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# Regulatory Requirements for Clinical Studies of Medical Devices and Diagnostics

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## 1. Introduction

The investigational device exemption (IDE) provides an release for medical devices from various sections of the federal Food, Drug, and Cosmetic (FD&C) Act.[1] Without the exemption, medical devices would have to comply with performance standard, premarket approval, or notification requirements to be lawfully shipped and used for investigational purposes.[2] Furthermore, itwould be exceedingly difficult—if not impossible—to conduct clinical trials for devices to support premarket approval applications (PMAs) or 510(k) premarket notifications without violating the act, if the IDE did not exist. Indeed, according to Congress and the Food and Drug Administration (FDA), the twin objectives of the exemption are "to encourage discovery and development of useful devices for human use"[3] and "to protect the public health by requiring safeguards for human subjects of investigations, sound ethical standards, and procedures to assure development of reliable scientific data."[4]

### *1.1. Brief History of Clinical Trial Regulation of Devices*

The IDE was enacted as part of the Medical Device Amendments of 1976 ("the Amendments").[5] As the FDA had regulated the investigational use of new drugs and biologics for years,[6] it was widely recognized that the new framework for medical device regulation required a corresponding—if not equivalent—framework for controlling investigational devices. The statutory provision granting the exemption, which can be found in Section 520(g) of the FD&C Act,[7] expressly authorized the Secretary of what was then called the Department of Health, Education and Welfare to regulate the investigational use of medical devices.

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Notably, Section 520(g) required the agency to issue regulations within 120 days of the effective date of the 1976 Amendments.[8] These regulations are now found in 21 C.F.R. Part 812. Although the IDE regulations vary from the investigational new drug regulations, they are substantively similar in many respects.[9] One fundamental difference, however, is that Section 520(g) of the act expressly permits FDA to vary the procedures and conditions of the regulation of investigational devices based on the nature of the device, the scope and duration of the trial, the number of human subjects involved, the need for changes to be made in the device during the investigation, and whether the purpose of the data is to obtain approval to commercially distribute the device.[10]

### 1.2. Investigational Devices Subject to Regulation

Clinical investigations for most new devices or for new uses of devices are subject to the IDE regulations in 21 C.F.R. Part 812. However, FDA exempted clinical investigations for the following types of devices:[11]

1. Pre-1976 Amendment devices that currently are being investigated for the same indications that existed before the 1976 Amendments.
2. Post-1976 Amendment devices that are being investigated for purposes that have been cleared through the 510(k) premarket notification process.
3. Diagnostic devices that meet certain requirements.
4. Devices undergoing consumer preference testing and other similar types of testing if the testing is not used to determine safety and efficacy and does not put subjects at risk.
5. Devices intended solely for veterinary use.
6. Devices being tested solely on or with laboratory animals.
7. Custom devices.[12]

### 1.3. Structure of FDA Regulation of the Investigational Device Exemption

As mentioned, the IDE regulations permit sponsors to conduct clinical studies on new devices or new device indications to collect the requisite safety and efficacy data to support PMAs and, in some instances, 510(k) premarket notifications. The IDE regulations establish minimum requirements that must be met before an investigational device study begins. For example, the sponsor of any clinical device investigation must obtain approval from an Institutional Review Board (IRB) and informed consent from study subjects before the study begins.

If the investigational device poses a serious risk to the health, safety, or welfare of a subject (i.e., a significant risk [SR] device),[13] the sponsor also must obtain FDA's approval of the IDE application. The IDE application must contain information concerning the study's investigational plan, prior investigations, device manufacture, IRB actions, investigator agreements, the subjects' informed consent forms, device labeling, the cost of the device, and other

matters related to the study. FDA has 30 calendar days from the date it receives the application to approve or disapprove the application.[14]

## 2. Regulations Relating to People and Institutions Engaged in Clinical Trials

The FDA has promulgated a number of regulations delineating the responsibilities of the key players involved in clinical trials for devices (i.e., sponsors, investigators, IRBs).

### *2.1. Sponsors*

A *sponsor* is a person, an institution, or a company that initiates, but does not actually conduct, an investigation.[15] Importantly, a *sponsor* is distinct from a *sponsor-investigator*, who both initiates and actually conducts or oversees an investigation.[16] Sponsor-investigators must comply with FDA's regulations for both sponsors and investigators.

FDA's regulations provide that sponsors generally are responsible for the following: (1) selecting investigators (i.e., individuals who actually conduct an investigation),[17] (2) providing investigators with necessary information to conduct the investigation, (3) ensuring proper monitoring of the investigation, (4) ensuring that the IRB review and approval are obtained, (5) submitting an IDE application to FDA, and (6) ensuring that any reviewing IRB and FDA are promptly informed of any significant new information about an investigation.[18] Sponsors must also comply with the labeling, reporting, and record-keeping requirements established in 21 C.F.R. Part 812 and refrain from engaging in promotional activities and the other prohibited activities enumerated in 21 C.F.R. §812.7 (e.g., commercializing an investigational device).[19]

FDA regularly issues warning letters to sponsors who fail to comply with these general responsibilities. For example, on October 3, 2003, FDA sent a warning letter to an orthopedic device company that sponsored a device investigation regarding its failure to comply with its responsibilities in Part 812 of the regulations.[20] Among violations mentioned in the warning letter, the company failed to submit an IDE application, failed to ensure that investigators received IRB approval before use of the investigational device, and failed to ensure proper monitoring of the study. As a result, 31 devices (the name of which has been redacted from the warning letter) were implanted in research subjects without FDA and IRB approval. Of those 31 devices, 12 devices were implanted using a procedure or instrument that was not part of the investigational plan, and nine devices were implanted in patients not enrolled in the study. Moreover, the warning letter cited a number of additional deviations from the IDE regulations. This warning letter demonstrates how failure to comply with the IDE regulations can expose patients—even those not enrolled in the study—to uncontrolled situations that may present unnecessary risks.

**Table 1**
**Information Required for Transfer of Sponsorship**

| Minimum information required for transfer[a] |
|---|
| • Identification of the new sponsor (e.g., name, address, contact person, telephone number)<br>• Effective date of transfer<br>• Certification that all relevant records will be transferred to the new sponsor by the effective date of the transfer<br>• An agreement from the new sponsor, stating that the new sponsor will assume all sponsor responsibilities for the study<br>• An agreement from the new sponsor, stating that the new sponsor will comply with any terms or outstanding conditions of approval of the investigation |
| Additional information requested by FDA after transfer[a] |
| • A statement: that there are no changes in the investigation caused by the transfer or requesting specific approval for changes in the investigation that could affect the scientific soundness of the investigation or the rights, safety, and welfare of the subjects<br>• Acknowledgment that all investigators and associated IRBs will be informed of the sponsorship change by the effective date<br>• Certification that the new sponsor will not permit investigators to participate in the investigation until they have signed the investigator agreement. |

[a]*See id.*

### *2.1.1. Transfer of Sponsorship*

To transfer sponsorship to another person, a sponsor must submit a minimum amount of information in the form of an IDE supplement to FDA.[21] Once FDA has acknowledged the transfer, the agency must request additional information. To streamline the process, original and new sponsors may want to consider submitting the minimum information required for acknowledgement of the transfer and the information in response to the required follow-up questions in the initial IDE supplement notifying the agency of the transfer. Table 1 summarizes the information required for the transfer of sponsorship in the initial IDE supplement and in response to FDA's follow-up questions.

## *2.2. Investigators*

An *investigator* is an individual who actually conducts a clinical investigation (i.e., the person who directly oversees the administration of a device to a

test subject). In situations in which there is a team of researchers, the investigator is the team leader.[22]

An investigator's general responsibilities include:[23] (1) ensuring that an investigation is conducted in accordance with a signed agreement, the investigational plan, and FDA regulations, (2) protecting the rights, safety, and welfare of subjects under the investigator's care, (3) controlling devices under the investigation (e.g., supervising device use and disposal),[24] and (4) ensuring that informed consent is obtained from subjects.[25] Investigators, like sponsors, are also subject to certain record-keeping and reporting requirements.[26]

The FDA does not hesitate to issue warning letters to investigators who fail to comply with these general responsibilities. For example, on July 26, 2004, FDA sent a warning letter to an investigator, citing him for conducting an investigation that made numerous deviations from the study protocol, including failing to exclude subjects who did not meet study criteria; failing to measure body mass index, as required by the study protocol; and failing to perform follow-up visits in a timely manner, also as specified by the protocol.[27]

### *2.2.1. Financial Disclosure Requirements*

When reviewing studies included in marketing applications, the FDA may consider clinical studies inadequate if it determines that the studies are biased. Bias in clinical studies can arise if investigators have a financial interest in the outcome of the study, a proprietary interest in the product, or an equity interest in the sponsor of the study.[28]

Thus, the FDA requires all investigators to disclose accurate financial information to the sponsor, so that the sponsor is able to submit to the FDA either: (1) certification that no suspect financial arrangements (e.g., compensation affected by the outcome of the study, significant equity interest in the sponsor of the study, or a proprietary interest in the tested product) exist, or (2) a disclosure statement disclosing any suspect arrangements and the steps that have been taken to minimize bias.[29]

In addition, FDA requires all investigators to promptly update their financial information if any relevant changes occur during the course of the investigation.[30] FDA uses this financial information, along with information about the design and purpose of the study, to assess whether the data in the study is reliable.[31]

### *2.2.2. Disqualification of Investigator*

The FDA may initiate the process to disqualify investigators and render them ineligible to receive investigational devices if it has information that: (1) the investigator has deliberately failed to comply with regulations governing IDEs,[32] protection of human subjects,[33] or IRBs;[34] or (2) the investigator has

repeatedly or deliberately submitted false information either to the sponsor of the investigation or in any required report.[35]

Once the FDA has received such information, the Center for Devices and Radiological Health (CDRH) will give the investigator written notice of the matter and offer the investigator an opportunity to explain it in an informal conference. If the CDRH accepts the explanation, it will stop the disqualification process; however, if CDRH does not accept the explanation, it will give the investigator an opportunity for a formal hearing on whether the investigator should be entitled to receive investigational devices.

If the process progresses to a formal hearing, the FDA Commissioner will consider all available evidence on the matter. If the commissioner then determines that the investigator should be disqualified, he or she notifies the investigator, the sponsor of any study in which the investigator is a participant, and the IRB that the investigator is not entitled to receive investigational devices.

Notably, the FDA rarely disqualifies investigators. In fact, from 1966 through June 2004, the FDA's list of disqualified investigators shows that only about 95 clinical investigators have been disqualified based on their investigations of drugs, biologics, and medical devices. Of the 95 disqualified investigators on FDA's list, only one was investigating medical devices.[36]

### *2.3. Institutional Review Boards*

An *IRB* is any board, committee, or other group formally designated by an institution to review biomedical research involving human subjects,[37] and it serves an important role in safeguarding the health and welfare of the subjects.

Under the FDA regulations, IRBs must review investigations, and continually monitor them throughout the length of the study.[38] IRBs also have the authority to approve, disapprove, or require modification of investigations.[39] IRBs typically use a group process to review investigation protocols and related materials, such as informed consent documents.

Notably, most established research institutions have an IRB and/or established researchers that are affiliated with a certain IRB; however, in the absence of an IRB affiliated with an institution or a researcher, independent IRBs can be contracted to act as an IRB for a given investigation or IRBs can be established in accordance with 21 C.F.R. Part 56. The FDA regulations set forth specific organization and membership requirements as well as requirements relating to review procedures, approval criteria, and record-keeping requirements.[40]

## 3. Pre-Investigation Device Exemption Process

FDA's Office of Device Evaluation (ODE) reviews IDE applications. FDA generally encourages applicants to begin communicating with the ODE before they submit an original IDE application via a pre-IDE meeting and/or a pre-IDE

submission.[41] Pre-IDE meetings are beneficial for the ODE reviewing division and the applicant because they increase the applicant's familiarity with the review process, increase the ODE's familiarity with the technology at issue, expedite the regulatory process, and minimize delays.

### 3.1. Pre-Investigational Device Exemption Meetings

The FDA encourages applicants to contact the FDA for a pre-IDE meeting before they submit their IDE application. Pre-IDE meetings are particularly beneficial for applicants who do not have previous experience with the agency and for those who are planning to study new technologies or new uses for existing technologies.

#### 3.1.1. Informal Guidance Meetings

Informal guidance meetings provide applicants with the opportunity to meet with the ODE reviewing division before they submit an IDE application.[42] Typically, the meetings serve as forums for the reviewers to provide advice regarding the development of pre-clinical data that would support an IDE application or the development of an investigational plan for the IDE application.

These meetings may be conducted via telephone, videoconference, or in person. During the meeting, the ODE reviewing division is responsible for recording the meeting. The minutes from the meeting generally include: (1) the date of the meeting, (2) the attendees, (3) whether material was submitted before the meeting for discussion or review, (4) a summary of the discussion, and (5) all of the ODE's recommendations for the sponsor. Applicants may schedule informal guidance meetings simply by contacting the ODE reviewing division or the IDE staff.

#### 3.1.2. Formal Guidance Meetings

The Food and Drug Modernization Act of 1997 expressly provided for two types of formal pre-IDE meetings to provide applicants with clear direction on the testing and development of devices requiring clinical investigations: *determination meetings* and *agreement meetings*.[43]

The main objective of a determination meeting is to provide anyone submitting a PMA or a product development protocol[44] with a determination regarding the type of valid scientific evidence that will be necessary to demonstrate that the device is effective for its intended use. Typically, determination meetings focus on deciding whether clinical studies are necessary to establish effectiveness. The meetings also focus on developing a broad outline of a clinical trial design that represents the least burdensome method of evaluating device efficacy and has a reasonable likelihood of success.[45] By statute, the FDA is required to provide a determination to the applicant in writing within 30 days

following the meeting[46] and the determinations are binding.[47] Applicants should submit requests for determinations in the form of a pre-IDE submission and identify the request as a "determination meeting request."[48]

The main objective of the agreement meeting is to establish the parameters of the investigational plan for the device, including the clinical protocol. Investigational plans include a written protocol describing the trial methodology, a risk analysis, and monitoring procedures.[49] Applicants should submit requests for agreement meetings in the form of a pre-IDE submission and identify them as an "agreement meeting request."[50] By statute, FDA must meet with the applicant no later than 30 days after receipt of the request. The written request should include: (1) a detailed description of the device, (2) a detailed description of the proposed conditions of use of the device, (3) a proposed plan (including a clinical protocol) for determining whether there is a reasonable assurance of effectiveness, and, if available, (4) information regarding the expected performance of the device.[51] Agreements reached during these meetings are binding, and the agreements, which must be put in writing, become part of the administrative record.[52]

### *3.2. Pre-Investigation Device Exemption Submissions*

In addition to informal and formal guidance meetings, sponsors may submit pre-IDE submissions to the ODE reviewing division if they would like informal guidance on certain parts of the IDE application (e.g., clinical protocol design, the preclinical testing proposal, preclinical test results, protocols for foreign studies used to support the FDA marketing applications). Pre-IDE submissions must be clearly identified as such and submitted in duplicate.

Once the FDA receives pre-IDE submissions, it logs them in its pre-IDE tracking system, where they are attached to a tracking sheet. The submission is then forwarded to the appropriate review division, which will send an acknowledgment letter to the sponsor. The review division must then issue a response via a letter, a meeting, or a telephone call to the sponsor within 60 days of receiving the submission. If the response is issued during a meeting or a telephone call, the division must prepare a memorandum memorializing the conversation.

## 4. Investigational Device Exemption Application

A study sponsor must have an approved IDE application before it can conduct clinical studies on an investigational device, which may be subject to certain exemptions (e.g., certain diagnostic devices, devices intended solely for veterinary use).[53] Furthermore, clinical investigations are subject to different levels of regulation, depending on the level of risk.

**Table 2**
**Examples of Significant Risk and Nonsignficant Risk Devices**

| Significant risk devices[a] | Nonsignificant risk devices[b] |
|---|---|
| Cardiac pacemakers | Daily wear contact lenses and solution |
| Orthopedic implants | Ultrasonic dental scalers |
| Sutures | Foley catheters |
| Hydrocephalus shunts | Denture repair kits |
| Respiratory ventilators | External insulin monitors |

[a]*See* Information Sheets. Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update. Available from: www.fda.gov/oc/ohrt/irbs/devices.html#risk;[b] *see also* Device Advice. Clinical Trial and IDE. Approval Process. Available from: www.fda.gov/cdrh/devadvice/ide/approval.shtml.

### *4.1. Significant Risk Devices vs Nonsignificant Risk Devices*

There are two paths to obtaining an IDE approval, depending on whether the product is an SR device or nonsignificant risk (NSR) device (*see* Table 2).[54] An SR device poses serious risk to the health, safety, or welfare of a subject.[55] An investigational device should be classified as an SR device if its studies pose life-threatening harm, could cause permanent physical damage or impairment, or would require medical intervention to prevent such damage.[56] An NSR device is any device that does not meet the SR definition.[57]

The determination of whether a device is SR or NSR has important implications for both research sponsors and regulators because SR device studies are subject to more stringent regulatory requirements.[58] SR and NSR device procedures differ primarily in the approval process as well as in record-keeping and reporting requirements.[59] If a sponsor determines that an investigational product is an SR device, the clinical investigation cannot begin until FDA approves the IDE application and the IRB approves the study.[60] Furthermore, the study sponsor and investigators for an SR device must comply with the full list of IDE requirements in 21 C.F.R. Part 812.[61]

In contrast, the FDA established the NSR device category to "avoid delay and expense where the anticipated risk to human subjects [does] not justify the [agency's] involvement."[62] As a result, an NSR device sponsor follows abbreviated IDE regulation requirements.[63] For instance, the FDA does not require an IDE application for an NSR device study, and the sponsor need only obtain approval from an IRB, not from the FDA. The IRB serves as FDA's proxy for the NSR review and approval process.[64]

FDA considers an NSR device study to have an approved IDE application if the sponsor complies with the abbreviated requirements,[65] and the sponsor may begin clinical trials once the IRB approves its study.[66] If the sponsor believes that the device it is studying is an NSR, it must explain this finding to the reviewing IRB and include other information that will help the IRB assess any risk posed by the investigation.[67] If the IRB agrees with the sponsor's NSR determination and approves the study, the sponsor may begin clinical trials immediately without submitting an IDE application to the FDA;[68] however, if the IRB concludes that the device poses a significant risk, the sponsor cannot begin investigating the device until it has received the agency's approval.[69]

### 4.2. Nonsignificant Risk Devices: Abbreviated Requirements

When an investigational device is designated as an NSR device, the sponsor participates in a streamlined approval and application process. In addition to bypassing FDA review of the device study, the sponsor of an NSR device is also subject to less stringent IDE regulations.[70] Section 812.2(b) of the FDA's IDE regulations outlines the abbreviated IDE requirements for an NSR device investigation.[71]

The abbreviated IDE regulations merely require the sponsor to: (1) label the NSR device in accordance with the regulations,[72] (2) obtain the reviewing IRB's approval for the NSR device study (and maintain that approval for the study's duration), (3) ensure that each investigator obtains and documents participating subjects' informed consent, (4) monitor the investigation to protect subjects and ensure compliance, (5) maintain certain records and make certain reports,[73] (6) ensure that participating investigators maintain certain records and make certain reports,[74] and (7) comply with the prohibitions against commercialization, promotion, and test marketing, among other things, in 21 C.F.R. §812.7.

### 4.3. Significant Risk Devices: Application Requirements

Once a device has been designated an SR device, its sponsor must comply with all the IDE regulations in 21 C.F.R. Part 812, including the application requirements. Section 812.20 of the IDE regulations provides a detailed list of the information a sponsor must include in the IDE application.[75]

As specified by the IDE regulations, the sponsor of an SR device study must provide the following information for the IDE application, in the following order:[76]

1. The sponsor's name and address.
2. A comprehensive report of previous investigations for the device and a complete investigational plan.[77]

3. A detailed description of the methods, facilities, and controls used for the device's manufacture, processing, packing, storage, and installation.
4. An example of the agreements that the investigators will sign to comply with their regulatory obligations, and a complete list of the names and addresses of the investigators who signed the agreement.[78]
5. A certification that all participating investigators have signed the agreement and that no investigator will be added without signing the agreement.
6. A list of the names, addresses, and chairpersons of each IRB that has been—or will be—asked to review the investigation, as well as a certification concerning each IRB's action in the investigation.
7. The name and address of any institution where part of the investigation may occur that has not yet been identified.
8. If the device will be sold, the price of the device and an explanation of why the sale does not qualify as commercialization.
9. An environmental assessment or a claim for categorical exemption from the requirement.
10. Copies of all labeling for the device.
11. Copies of all informed consent forms and informational materials that will be given to study subjects.
12. Any other relevant information that FDA requests to review the IDE application.[79]

Notably, the FDA provides an administrative checklist that sponsors can use to ensure that their applications are complete. It is available from www.fda.gov/cdrh/devadvice/ide/application.shtml#modifications. Once the sponsor of an SR device study is sure that the application is complete, it must submit three copies of the signed IDE application and a cover letter to the FDA.[80]

### *4.4. Modifications to Investigation Device Exemption Applications*

Although sponsors of SR device studies can make some modifications to IDE applications without prior approval, any changes to the investigational plan affecting the study design's scientific soundness or data validity require regulatory review.[81] Before making such a change to the investigational plan, the sponsor must submit a supplemental IDE application to FDA and obtain IRB approval.[82] Investigational plan modifications requiring a supplemental IDE include:

1. A change in indication.[83]
2. A change in type or nature of study control.[84]
3. A change in primary endpoint.[85]
4. A change in the method of statistical evaluation.[86]
5. Early termination of the study.[87]
6. Increasing the number of study subjects.[88]
7. Increasing the number of investigational sites.[89]

Under certain circumstances, a sponsor may modify a device or the investigational study without submitting a supplemental IDE application, but the FDA must be notified of the change within 5 working days.[90] For instance, if the sponsor departs from investigational protocol for emergency use (i.e., to protect the subject's life or welfare), it does not need FDA approval before implementing the change.[91] Similarly, notice of 5 working days is sufficient for developmental changes that do not significantly alter the device's design or operation and for certain changes to clinical protocol, as long as the protocol changes do not affect the data validity, information on the approved protocol, or the risk/benefit ratio for subjects; the investigational plan's scientific soundness, or the study subjects' rights, safety, or welfare.[92] Notably, the changes to the development and protocol have to meet the exceptions for submitting a supplemental IDE application on the basis of "credible information," which is specifically defined in the regulations.[93]

Notably, for extremely minor changes, sponsors need not submit an IDE supplement or provide the agency with 5 day notice. Sponsors need only report changes in the annual progress report if the changes are in the following areas:

1. The purpose of the study.
2. Risk analysis.
3. Monitoring procedures.
4. Labeling.
5. Informed consent materials.
6. IRB information, if the changes do not affect the data validity, information on the approved protocol, or the risk–benefit ratio for subjects; the investigational plan's scientific soundness; or the study subjects' rights, safety, or welfare.[94]

### 4.5. Disapproval or Withdrawal of Approval of Investigation Device Exemption Applications

The FDA can approve an IDE application as submitted or with modification, or it can disapprove or even withdraw approval of an IDE application.[95] The IDE regulations list the various grounds for IDE disapproval or withdrawal.[96] The FDA may disapprove or withdraw an IDE application if:

1. The sponsor has not complied with the applicable IDE regulatory requirements, statutes or regulations, or any condition imposed by the IRB or the FDA.
2. The application or report contains false statements or misleading information.
3. The sponsor does not respond to the FDA's request for additional information in a timely fashion.
4. The benefits of the study or its importance do not outweigh the risks, informed consent is inadequate, the investigation is scientifically unsound, or the device is used ineffectively.

5. It is unreasonable to begin or continue the investigation because of how the device is used.
6. There is an inadequacy in the investigational plan; the methods, facilities, and controls used to manufacture, process, package, store, and install the device; or the monitoring of the investigation.[97]

Both a disapproval order and a proposed withdrawal of approval of an IDE application must state the reasons for disapproval or withdrawal, and they must give the sponsor notice that it has the opportunity to request a hearing,[98] although the FDA should communicate with the sponsor in other manners before issuing a proposed withdrawal.[99] For instance, the ODE should send correspondence to the sponsor stating its concerns and referencing the basis for its concerns.[100] If the ODE believes that a meeting may alleviate its concerns, it may request a meeting with the sponsor.[101] Under certain circumstances, the Office of Compliance (OC) should send warning letters specifying any issues that need to be addressed.[102]

### *4.6. Closing an Investigation Device Exemption*

The complexity of closing procedures depends on when the sponsor decides to close the IDE.[103] If the decision comes early in the IDE process, the sponsor has fewer requirements to satisfy. For example, if the FDA has not yet approved the IDE, the sponsor can simply request to withdraw the IDE application.[104] Moreover, even if the FDA has already approved the IDE application, the sponsor may still request withdrawal if it has not yet enrolled any subjects.[105]

Once a sponsor has enrolled subjects in a study, the sponsor must conform to stricter requirements. Although the sponsor can stop enrolling subjects in the study at this stage, the sponsor must follow-up with all enrolled subjects in accordance with the investigational plan before closing the IDE.[106] The IDE is not officially closed until the sponsor has followed up with all study subjects and has submitted a final report to the FDA and the reviewing IRBs within 6 months thereafter.[107]

## 5. Investigation Device Exemption Study Requirements

After the necessary approval for the IDE application is obtained, clinical studies authorized under the application must be conducted in accordance with the requirements and regulations collectively referred to as Good Clinical Practices (GCPs). The GCPs require, among other things, oversight by an IRB (*see* Section 2.3), informed consent, and monitoring of the clinical study as well as submission of reports and records maintenance. Additionally, during the clinical studies, certain behavior, such as promotion or commercialization of the investigational device, is prohibited.

### 5.1. Informed Consent

Generally, investigators must obtain a written informed consent form from the patient or the patient's representative before the patient participates in a clinical study under an IDE application.[108] Because the FDA established the informed consent regulations in part to protect patients, the regulations require informed consents to contain adequate information in understandable language to allow patients to determine whether to participate in the study. They also require that the patients have adequate time to consider participation in the study, to minimize the possibility of coercion or undue influence. In addition, they prohibit exculpatory language that in any way appears to require the patient to waive any legal rights or release the investigator, sponsor, or institution from liability for negligence.

The following basic elements must be included in the informed consent:[109]

1. A study summary (i.e., a statement that the study involves research, an explanation of the purposes of the research, a statement regarding the expected duration of the subject's participation, and a description of the procedures to be followed and identification of any procedures that are experimental).
2. A description of any reasonably foreseeable risks or discomfort to the patient.
3. A description of any benefits to the subject or to others that may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. 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 FDA may inspect the records.
6. For research involving more than minimal risk, an explanation regarding any compensation and whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
7. 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.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits.

The informed consent form must also include any of the following provisions, as appropriate:[110]

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

2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research that may be related to the subject's willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.

As part of the IDE process, the FDA must review and approve sample informed consent documents to ensure that they contain the necessary information. The IRB must also review the documents and may modify the language and format to be consistent with the institution's policies and requirements. The informed consent form must be signed by the patient (or legal representative) and maintained by the clinical investigator, and a copy must be given to the patient.

Importantly, the FDA will issue warning letters to investigators who fail to comply with the informed consent regulations. For example, on July 30, 2003, the FDA sent a warning letter to an investigator who failed to include several basic elements in his informed consent forms, such as the expected duration of the study and an identification of the procedures that were experimental.[111] The letter also cited the investigator for failing to obtain signed and dated copies of the informed consent forms and for not providing the person signing the consent form with a copy of the form. According to the letter, all of the informed consent forms were signed by the investigator and/or a witness who had read the forms to the subjects over the telephone—which was insufficient to meet the requirements of the informed consent regulations.

### *5.2. Exception to Informed Consent: Emergency Research*

The FDA provides exceptions to the informed consent requirements,[112] including an exception for emergency research.[113] The exception for emergency research addresses circumstances in which the human subject is in a life-threatening situation[114] and it is not feasible to obtain informed consent.[115] The emergency research exception is appropriate only if:[116]

1. Participation in the research holds out the prospects of direct benefit to the subjects (for the reasons enumerated in the regulations).[117]
2. The clinical investigation could not practicably be carried out without the waiver.[118]

3. The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence.[119]
4. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with the elements of informed consent.[120]
5. Additional protections of the rights and welfare of the subjects will be provided, including the minimum protections enumerated in Section 50.24(a)(7) of the regulations.[121]

### 5.3. Monitoring Clinical Investigations

Under the IDE regulations, sponsors are responsible for ensuring that clinical investigations are appropriately monitored.[122] Accordingly, the regulations require sponsors to identify the name and address of a monitor who has appropriate training and experience.[123] Notably, the FDA's published guidelines on acceptable monitoring approaches[124] require that sponsors provide written monitoring procedures for all studies involving more than one investigator.

Sponsors are also responsible for securing compliance with the signed agreement, the investigational plan, the IDE regulations, and other conditions imposed by the FDA or an IRB. Sponsors who discover that an investigator is not complying must discontinue shipments of the device to the investigator promptly and terminate the investigator's participation in the study. Sponsors must also require the investigator to return or otherwise dispose of the device, unless it would jeopardize a research subject.[125]

Sponsors who fail to secure compliance are subject to warning letters. For instance, the FDA sent Silimed, Inc., a warning letter on August 21, 2003. The agency cited Silimed for failing to document that the occurrence of a study initiation visit, which was needed ensure that investigators were complying with the regulations and study protocol, in accordance with the IDE monitoring plan.[126]

The regulations also require sponsors to immediately conduct evaluations of any unanticipated adverse effect of a device. If the sponsor determines that the device presents an unreasonable risk to research subjects, the sponsor must terminate all investigations (or the parts of the investigations that present the risk) immediately (i.e., not later than 5 working days after the sponsor makes the determination and not later than 15 working days after the sponsor receives notice of the effect).[127] If the study is terminated because the sponsor has determined that the device presents an unreasonable risk, the sponsor cannot resume the investigation without express approval of the FDA and IRB(s), regardless of whether the study involves an SR or NSR device.[128]

### 5.4. Records and Reports

During the IDE study, sponsors and investigators have significant responsibilities to maintain accurate, complete, and current records and to make timely required reports. Record-keeping responsibilities for sponsors and investiga-

**Table 3**
**Record-Keeping Requirements for Sponsors[a]**

| SR devices |
|---|
| • All correspondence with another sponsor, an investigator, a monitor, an IRB, and the FDA, including required reports<br>• Shipment records, including name and address of consignee, type and quantity of the device, date of shipment, and batch number or code<br>• Disposition records, such as batch number or code of any devices returned to the sponsor and devices repaired or disposed of in other ways and reason for the method of disposal<br>• Signed investigator agreements including financial disclosure information<br>• Records concerning complaints and adverse effects, regardless of whether they are anticipated<br>• Any other records that the FDA requires to be maintained by regulation or specific requirement for a category of investigation or a particular investigation |
| **NSR devices** |
| • Records concerning the following: (1) name and intended use of the device; (2) objectives of the investigation; (3) a brief explanation of why the device is not an SR device; (4) name and address of each investigator; (5) name and address of each IRB; and (6) statement of the extent to which the good manufacturing practices will be followed in manufacturing the device<br>• Records concerning complaints and adverse device effects, regardless of whether they are anticipated |

[a]*See id.* §812.140.

SR, significant risk; NSR, nonsignificant risk; IRB, Institutional Review Board; FDA, Food and Drug Administration.

tors vary depending on whether the device being investigated presents a significant risk or a nonsignificant risk (*see* Tables 3 and 4).

The FDA regularly issues sponsors warning letters record-keeping violations. For example, on August 30, 2000, the FDA sent a warning letter to Paradigm Medical Industries, Inc., citing the company for failure to maintain financial disclosure information for investigators and records of correspondence with investigators, monitors, and IRBs.[129] Regarding records of correspondence, the FDA found that the company had no documentation showing that the sites were sent revised protocols and given permission to deviate from the protocol requirement of using independent laboratories to perform certain functions. Moreover, the FDA found that there were no copies of progress reports from the investigational sites and no records to show when the data was received from the sites and entered into the database.

**Table 4**
**Record-Keeping Requirements for Investigators[a]**

| SR devices |
|---|
| • All correspondence, including required reports, with another investigator, an IRB, the sponsor, a monitor, or the FDA<br>• Records of receipt, use, or disposition of the investigational device, including type and quantity of device; date of receipt; batch number or code; name of person who received, used, or disposed of each device; and why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of<br>• Records of each subject's case history and exposure to the device, including signed and dated consent forms, condition of each subject upon entering the study, relevant previous medical history, record of the exposure to the investigational device (date and time of each use), observations of adverse device effects, medical records, results of diagnostic tests, case report forms, and any other supporting information<br>• Protocol and documentation (date and reason) for each deviation from the protocol<br>• Any other records that the FDA requires to be maintained by regulation or specific requirement for a category of investigation or a particular investigation |
| NSR devices |
| • Records of each subject's case history and records of exposure to the device. Such records must include documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual must document that informed consent was obtained prior to participation in the study |

[a]21 C.F.R. §812.140.
SR, significant risk; NSR, nonsignificant risk; IRB, Institutional Review Board; FDA, Food and Drug Administration.

The FDA takes all record-keeping requirements for investigators seriously and regularly issues warning letters to those who fail to comply. For example, on Nov. 7, 2003, the FDA sent a warning letter to an investigator, noting that the investigator had failed to maintain records of receipt and disposition of the investigational devices as well as each subject's case history and exposure to the device, including pre- and postoperative X-ray reports, X-ray reports for 6- and 12-month study visits, and a signed and dated informed consent form for one subject.[130]

### 5.4.1. Maintenance of Records

Sponsors and investigators must maintain the required records for 2 years after the date the investigation is completed or terminated or until the records are no longer required to support a PMA or product development protocol, whichever date is later.[131] However, an investigator or sponsor may transfer custody of the records to another person to maintain them during that period.[132] Investigators or sponsors who transfer custody of the records to another person must notify the FDA within 10 working days after the transfer occurs.

Sponsors, IRBs, and investigators are required to permit authorized FDA employees reasonable access at reasonable times to inspect and copy all investigation records.[133] After giving notice, FDA may inspect and copy records that identify subjects. FDA has authority to inspect facilities at which investigational devices are being held, including any establishments where devices are manufactured, packed, installed, used, or implanted.

### 5.4.2. Sponsor and Investigator Reports to FDA

To keep the FDA and/or IRBs up to date with the progress of the clinical study, the sponsor and investigators are responsible for submitting reports and notifications on various aspects of the study.[134] Table 5 lists the required reports and notifications.

## 5.5. Prohibitions of Promotion and Other Practices

The IDE regulations prohibit the promotion and commercialization of an SR or NSR device that has not been cleared or approved for marketing by FDA.[135] This prohibition applies to sponsors and investigators (or any person acting on behalf of a sponsor or investigator). These individuals may *not*: (1) promote or test market an investigational device; (2) charge subjects or investigators for the device a price larger than is necessary to recover the manufacturing, research, development, and handling costs; (3) prolong an investigation beyond the point needed to collect data required to determine whether the device is safe and effective; or (4) represent that the device is safe or effective for the purposes for which it is being investigated.

Importantly, the prohibition against promotion does not proscribe efforts to publicize an investigational device for the purpose of obtaining clinical investigators or subjects to participate in a clinical study. The FDA has published a guidance document providing the parameters for solicitations that is intended to ensure that such recruitments efforts are bona fide.[136]

The FDA monitors solicitation efforts and issues warning letters to individuals who do not comply with its regulations. On January 25, 2001, the FDA issued a warning letter to a device manufacturer for making particularly blatant

**Table 5**
**Sponsor/Investigator Reports and Notifications[a,b]**

| Sponsor |
|---|
| • *Unanticipated adverse device effects*: The sponsor must report the results of an evaluation of an unanticipated adverse device effect to the FDA, all reviewing IRBs, and investigators within 10 working days after the sponsor first receives notice of the adverse effect[c] |
| • *Withdrawal of IRB approval*: The sponsor must notify the FDA, all reviewing IRBs, and participating investigators of the withdrawal of IRB approval of an investigation (or any part of an investigation) within 5 working days of receipt of the withdrawal of approval[c] |
| • *Withdrawal of FDA approval*: The sponsor must notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval within 5 working days after receipt of the notice[c] |
| • *Current list of investigators*: Every 6 months the sponsor must submit to the FDA a current list of the names and addresses of all investigators participating in an SR device investigation |
| • *Progress reports (or annual reports)*: At regular intervals and at least yearly, the sponsor must provide progress reports to all reviewing IRBs. For an SR device, the sponsor must also submit the progress report to the FDA[c] |
| • *Recalls and device disposition*: The sponsor must notify the FDA and all reviewing IRBs of any request that an investigator return, repair, or dispose of any unit of an investigational device. The notice must be made within 30 working days after the request is made and must state why the request was made[c] |
| • *Final report*: For an SR device, the sponsor must notify FDA and all reviewing IRBs within 30 working days of the completion or termination of the investigation. The sponsor must also submit a final report to the FDA, all reviewing IRBs, and participating investigators within 6 months after the completion or termination of the investigation. For an NSR device, the sponsor must submit a final report to all reviewing IRBs within 6 months after completion or termination[c] |
| • *Informed consent*: Sponsors must submit a copy of any investigator's report of the device's use without first obtaining informed consent. The report must be made to FDA within 5 working days after receipt of the notice of such use[c] |
| • *SR device determination*: If an IRB determines that the device is an SR device and not an NSR device as the sponsor had proposed to the IRB, a report must be submitted to FDA within 5 working days after the sponsor learns of the IRB's determination[c] |
| • *Other reports*: The sponsor must provide accurate, complete, and current information about any aspect of the investigation on request from the reviewing IRB or FDA[c] |

*(continued)*

**Table 5 (Continued)**

| Investigator |
|---|
| • *Unanticipated adverse device effects*: The investigator must submit to the sponsor and the reviewing IRB a report of any unanticipated adverse device effect as soon as possible, but no later than 10 working days, after the investigator first learns of the effect[c] |
| • *Withdrawal of IRB approval*: The investigator must report to the sponsor a withdrawal of approval of the reviewing IRB within 5 working days[c] |
| • *Progress reports*: The investigator must submit progress reports to the sponsor, the monitor, and the reviewing IRB at regular intervals but no less than on a yearly basis |
| • *Deviations from the investigational plan*: The investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. The notice must be provided as soon as possible but no later than 5 working days after the emergency occurred. If it is not an emergency, prior approval from the sponsor is required for changes in or deviations from the investigational plan. If the change or deviation may affect the scientific soundness of the investigational plan or the rights, safety, or welfare of the subject, the sponsor is required to obtain prior IRB approval and obtain FDA approval for an SR device investigation by submitting a supplemental application |
| • *Informed consent*: If an investigator uses a device without obtaining informed consent, he or she must report the use to the sponsor and the reviewing IRB within 5 working days after the use occurs[c] |
| • *Final report*: The investigator must submit a final report to the sponsor and to the reviewing IRB within 3 months after termination or completion of the investigation |
| • *Other reports*: The investigator must provide accurate, complete, and current information about any aspect of the investigation on request from the reviewing IRB or FDA |

[a]*See id.* §812.150(b).
[b]*See id.* §812.150(a).
[c]These reports and notifications are required for NSR devices as well as SR devices.
FDA, Food and Drug Administration; IRB, Institutional Review Board; SR, significant risk; NSR, nonsignificant risk.

claims that a particular device was safe and effective for the purpose for which it was being investigated.[137] In that case, the company claimed in a brochure that the device was able to "alleviate a wide variety of illnesses: neurodegenerative diseases like Alzheimer's, multiple sclerosis, and Parkinson's; cerebral palsy, autism, and epilepsy; and migraine headaches" during studies at multiple clinical facilities in the United States and Europe. The company also claimed that the

FDA had determined that the devices generally presented "no significant risk," despite the fact that the FDA's determination of NSR applied only when the device was used to treat a certain disease. In addition, the company's advertisements to recruit subjects expressly stated that the treatment was safe.

## 6. Patient Access to Unapproved Medical Devices

Typically, a patient cannot access a medical device that has not been approved or cleared with a PMA or a 510(k), unless the device has an approved IDE application and the patient meets the criteria to participate in the clinical trials for the device.[138] In certain instances, however, physicians may wish to use unapproved devices to save a patient's life or to help a patient who is suffering from a serious disease or condition for which there is no alternative approved therapy. FDA regulations and guidance documents provide the following exceptions to the typical IDE and device approval requirements: (1) emergency use, (2) compassionate use, (3) treatment use, and (4) continued access during PMA preparation and review.

These exceptions can provide patients crucial access during different, although sometimes overlapping, periods of device development. Table 6 summarizes the criteria for each exception, the period during which each exception may be used, and whether the exception requires prior FDA approval. In addition, more detailed discussions of each exception follow.

### *6.1. Emergency Use*

The need for emergency use of an unapproved device may arise any time before or after the initiation of a clinical trial, when an IDE does not exist, when the physician wants to use the device in a way that is outside the scope of the IDE, or when the physician is not a part of the clinical study.[139] The FDA will permit such use, as long as three criteria are met: (1) the patient has a life-threatening condition that needs immediate treatment, (2) there is no alternative treatment, and (3) there is no time to obtain FDA approval.[140]

Of note, physicians who have patients who are potential candidates for emergency use can contact the ODE to discuss a patient's condition, and the ODE may act in an advisory capacity. However, the final decision of whether a situation warrants emergency use lies with the physician—no prior approval by the FDA is required.[141]

The FDA expects that any physician providing a patient with access to an unapproved device under the emergency use exemption would follow as many patient protection procedures as possible (e.g., obtaining an independent assessment from another physician, obtaining an informed consent).[142] In addition, any IDE sponsor shipping an unapproved device to a physician for emergency use should notify the FDA within 5 working days after the shipment is made.[143] An unapproved device may not be shipped in anticipation of an emergency.

**Table 6**
**Early/Expanded Patient Access**

| | Criteria | Time period | Prior FDA approval required |
|---|---|---|---|
| Emergency use | (1) Life-threatening condition that needs immediate treatment<br>(2) No alternative<br>(3) No time for FDA approval | Before the IDE, market approval | No |
| Compassionate use | (1) Serious disease or condition<br>(2) No alternative | After clinical trials have begun, market approval | Yes |
| Treatment use | (1) Serious or immediately life-threatening disease<br>(2) No alternative<br>(3) Device is under investigation in a controlled clinical trial for the same use under an approved IDE (or the clinical trials have been completed)<br>(4) Sponsor of the study is actively pursuing marketing approval or clearance with due diligence | Serious diseases: after the completion of the clinical trial, market approval<br>Life-threatening diseases: immediately after the clinical trial has begun and looks promising, market approval | Yes |
| Continued access (extended investigation) | (1) Public health need<br>(2) Preliminary evidence shows that the device will be effective and there are no significant safety concerns | After IDE investigation completion, market approval | Yes |

FDA, Food and Drug Administration; IDE, investigational device exemption.

As discussed, an IRB may also approve emergency research without an informed consent when obtaining the informed consent is not feasible (e.g., the subject cannot give informed consent as a result of his or her medical condition).[144] Sponsors must monitor the progress of all investigations involving emergency research and file certain information with the FDA.[145]

### 6.2. Compassionate Use

After IDE clinical trials have begun, the FDA recognizes a compassionate use exception for patients who do not have life-threatening conditions and do not meet study criteria.[146] Candidates for the compassionate use exemption must have a serious disease or condition and no available treatment alternative.

Unlike the emergency use exception, the compassionate use exception may be used only with FDA approval, which requires an IDE supplement requesting protocol deviation. The request must include (1) a description of the patient's condition and the circumstances necessitating treatment, (2) a discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition, (3) the identification of any deviations in the approved clinical protocol that are needed to treat the patient, and (4) the patient protection measures that will be followed.[147]

If the FDA approves the request, the attending physician should devise an appropriate schedule for monitoring the patient to detect any problems associated with the device. A follow-up report must be submitted to FDA as an IDE supplement.

The compassionate use exception may also be used for a small number of patients. To use the exemption for more than one patient, the physician should speak to the sponsor to request access to the investigational device, and the sponsor should submit to the FDA an IDE supplement with the same information that would be included in the request for a single patient. If the FDA approves the request, sponsors should implement the same procedures that they would follow for a single patient.

### 6.3. Treatment Use

The FDA also provides a *treatment use* exception that provides expanded access to an investigational device after a clinical trial has already begun and before any final decision is made on the PMA.[148] If an ongoing clinical trial yields promising results and indicates that a device is effective, it may be expanded to include other people with serious or immediately life-threatening diseases. The purpose of this exception is to expedite the availability of promising new devices to desperately ill patients as early in the device development process as possible.[149] This exception covers both diagnostic and therapeutic devices.[150]

The treatment use exception distinguishes between *serious diseases* and *immediately life-threatening diseases* (i.e., a stage of disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment). For serious diseases, the device generally would not be made available to additional patients until all clinical trials have been completed (but before a final decision is made on the PMA), whereas the device would be made available to patients with immediately life-threatening diseases while trials are underway.[151]

The FDA would consider the use of an investigational device under the treatment use exception if:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease.
2. There is no alternative therapy.
3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE (or the clinical trials have been completed).
4. The sponsor of the study is actively pursuing marketing approval or clearance with due diligence.[152] Treatment use of an investigational device is also contingent on sponsors and investigators following the safeguards of the IDE process, informed consent regulations, and the IRB procedures.[153] Those applying for treatment use exceptions must complete applications that contain the detailed information required by FDA regulations.[154]

Sponsors may begin using the device 30 days after the FDA receives the treatment use application, unless the FDA notifies the sponsor earlier that treatment may or may not begin.[155] The FDA may disapprove or withdraw treatment use IDEs, after following certain procedures,[156] for the following reasons:

1. The criteria for the treatment use exception have not been met.
2. The device is intended for a serious disease or condition, and there is insufficient evidence of safety and efficacy.
3. The device is intended for an immediately life-threatening disease or condition, and the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the device is safe and effective.[157]
4. There is reasonable evidence that the treatment use has impeded enrollment or otherwise interfered with the controlled investigation of the same or another investigational device.
5. The device has received marketing approval or clearance or another comparable device or therapy has become available.
6. The sponsor of the clinical trial has not pursuing marketing approval or clearance with due diligence.
7. Approval of the IDE for the controlled clinical trial has been withdrawn.
8. The clinical investigators named in the treatment IDE are not qualified based on their scientific training and/or experience.

9. There has been a failure to comply with any applicable legal requirement.
10. The application contains an untrue statement of material fact or omits material information required by the FDA's regulations.
11. The sponsor has not responded to a request for additional information.
12. There is reason to believe that the risks associated with the device's benefits do not outweigh its risks or that the device is ineffective.
13. It is otherwise unreasonable to begin or continue the use because of the way the device is used or the inadequacy of certain components of the investigation.[158]

Until a manufacturer has filed a marketing application, sponsors of treatment IDEs must submit progress reports to the FDA and all reviewing IRBs on a semiannual basis.[159]

### 6.4. Continued Access Policy During Premarket Approval Preparation and Review

The FDA may permit subjects to continue using investigational devices after the completion of a clinical trial under certain circumstances, providing there is a public health need or preliminary evidence that the device will be effective and there are no significant safety concerns.[160] Periods when a subject might use the device beyond the investigation include extended investigations, while the sponsor is preparing the marketing application, and while FDA is reviewing the application.

To request an extended investigation, a sponsor should submit an IDE supplement that includes the following:

1. A justification for the extension.
2. A summary of the preliminary safety and efficacy data generated under the IDE;
3. A brief discussion of the risks posed by the device.
4. The proposed rate of continued enrollment (i.e., number of sites and subjects).
5. The clinical protocol (if it differs from the initial clinical trial) and the proposed objectives of the extended study.
6. A brief discussion of the sponsor's progress in obtaining market approval or clearance.[161]

The treatment use exception and the continued access policy overlap in that they are both intended to provide individuals with continued access to a promising device during the market clearance or approval process. Although the treatment use exception can be helpful during the course of a clinical trial (whereas the continued access policy is useful only after the trial has been completed), the treatment use exception is actually somewhat narrower than the continued access policy, since it provides access only to individuals with a serious or an immediately life-threatening disease.[162]

## 7. In Vitro Diagnostic Device Studies

Investigational in vitro diagnostic devices (IVDs) are subject to less stringent regulation than other investigational devices are. IVDs are defined as:

> reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.[163]

Although in certain circumstances, IVDs must comply with IRB and informed consent requirements,[164] IVDs are exempt from IDE requirements if the testing is noninvasive, does not require invasive sampling presenting significant risk, does not introduce energy into a subject, and is not used diagnostically without confirming the diagnosis with another medically established device or procedure.[165]

Although requirements for IVDs are less stringest, these devices must bear one of the following labeling statements, whichever is applicable, during shipment or delivery: "For Research Use Only. Not for use in diagnostic procedures," or "For Investigational Use Only. The performance characteristics of this product have not been established."[166] In addition, the provisions concerning investigator disqualification apply to IDE-exempt IVDs.[167]

Typically, if IVDs are truly exempt from the IDE requirements and comply with the labeling requirement, the FDA's Division of Bioresearch Monitoring will refrain from issuing warning letters for IDE requirement violations, except in unusual circumstances. Even in unusual circumstances, it would not issue a warning letter without first consulting the Office of Chief Counsel, the OC, and the ODE management.

If the IVD testing fails to meet the criteria for exemption from IDE requirements, the IDE, IRB, and informed consent requirements apply.

## 8. International Issues

### *8.1. European Standards for Device Studies*

Medical devices were first regulated in a harmonized manner in Europe in 1990, with the Active Implantable Medical Device Directive,[168] and in 1992, with the Medical Device Directive.[169] The following year, the European standard, EN 540: Clinical Investigation of Medical Devices for Human Subjects,[170] was issued to provide medical device manufacturers with guidelines for conducting clinical trials in Europe. The countries subject to the standard included all European Union members, as well as Austria, Finland, Iceland, Norway, Sweden, and Switzerland.[171] The primary purpose of EN 540 was to protect human subjects participating in clinical trials.

Two new harmonized standards were published in 2003 by the International Organization for Standardization (ISO): ISO 14155-1: Clinical Investigation of Medical Devices for Human Subjects—Part 1: General Requirements[172] and ISO 14155-2: Clinical Investigation of Medical Devices for Human Subjects—Part 2: Clinical Investigation Plans.[173] These standards include most of the guidelines that were in EN 540, although they are more comprehensive. The ISO standards essentially replace EN 540.[174]

ISO 14155 Part 1 establishes procedures for conducting investigational device studies and specifies general requirements to protect human subjects.[175] Although the first part does not apply to IVDs, ISO 14155 Part 2 applies to all medical devices being tested for safety and efficacy in human subjects. Part 2 specifically requires that devices in clinical studies be used in the manner that they would be used during normal clinical use, and attempts to ensure that adverse events that would be experienced under normal conditions of use will be observed during the clinical trial. It also attempts to make sure that the investigation will permit sponsors and investigators to assess the risks associated with the investigational device and contains requirements regarding clinical trial organization, conduct, monitoring, data collection, and documentation.[176]

Unlike the FD&C Act and IDE regulations in the United States, the ISO standards are strictly voluntary and serve only as guidelines.[177] Before conducting an investigational device study in a European country, sponsors should consult the specific laws of that country, as well as the ISO 14155 guidelines.

### *8.2. Clinical Studies Conducted Outside the United States*

Generally, the FDA will accept data from a clinical study conducted outside of the United States if the study was conducted under an IDE and complies with all applicable regulations.[178] The FDA will also recognize data that constitute valid scientific evidence[179] and was collected from studies conducted pursuant to the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever provides greater protection to human subjects.[180] The FDA defines *valid scientific evidence* as:

> [E]vidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use.[181]

The FDA's regulations further state that "[i]solated case reports, random experience, reports lacking sufficient detail to permit scientific evaluation, and un-

substantiated opinions" do not constitute valid scientific evidence, although they may be considered in identifying a device with questionable safety and efficacy.[182]

Regarding the second element of the test, an applicant who chooses to follow the laws of an individual country must state the differences between the Declaration of Helsinki and the country's standards in detail and explain why the country's standards offer more protection.[183]

In addition, the FDA will approve a PMA that otherwise meets the criteria for approval, based *solely* on foreign clinical data if the foreign data are applicable to the US population and medical practice,"[t]he studies have been performed by clinical investigators of recognized competence," and the data may be considered valid without the need for an on-site inspection by the FDA. The FDA can perform an on-site investigation if it deems it necessary or can validate data through other appropriate means.[184] The FDA encourages applicants for PMAs based solely on foreign clinical data to meet with the FDA in a presubmission meeting.[185]

### *8.3. Exportation of Unapproved Devices for Investigational Use*

Although the FDA does not have jurisdiction over how investigational studies are conducted outside the United States, it does have jurisdiction over unapproved devices that are being exported for use in foreign studies. The FDA has a two-tier system for the exportation of unapproved investigational devices, depending on the recipient country. For countries in the first tier, unapproved investigational devices may be exported under Section 802(c) of the FD&C Act[186] without FDA approval; however, unapproved investigational devices may only be exported to countries that are not in Tier I with FDA approval under Section 801(e)(2)[187] of the FD&C Act.[188]

Tier I countries include Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, and member countries of the European Union or the European Economic Area.[189] Section 802(c) of the FD&C Act permits unapproved investigational devices to be exported to these countries without FDA approval, if the unapproved device is exported in accordance with the laws of that country.[190] The device must also:

1. Be in compliance with the specifications of the foreign purchaser.
2. Not be in conflict with the laws of the country to which it is intended for export.
3. Be in a shipping packaged labeled on the outside that it is intended for export.
4. Not be sold or offered for sale in the US commerce.
5. Be in substantial conformity with the current good manufacturing practices or be certified as meeting international standards by a recognized organization.
6. Not be adulterated (other than by lack of marketing approval).
7. Not present an imminent hazard to public health.

8. Be labeled and promoted in accordance with the laws of the country to which the device is being exported.[191]

Devices that are exported under Section 802(c) need not comply with the other IDE requirements in 21 C.F.R. Part 812. When a foreign purchaser requests proof of compliance with US law before export, the FDA will provide a certificate of exportability.[192]

Similar to the rules for Tier I countries, exporting unapproved investigational devices to non-Tier I countries requires that the devices comply with the specifications of the foreign purchaser, not be in conflict with the laws of the country to which it is intended for export, be shipped in a package labeled that it is intended for export, and not be sold or offered for sale in the US commerce. The FDA must also approve these devices for export under Section 801(e)(2). FDA will approve the device for export only if it determines that exporting the device is "not contrary to public health and safety" and "has the approval of the country to which it is intended for export."[193]

Exporters shipping unapproved devices to Tier I countries must also provide the FDA with simple notification when the exporter first begins to export the device to another country; similarly, exporters shipping unapproved devices to non-Tier I countries must notify the FDA of the device and the country involved. All exporters must maintain records regarding exported devices and the countries to which they were exported.[194]

## References

1. *See* 21 U.S.C. §320j(g) (Supp. 2003); *see also* 21 C.F.R. § 812.1(a) (2003) (exempting investigational devices from various sections of the Act, such as those governing misbranding, registration, listing, premarket notification, performance standards, and premarket approval).
2. *See* 21 C.F.R. § 812.1(a) (2003).
3. Proposed Investigational Device Exemptions; Cross-Reference Amendments, 41 Fed. Reg. 35282 (Aug. 20, 1976); *see also* 21 U.S.C. §320j(g) (Supp. 2003); 21 C.F.R. §812.1(a) (2003).
4. Proposed Investigational Device Exemptions; Cross-Reference Amendments, 41 Fed. Reg. 35282 (Aug. 20, 1976); *see also* 21 U.S.C. §320j(g) (Supp. 2003); 21 C.F.R. §812.1(a) (2003).
5. Medical Device Amendments of 1976, P.L. 94-205 (1976).
6. *See* 41 Fed. Reg. at 35283.
7. 21 U.S.C. §320j(g) (Supp. 2003).
8. *See* 21 U.S.C. §320j(g)(2)(A) (Supp. 2003).
9. *See* 41 Fed. Reg. at 35283
10. *See* 21 U.S.C. §320j(g)(2)(C) (Supp. 2003).
11. *See* 21 C.F.R. §812.2(c) (2003).

12. A "custom device" is a device that: (1) necessarily deviates from an applicable performance standard or approval requirement in order to comply with the order of an individual physician or dentist, (2) is not generally available to, or generally used by, other physicians or dentists, (3) is not generally available in finished form for purchase or for dispensing upon prescription, (4) is not offered for commercial distribution through labeling or advertising, and (5) is intended for use by an individual patient named in the order of the physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice. *See id.* §812.3(b) (2003).
13. *See* 21 C.F.R. §812.3(m) (2003); Device Advice, Clinical Trial and IDE, Approval Process, http://www.fda.gov/ cdrh/devadvice/ide/approval.shtml.
14. *See generally* 21 C.F.R. pt. 812 (2003); *see also* Device Advice, Clinical Trial and IDE, Introduction, http://www.fda.gov /cdrh/devadvice/ide/index.shtml#IDE_Over.
15. *See* 21 C.F.R. §812.3(n) (2003).
16. *See id.* §812.3(n).
17. *See id.* §812.3(i).
18. *See* 21 C.F.R. pt. 812, subpt. C (2003).
19. *See infra*, discussion at Section V.
20. *See* FDA Warning Letter to Plus Orthopedics, dated Oct. 3, 2003.
21. *See* Guidance on IDE Policies and Procedures, IDE Staff, Office of Device Evaluation, Center for Devices and Radiological Health, FDA (Jan. 20, 1998) ("Guidance on IDE Policies and Procedures"), at 6-7.
22. *See* 21 C.F.R. §812.3(i) (2003).
23. *See id.* at pt. 812, subpt. E.
24. *See id.* §812.110.
25. *See also* 21 C.F.R. at pt. 50 (2003).
26. *See id.* §§812.140, 812.150; *see infra*, discussion at Section V(D).
27. *See* FDA Warning Letter to Hans C. Kioschos, M.D., dated July 26, 2004.
28. *See* 21 C.F.R. §54.1 (2003).
29. 21 C.F.R. §§54.4, 812.110(d); *see also* Guidance: Financial Disclosure by Clinical Investigators, FDA (Mar. 20, 2001); Device Advice, Responsibilities, http://www.fda.gov/cdrh/devadvice/ide/ responsibilities.shtml#ResponInvestigators.
30. *See* 21 C.F.R. §812.110(d) (2003).
31. *See id.* §54.1.
32. *See id.* at pt. 812.
33. *See id.* at pt. 50.
34. *See id.* at pt. 56.
35. *See id.* §812.119.
36. *See* Disqualified/Totally Restricted List for Clinical Investigators, FDA, http://www.fda.gov/ora/compliance_ref /bimo/disqlist.htm.
37. *See* 21 C.F.R. §812.3(f) (2003).
38. *See id.* §§812.62, 812.64.

39. *See id.* §812.62(a).
40. *See id.* at pt. 56.
41. Guidance on IDE Policies and Procedures, at 1.
42. *See id.*
43. 21 U.S.C. §§360c(a)(3)(D), 360j(g)(7) (Supp. 2003).
44. A product development protocol is an alternative to the PMA process for Class III devices, which allows sponsors to come to early agreement with the FDA as to what needs to be done to demonstrate the safety and effectiveness of a new device. *See* Draft Guidance for Industry – Contents of a Product Development Protocol, ODE (Jan. 27, 1998).
45. *See* Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff, at 1.
46. *See* 21 U.S.C. §§360c(a)(3)(D) (Supp. 2003).
47. *See* Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff, at 3.
48. *See* Device Advice, Clinical Trial and Investigational Device Exemption ("IDE"), http://www.fda.gov/cdrh/devadvice/ide/approval.shtml#pre_ide
49. *See* 21 C.F.R. §812.25 (2003).
50. *See* 21 U.S.C. §§360j(g)(7) (Supp. 2003); Device Advice, Clinical Trial and Investigational Device Exemption ("IDE"), Approval Process, http://www.fda.gov/cdrh/devadvice/ide/approval.shtml#pre_ide
51. *See* 21 U.S.C. §§360j(g)(7) (Supp. 2003); Device Advice, Clinical Trial and IDE, Approval Process, http://www.fda.gov/cdrh/devadvice /ide/approval.shtml#pre_ide; *see supra*, discussion at Section I(C).
52. *See* 21 U.S.C. §§360j(g)(7) (supp. 2003); Early Collaboration Meetings Under the FDA Modernization Act (FDAMA), Final Guidance for Industry and for CDRH Staff, Feb. 28, 2001, at 3, http://www.fda.gov/cdrh/ode/guidance/310.html.
53. *See* 21 U.S.C. §360j(g) (Supp. 2003); 21 C.F.R. §812.1 (2003); FDA, Device Advice, Clinical and IDE Approval Process, Introduction, http://www.fda.gov/cdrh/devadvice/ide/index.shtml.
54. *See* Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update, http:// www.fda.gov/oc/ohrt/irbs/devices.html#risk.
55. *See* 21 C.F.R. §812.3 (2004); Device Advice, Clinical Trial and IDE, Approval Process, http://www.fda.gov/ cdrh/devadvice/ide/approval.shtml. The full regulatory definition states that a significant risk device is "an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject; (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to a subject." 21 C.F.R. §812.3(m) (2003).

56. *See* 21 C.F.R. §812.3(m) (2003); Device Advice, Clinical Trial and IDE, Approval Process, http://www.fda.gov/cdrh/devadvice/ide/approval.shtml.
57. *See* Device Advice, Clinical Trial and IDE, Approval Process, http:// www.fda.gov/cdrh/devadvice/ide/approval.shtml.
58. Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update, http:// www.fda.gov/oc/ohrt/irbs/devices.html#risk; *see also* Device Advice, Clinical Trial and IDE, Approval Process, http:// www.fda.gov/ cdrh/devadvice/ide/approval.shtml; David G. Adams, *et al.*, 2 Fundamentals of Law and Regulations: An In-Depth Look at Therapeutic Products 280 (1997).
59. *See* Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update, http:// www.fda.gov/oc/ohrt/irbs/devices.html#risk.
60. *See id.*
61. *See* 21 C.F.R. pt. 812 (2003); *see also* Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update, http:// www.fda.gov/oc/ohrt/irbs/devices.html#risk
62. Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators, 1998 Update, http:// www.fda.gov/oc/ohrt/irbs/devices.html#risk
63. *See id.*
64. *See id.*
65. FDA will otherwise notify the sponsor if the IDE application has been disapproved. *See* Device Advice, Clinical Trial and IDE, Approval Process, http:// www.fda.gov/ cdrh/devadvice/ide/approval.shtml.
66. *See id.* In contrast, a sponsor cannot begin trials on a SR device until FDA has approved the application. FDA considers the IDE application approved 30 days after its receipt, unless the agency notifies the sponsor otherwise.
67. *See id.*
68. Once the IRB agrees the device poses a non-significant risk and approves the study, FDA considers the device approved. *See id.*
69. If the IRB thinks the device poses a significant risk, the sponsor must report this finding to the FDA within five working days. *See* 21 C.F.R. §812.150(b)(9) (2003); *see also* Device Advice, Clinical Trial and IDE, Approval Process, http:/ /www.fda.gov/ cdrh/devadvice/ide/approval.shtml.
70. *See* 21 C.F.R. §812.2(b) (2003).
71. *See id.*
72. *See id.* §812.2(b)(1)(i). The label must include the name and business address of the manufacturer, packer, or distributor. If applicable, the label must list content quantity. The label also must contain the statement "CAUTION—Investigational Device. Limited by Federal (or United States) law to investigational use." *Id.* §812.5. The label must describe the relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. The label cannot contain any false or misleading statements and cannot imply that the device is safe or effective for the uses being investigated. Finally, the sponsor should

provide detailed information on labeling in the investigational protocol. *See id. See also* Device Advice, Clinical Trial and IDE, Application, http://www.fda.gov/cdrh/devadvice/ide/application.shtml#modifications.

73. *See* 21 C.F.R. §§812.140(b)(4),(5), 812.150(b)(1)-(3), (5)-(10) (2003).
74. *See id.* §§812.140(a)(3)(i), 812.150(a)(1),(2),(5), and (7).
75. *See* 21 C.F.R. §812.20 (2003).
76. *See id.* §812.20(b).
77. *See id.* §812.20(b)(2). For a list of the information that must be included in the report of previous investigations, *see id.* §812.27(2003); for the investigational plan requirements, *see id.* §812.25.
78. *See id. See also* 21 C.F.R. §812.43 (listing the information that the agreement must include).
79. *See id.* §812.20(b) (listing all of the application requirements); *see also* Device Advice, Clinical Trial and IDE, Application, http://www.fda.gov/cdrh/devadvice/ide/application.shtml#modifications (providing a detailed guide for preparing the IDE application).
80. *See* 21 C.F.R. §812.20(a)(3) (2003). *See generally* Device Advice, Clinical Trial and IDE, Approval Process, http://www.fda.gov/ cdrh/devadvice/ide/approval.shtml (with suggested content for the cover letter).
81. *See* 21 C.F.R. §812.35 (2003).
82. *See id.* §812.35; *see also* Device Advice, Clinical Trial and IDE, Application, http://www.fda.gov/cdrh /devadvice/ide/application.shtml#modifications.
83. *See* Device Advice, Clinical Trial and IDE, Application, http://www.fda.gov/cdrh/devadvice/ide /application.shtml#modifications.
84. *See id.*
85. *See id.*
86. *See id.*
87. *See id.*
88. *See id.*
89. *See id*
90. *See id.*
91. *See id.* (noting that the sponsor still must report the change to FDA within five working days).
92. *See* 21 C.F.R. §812.35(a)(3) (2003); *see also* Device Advice, Clinical Trial and IDE, Application, http://www.fda.gov/cdrh /devadvice/ide/application.shtml#modifications.
93. *See* 21 C.F.R. §812.35(a)(3)(iii) (2003).
94. *See* 21 C.F.R. §812.150(b)(5) (2003); *see also* Device Advice, Clinical Trial and IDE, Application, http://www.fda.gov/cdrh /devadvice/ide/application.shtml#modifications.
95. *See* 21 C.F.R. §812.30 (2003).
96. *See id.* §812.30.
97. *See id.* §812.30(b). *See also* Device Advice, Clinical Trial and IDE, Application, http://www.fda.gov/cdrh/devadvice/ ide/application.shtml#modifications.

98. *See* 21 C.F.R. §812.30(c) (2003); Device Advice, Clinical Trial and IDE, Approval Process, http://www.fda.gov/ cdrh/devadvice/ide/approval. shtml.
99. *See* Guidance on IDE Policies and Procedures, at 8.
100. *See id.*
101. *See id.*
102. *See id.*
103. *See id.* at 7.
104. *See id.*
105. *See id.*
106. *See id.*
107. *See id. See also* 21 C.F.R. §812.150 (2003); Device Advice, Clinical Trial and IDE, Reports, http://www.fda.gov/cdrh/devadvice/ide /reports.shtml
108. *See* 21 C.F.R. §50.20 (2003).
109. *See id.* §50.25(a).
110. *See id.* §50.25(b).
111. *See* FDA Warning Letter to James Yanney, DDS, MD, dated July 30, 2003.
112. *See* 21 C.F.R. §50.23 (2003).
113. *See id.* §50.24.
114. *See id.* §50.24(a)(1) (requiring that the "human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions").
115. *See id.* §50.24(a)(2) (providing that obtaining informed consent must be infeasible because: (1) subjects will not be able to give their informed consent as a result of their medical condition, (2) the intervention under investigation must be administered before consent from the legally authorized representatives is feasible, and (3) there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation).
116. *See id.* §50.24(a).
117. *See id.* §50.24(a)(3) (providing that there must be a direct benefit because: (1) subjects are facing a life threatening situation that necessitates intervention; (2) appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for intervention to provide a direct benefit to the subjects, and (3) risk associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits, if any, and what is known about the risks and benefits of the proposed intervention or activity).
118. *See id.* §50.24(a)(4).
119. *See id.* §50.24(a)(5) (requiring the investigator to contact the legally authorized representative during that window, among other things).
120. *See id.* §50.24(a)(6).
121. *See id.* §50.24(a)(7).

122. *See id.* §812.40.
123. *See id.* §§812.43(d), 812.46.
124. *See* FDA, Guidelines for Monitoring of Clinical Investigations (Jan. 1988).
125. *See* 21 C.F.R. §812.46(a) (2003).
126. *See* FDA Warning Letter to Silimed, Incorporated, dated August 21, 2003.
127. *See* 21 C.F.R. §812.46(b) (2003).
128. *See id.* §812.46(c).
129. FDA Warning Letter to Paradigm Medical Industries, Inc., dated Aug. 30, 2000.
130. *See* FDA Warning Letter to Wesley Kinzie, M.D., dated Nov. 7, 2003.
131. *See* 21 C.F.R. §812.140(d).
132. *See id.* §812.140(e).
133. *See id.* §812.145.
134. *See id.* §812.150.
135. *See id.* §812.7.
136. *See* Guidance for Industry and FDA Staff, Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects, FDA (March 19, 1999).
137. *See* FDA Warning Letter to Jacobson Resonance Enterprises, Inc., dated Jan. 25, 2001.
138. *See* 21 U.S.C. §360j(g) (Supp. 2003); 21 C.F.R. §812.1 (2003); FDA, Device Advice, Clinical Trials & Investigational Device Exemption (IDE), Early/Expanded Access, http://www.fda.gov/cdrh/devadvice/ide/print/ early.html# emergencyuse.
139. *See* 21 C.F.R. §§50.25, 812.35, 812.47 (2003); Guidance for Emergency Use of Unapproved Medical Devices (Oct. 22, 1985), http://www.fda.gov/cdrh/manual/ unappr.html.
140. *See* Guidance for Emergency Use of Unapproved Medical Devices (Oct. 22, 1985), http://www.fda.gov/cdrh/manual/unappr.html; *see also* FDA, Device Advice, Clinical Trials & Investigational Device Exemption (IDE), Early/Expanded Access, http://www.fda.gov/cdrh/devadvice/ide/print/ early.html#emergency use.
141. *See* Guidance on IDE Policies and Procedures, at 17-19.
142. *See* Guidance for Emergency Use of Unapproved Medical Devices (Oct. 22, 1985), http://www.fda.gov/cdrh/manual/unappr.html.
143. *See* 21 C.F.R. §812.35 (2003); Guidance on IDE Policies and Procedures, at 17-19.
144. *See* 21 C.F.R. §50.24 (2003); *see supra*, discussion at Section V(B).
145. *See* 21 C.F.R. §812.47 (2003); *see also* FDA, Device Advice, Clinical Trials & Investigational Device Exemption (IDE), Early/Expanded Access, http:// www.fda.gov/cdrh/devadvice/ide/print/ early.html#emergencyuse.
146. *See* Guidance on IDE Policies and Procedures, at 19-20; FDA, Device Advice, Clinical Trials & Investigational Device Exemption (IDE), Early/Expanded Access, http://www.fda.gov/cdrh/devadvice/ide/print/ early.html#emergencyuse.

147. *See* 21 C.F.R. §812.35 (2003); *see also* Guidance on IDE Policies and Procedures, at 19-20; FDA, Device Advice, Clinical Trials & Investigational Device Exemption (IDE), Early/Expanded Access, http://www.fda.gov/cdrh/devadvice/ide /print/early.html#emergencyuse.
148. *See* 21 C.F.R. §812.36 (2003); Guidance on IDE Policies and Procedures, at 20-22; FDA, Device Advice, Clinical Trials & Investigational Device Exemption (IDE), Early/Expanded Access, http://www.fda.gov/cdrh/devadvice/ide /print/early.html#emergencyuse.
149. *See* 21 C.F.R. §821.36(a) (2003).
150. *See id.*
151. *See id.*
152. *See id.* §812.36(b)(1)-(4).
153. *See id.* §812.36(e).
154. *See id.* §812.36(c); *see also* FDA, Device Advice, Clinical Trials & Investigational Device Exemption (IDE), Early/Expanded Access, http://www.fda.gov/cdrh/devadvice/ide /print/early.html#emergencyuse.
155. *See* 21 C.F.R. §812.36(d) (2003).
156. *See id.* §§812.30(c); 812.36(d)(3).
157. *See id.* §812.36(d)(2)(iv) (establishing a specific test).
158. *See id.* §§812.30(b); 812.36(d)(2); *see also* FDA, Device Advice, Clinical Trials & Investigational Device Exemption (IDE), Early/Expanded Access, http://www.fda.gov/cdrh/devadvice/ide /print/early.html#emergencyuse.
159. *See* 21 C.F.R. §812.36(f) (2003); *see also* Suggested Format for IDE Progress Report, http://www.fda.gov/cdrh/dsma /311.html.
160. *See* FDA, Device Advice, Clinical Trials & Investigational Device Exemption (IDE), Early/Expanded Access, http://www.fda.gov/cdrh/devadvice/ide/print/early.html#emergencyuse.
161. *See id.*
162. *See id.*
163. 21 C.F.R. §809.3 (2003).
164. *See id.* at pts. 50 and 56; Guidance for FDA Staff Regulating *In Vitro* Diagnostic Device ("IVD") Studies, Office of Compliance, Division of Bioresearch Monitoring, CDRH, FDA (Dec. 17, 1999).
165. *See* 21 C.F.R. §812.2(c)(3) (2003).
166. *Id.* §§809.10(c)(2); 812.2(c)(3) (2003).
167. *See* Guidance for FDA Staff Regulating *In Vitro* Diagnostic Device ("IVD") Studies, Office of Compliance, Division of Bioresearch Monitoring, CDRH, FDA (Dec. 17, 1999).
168. Council Directive 90/385/EEC on Active Implantable Medical Devices (1990).
169. Council Directive 93/43/EEC on Medical Devices (1992).
170. Clinical Investigation of Medical Devices for Human Subjects, Doc. No. 540, European Commission of Standardization (1993).
171. *See id.*

172. *See* ISO 14155-1:2003 Clinical Investigation of Medical Devices for Human Subjects – Part 1: General Requirements.
173. *See* ISO 14155-2: Clinical Investigation of Medical Devices for Human Subjects – Part 2: Clinical Investigation Plans.
174. *See* Danielle Giroud, *A Revised Guideline for Medical Device Clinical Investigations: ISO 14155 part 1 and 2: 2003*, Qual. Assur. J. (2004).
175. *See* ISO 14155-1:2003 Clinical Investigation of Medical Devices for Human Subjects – Part 1: General Requirements.
176. *See* ISO 14155-2: Clinical Investigation of Medical Devices for Human Subjects – Part 2: Clinical Investigation Plans.
177. *See* ISO 14155-1:2003 Clinical Investigation of Medical Devices for Human Subjects – Part 1: General Requirements; ISO 14155-2: Clinical Investigation of Medical Devices for Human Subjects – Part 2: Clinical Investigation Plans; *see also* ISO Website, About Us, http://www.iso.org/iso/en/aboutiso/introduction/index.html.
178. *See* 21 C.F.R. pt. 812 (2003).
179. *See id.* §860.7.
180. *See id.* §814.15(b); *see also* Guidance for Industry Acceptance of Foreign Clinical Studies, FDA (Mar. 2001).
181. 21 C.F.R. §860.7(c)(2) (2003).
182. *See id.*
183. *See id.* §814.15(b).
184. *Id.* §814.15(d).
185. *See id.* §814.15(e).
186. 21 U.S.C. §382(c) (Supp. 2003).
187. *Id.* §381(e)(2) (Supp. 2003).
188. *See* 21 C.F.R. §812.18(b) (2003).
189. *See* 21 U.S.C. §382(b)(1)(A)(i)-(ii) (Supp. 2003).
190. *See id.* §382(c).
191. *See id*. §382(f).
192. *See* FDA Guidance to Industry on: Exports and Imports Under the FDA Export Reform and Enhancement Act of 1996 (Draft) Feb. 1998, http://www.fda.gov/opacom/fedregister/frexport.html#general; *see also* Device Advice, Import and Export of Investigational Devices, http://www.fda.gov/cdrh/devadvice/ide/import_export.shtml; Device Advice, Exporting Medical Devices, http://www.fda.gov/cdrh/devadvice/39.html.
193. 21 U.S.C. §381(e)(2) (Supp. 2003). For information regarding the precise materials that should be filed with a request for approval under Section 801(e)(2), *see* Device Advice, Import and Export of Investigational Devices, http://www.fda.gov/cdrh/devadvice/ide /import_export.shtml.
194. *See* 21 U.S.C. §383(g) (Supp. 2003); 64 Fed. Reg. 15944 (Apr. 2, 1999); *see also* Device Advice, Import and Export of Investigational Devices, http://www.fda.gov/cdrh/devadvice/ide/import_export.shtml.

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