contrary to the public interest. The absence of this exception was an impediment to the most efficient and effective public health response to the SARS outbreak. We do not want the absence of such an exception to be an impediment to our response to an outbreak of Avian flu or some other public health emergency. It is critical that FDA act quickly now to ensure that, in the future, individuals who may have been exposed to a chemical, biological, radiological, or nuclear agent have the benefit of the timely use of the most appropriate diagnostic devices, including those that are investigational. For the same reasons, the agency is making this interim final rule effective as of the date of publication.

VII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this interim final rule 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.

VIII. Analysis of Impacts

FDA has examined the impacts of this interim 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 (Public Law 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches

that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this rule is consistent with the regulatory philosophy and principles identified in the Executive order. In addition, the rule is not an economically 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 this interim final rule provides an exception from an otherwise applicable requirement for investigators, FDA believes that it does not impose a significant burden. The agency therefore certifies that this rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing "any rule that includes any Federal mandate that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this interim final rule to result in any 1-year expenditure that would meet or exceed this amount.

IX. Paperwork Reduction Act of 1995

This interim final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). The

information collection requirements for this interim final rule have been approved under the emergency processing provisions of the PRA. The assigned OMB approval number for this collection of information is 0910-0586. This approval expires on November 30, 2006.

A description of these provisions is given in the following paragraphs with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on the following topics: (1) Whether the collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Medical Devices: Informed Consent: Investigational In Vitro Diagnostic Device To Identify a Chemical, Biological, Radiological, or Nuclear Threat Agent

Description: This interim final rule amends FDA's informed consent regulation to provide an exception from the general requirement to obtain informed consent from the subject of an investigation involving an unapproved or not cleared in vitro diagnostic device intended to identify a chemical, biological, radiological, or nuclear agent. For the exception to apply, it is necessary for the investigator and an independent licensed physician to make the determination and certify in writing certain facts concerning the need for

use of the investigational in vitro diagnostic device without informed consent. The investigator submits this written certification to the IRB. When reporting the test results to the subject's health care provider and, possibly, to the appropriate public health authorities, the investigator must disclose the investigational status of the in vitro diagnostic device. The investigator must also provide the IRB with the information required in § 50.25 and the procedures that will be used to provide this information to each subject or the subject's legally authorized representative at the time the test results are provided to the subject's health care provider and possibly to the public health authorities.

Description of Respondents: Clinical laboratories, physicians.

FDA estimates the burden of the collection of information as follows:

TABLE 1.—ESTIMATED AVERAGE ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
50.23(e)(1) and (e)(2)	150	3	450	2	900
50.23(e)(4)	150	3	450	1	450
Total Hours					1,350

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

FDA is adding § 50.23(e)(1) to provide an exception to the general rule that informed consent is required for the use of an investigational in vitro diagnostic device for the purpose of preparing for and responding to a chemical, biological, radiological, or nuclear terrorism event or other public health emergency, if the investigator and an independent licensed physician make the determination and later certify in writing that: (1) There is a life-threatening situation necessitating the use of the investigational device; (2) obtaining informed consent from the subject is not feasible because there was no way to predict the need to use the investigational device when the specimen was collected, and there is not sufficient time to obtain consent from the

subject or the subject's legally authorized representative; and (3) no satisfactory alternative device is available. Under this interim final rule these determinations are made before the device is used, and the written certifications are made within 5 working days after the use of the device. If use of the device is necessary to preserve the life of the subject and there is not sufficient time to obtain the determination of the independent licensed physician in advance of using the investigational device, § 50.23(e)(2) provides that the certifications must be made within 5 working days of use of the device. In either case, the certifications are submitted to the IRB within 5 working days of the use of the device. From its knowledge of the industry, FDA estimates that there are approximately 150 laboratories that could perform this type of testing. FDA estimates that in the United States each year there are approximately 450 naturally occurring cases of diseases or conditions that are identified in CDC's list of category 'A' biological threat agents. The number of cases that would result from a terrorist event or other public health emergency is uncertain. Based on its knowledge of similar types of submissions, FDA estimates that it will take about 2 hours to prepare each certification.

Section 50.23(e)(4) provides that an investigator must disclose the investigational status of the device and what is known about the performance characteristics of the device at the time test results are reported to the subject's health care provider and public health authorities. Under this interim final rule, the investigator provides the IRB with the information required by § 50.25 and the procedures that will be used to provide this information to each subject or the subject's legally authorized representative. Based on its knowledge of similar types of submissions, FDA estimates that it will take about 1 hour to

prepare this information and submit it to the health care provider and, where appropriate, to public health authorities.

X. Federalism

FDA has analyzed this interim final rule in accordance with the principles set forth in Executive Order 13132 on Federalism (64 FR 43255, August 10, 1999). FDA has concluded that the rule raises federalism implications because, in accordance with section 521 of the act, this rule preempts State and local laws that require that informed consent be obtained before an investigational in vitro diagnostic device may be used to identify a chemical, biological, radiological, or nuclear agent in suspected terrorism events and other potential public health emergencies that are different from, or in addition to, the requirements of this regulation.

In accordance with the Executive order, preemption of State law is restricted to the minimum level necessary to achieve the objective of the statute to protect the public health by ensuring that individuals who may have been exposed to such an agent are able to benefit from the timely use of the most appropriate diagnostic devices, including those that are investigational. Also in accordance with the Executive order, officials at FDA consulted with the States on the effect of this rule on State law.

The new exception from informed consent is available in a very narrowly defined set of circumstances. Under these circumstances, a specimen already would have been taken from the individual. The individual would not be subjected to any further specimen collection or other procedure in order for the investigational device to be used on the specimen. In addition, in the circumstances in which the exception would apply, it is not only the health of the individual from whom the specimen was taken that would be at risk.

It is possible that other people, perhaps many other people, would have been exposed to the chemical, biological, radiological, or nuclear agent as well.

In conclusion, the agency believes that it has complied with all of the applicable requirements under Executive Order 13132 and has determined that this final rule is consistent with the Executive order.

XI. Civil Justice Reform

This rule has been reviewed under Executive Order 12988, Civil Justice Reform. This regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of Executive Order 12988.

XII. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this interim final rule. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

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 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 50.23 is amended by adding paragraph (e) to read as follows:

§ 50.23 Exception from general requirements.

(e)(1) Obtaining informed consent for investigational in vitro diagnostic devices used to identify chemical, biological, radiological, or nuclear agents will be deemed feasible unless, before use of the test article, both the investigator (e.g., clinical laboratory director or other responsible individual) and a physician who is not otherwise participating in the clinical investigation make the determinations and later certify in writing all of the following:

(i) The human subject is confronted by a life-threatening situation necessitating the use of the investigational in vitro diagnostic device to identify a chemical, biological, radiological, or nuclear agent that would suggest a terrorism event or other public health emergency.

(ii) Informed consent cannot be obtained from the subject because:

(A) There was no reasonable way for the person directing that the specimen be collected to know, at the time the specimen was collected, that there would be a need to use the investigational in vitro diagnostic device on that subject's specimen; and

(B) Time is not sufficient to obtain consent from the subject without risking the life of the subject.

(iii) Time is not sufficient to obtain consent from the subject's legally authorized representative.

(iv) There is no cleared or approved available alternative method of diagnosis, to identify the chemical, biological, radiological, or nuclear agent that provides an equal or greater likelihood of saving the life of the subject.

(2) If use of the investigational device is, in the opinion of the investigator (e.g., clinical laboratory director or other responsible person), required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (e)(1) of this section in advance of using the investigational device, the determinations of the investigator shall be made and, within 5 working days after the use of the device, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(3) The investigator must submit the documentation required in paragraph (e)(1) or (e)(2) of this section to the IRB within 5 working days after the use of the device.

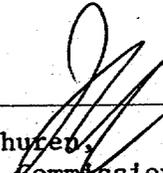
(4) An investigator must disclose the investigational status of the in vitro diagnostic device and what is known about the performance characteristics of the device in the report to the subject's health care provider and in any report to public health authorities. The investigator must provide the IRB with the information required in § 50.25 (except for the information described in § 50.25(a)(8)) and the procedures that will be used to provide this information to each subject or the subject's legally authorized representative at the time the test results are provided to the subject's health care provider and public health authorities.

(5) The IRB is responsible for ensuring the adequacy of the information required in section 50.25 (except for the information described in § 50.25(a)(8)) and for ensuring that procedures are in place to provide this information to each subject or the subject's legally authorized representative.

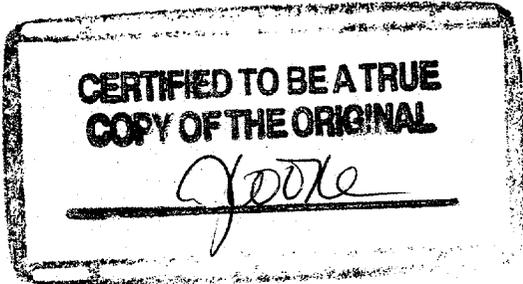
(6) No State or political subdivision of a State may establish or continue in effect any law, rule, regulation or other requirement that informed consent

be obtained before an investigational in vitro diagnostic device may be used to identify chemical, biological, radiological, or nuclear agent in suspected terrorism events and other potential public health emergencies that is different from, or in addition to, the requirements of this regulation.

Dated: 5/31/06
May 31, 2006.



Jeffrey Shuren,
Assistant Commissioner for Policy.



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