Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

Frequently Asked Questions About Medical Devices

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Contains Nonbinding Recommendations

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors[1] Frequently Asked Questions About Medical Devices

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist clinical investigators and institutional review boards (IRBs) by answering common questions FDA receives concerning medical devices. This document supersedes *Medical Devices*, *Frequently Asked Questions about IRB Review of Medical Devices*, and *Emergency Use of Unapproved Medical Devices* (September 1998) Office of Health Affairs, Food and Drug Administration. This document was revised to make it consistent with the Agency's good guidance practices regulations (21 CFR 10.115).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. FREQUENTLY ASKED QUESTIONS ABOUT MEDICAL DEVICES

[1] This guidance document was developed by the Good Clinical Practice Program in coordination with the Agency Centers. This guidance document does not address medical devices subject to licensure as a biological product. Please direct questions concerning those devices to the Center for Biologics Evaluation and Research.

Contains Nonbinding Recommendations

1. What is a medical device?

A medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

- recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes (21 U.S.C. 321(h)).

2. How does FDA classify medical devices?

In accordance with the Federal Food, Drug, and Cosmetic Act, FDA places all medical devices into one of three regulatory classes based on the level of control necessary to ensure safety and effectiveness of the device. Classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in determining the class to which it is assigned.

Devices in all three classes are subject to general controls which require, in part, that companies: (1) register their establishments and list the medical devices they market with FDA; (2) manufacture their devices in accordance with Good Manufacturing Practices; and (3) label their devices in accordance with labeling regulations.

Class I devices are subject only to general controls. They typically present the lowest potential for harm and are simpler in design than Class II or Class III devices. Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments.

Class II devices are those for which general controls alone are insufficient to provide a reasonable assurance of safety and effectiveness. In addition to complying with general controls, Class II devices are also subject to special controls identified by the agency, which may include special labeling requirements, performance standards and postmarket surveillance. Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.

Class III devices generally are those for which insufficient information exists to determine that general or special controls are sufficient to provide a reasonable assurance of safety and effectiveness. Examples of Class III devices include replacement heart valves, silicone gel-filled breast implants, and implanted cerebellar stimulators.

3. What are examples of medical devices?

Examples of medical devices include surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. A longer list of examples of medical devices is in the FDA Information Sheet Guidance, "Significant Risk vs. Non-Significant Risk Devices."

Medical devices also include diagnostic products. Examples of diagnostics include in vitro diagnostic reagents and test kits such as pregnancy test kits, and imaging systems such as magnetic resonance imaging (MRI).

4. What is a premarket notification (510(k)) submission?

A premarket notification, or 510(k), is submitted to FDA before a manufacturer proposes to market a medical device. If FDA agrees the new device is substantially equivalent to a legally marketed device for which premarket approval is not required, the manufacturer may market it immediately. FDA does not require clinical data in most 510(k)s. However, if clinical data are necessary to demonstrate substantial equivalence, the clinical study must comply with the IDE, IRB, and human subject protection (informed consent and additional safeguards for children in research) regulations. See section 520(g) of the act and 21 CFR Parts 812, 56 and 50.

5. What is a premarket approval (PMA) application?

A premarket approval (PMA) application is the most stringent type of device marketing application for medical devices. FDA approves a PMA if it determines that the application contains sufficient valid scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use(s).

6. Where can I find more information about 510(k)s and PMAs?

Additional information is available about these programs on the Center for Devices and Radiological Health's website at: www.fda.gov/cdrh/devadvice/.

7. What is a humanitarian use device (HUD)?

An HUD is a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in fewer than 4,000 individuals in the United States per year. The Office of Orphan Products Development (OOPD) determines if a device meets specific requirements, including scientific rationale and population prevalence, for designation as a HUD.

8. What is a humanitarian device exemption (HDE) application?

A Humanitarian Device Exemption (HDE) application is similar to a PMA, but because a HUD is exempt from the effectiveness requirements of a PMA, an HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. However, the HDE must contain sufficient information for FDA to determine that the probable benefit to health outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Section 520(m)(2)(C). An approved HDE authorizes marketing of an HUD.

Under the statute, once the HDE is approved, the HDE holder is responsible for ensuring that the approved HUD is only administered at institutions that have an IRB constituted and acting pursuant to 21 CFR 56, including conducting continuing review of the use of the HUD. In addition, an HUD should be administered only if such use has been approved by the Institutional Review Board (IRB) located at the facility, or by a similarly constituted IRB that has agreed to oversee such use and to which the local IRB has deferred in a letter to the HDE holder. An HDE holder may wish to ensure that this happens by not shipping the HUD to the facility until it has received confirmation of IRB approval.

NOTE: HUDs should not be used until AFTER the HDE applicant obtains approval of the HDE from FDA and the IRB approves its use. IRBs should ensure that HDE approval has been granted before approving the device for use at their institution.

9. What are the responsibilities of the IRBs regarding HDEs?

Initial review:
Initial IRB approval should be performed at a convened IRB meeting. The IRB does not need to review and approve individual uses of an HUD, but rather the IRB may approve use of the device as it sees fit. That is, the IRB may approve use of the HUD without any further restrictions, under a protocol, or on a case-by-case basis.

Continuing review:
IRBs may approve the use of the device for a period of time, not to exceed one year. 21 CFR 56.109(f). In some higher risk cases, IRBs have approved HUDs for a specific number of patients and have required a summary report before approving the use in additional patients. Continuing review should follow the requirements found at 21 CFR 56, and may be conducted using the expedited review procedures (see 21 CFR 56.110) unless the IRB determines that full board review should be performed. The agency believes that the expedited review procedures are appropriate for continuing review since the initial review would have been performed by the full board and use of the HUD within its approved labeling does not constitute research.

10. Is informed consent required when treating/diagnosing a patient with an HUD?

The act and the HDE regulations do not require informed consent. Because an HDE provides for marketing approval, use of the HUD does not constitute research or an investigation which would normally require consent from the study subjects. However, there is nothing in the law or regulations that prohibits a state or institution from requiring prospective informed consent, when feasible. In fact, most HDE holders have developed patient labeling that incorporates information that may be used to assist a patient in making an informed decision about the use of the device. For example, the patient labeling may contain a discussion of the potential risks and benefits of the HUD, as well as any procedures associated with the use of the device. The HUD labeling also states that the device is a humanitarian use device for which effectiveness for the labeled indication has not been demonstrated. See 21 CFR 814.104(b)(4)(ii).

Unless it is an emergency, before an HUD is used off-label, the agency recommends that the HDE holder obtain FDA approval of the use following the compassionate use policy for unapproved devices. (See Chapter III Expanded Access to Unapproved Devices of the "IDE Policies and Procedures Guidance."[2]) If FDA approves the compassionate use request, the physician should ensure that the patient protection measures are addressed before the device is used and should devise an appropriate schedule for monitoring the patient. If the situation is life-threatening and there is not time to get FDA approval for the off-label use, FDA recommends that the emergency use procedures outlined in the above referenced guidance be followed.

Sometimes a physician or HDE holder may develop a research protocol designed to collect safety and effectiveness data to support a PMA for the device. In that case, an IDE is not needed if the research is within the approved labeling; however, IRB approval for the investigational study must be obtained before the research may begin. Informed consent must also be obtained from the subjects participating in the study. If the research is for a **new use**, the IDE regulation must be followed. 21 CFR Parts 812, 50, and 56.

11. What statute and regulations apply to medical device clinical investigations?

In accordance with section 520(g) and the regulations, clinical studies of medical devices must comply with FDA's human subject protection requirements (informed consent and additional safeguards for children in research) (21 CFR Part 50), Institutional Review Board (IRB) requirements (21 CFR Part 56), Investigational Device Exemptions (IDE) requirements (21 CFR Part 812), Financial Disclosure for Clinical Investigators requirements (21 CFR Part 54) regulations, as well as any other applicable regulations, including pertinent regulations at 21 CFR Part 809 (In Vitro Diagnostic Devices For Human Use).

12. What types of device studies do the IDE regulations (21 CFR Part 812) cover?

[2] This guidance may be found at www.fda.gov/cdrh/ode/idepolcy.html

There are three types of studies described in the regulations at 21 CFR Part 812: significant risk (SR) device studies, non-significant risk (NSR) device studies, and exempt studies. A brief description of these types of studies follows. Please refer to the FDA Information Sheet Guidance "Significant Risk and Nonsignificant Risk Medical Device Studies" for more detailed information about SR and NSR device studies, the importance of the IRB's review, the regulatory requirements for these studies, and examples of devices in each category.

A. Significan t Risk Device Studies

A significant risk device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- 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
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (21 CFR 812.3(m))

Sponsors of investigational SR device studies are required to get an approved IDE from FDA before starting their study. 21 CFR 812.20 (FDA gives each IDE a number - for example #GXX0000, where XX denotes the year of the submission). Sponsors and clinical investigators of these studies must comply with the regulations at 21 CFR Part 812, "Investigational Device Exemptions."

If FDA disapproves an IDE, FDA's letter will describe the reasons for the disapproval. If the sponsor submits an IDE amendment satisfactorily addressing the issues in FDA's letter, the agency sends an IDE approval letter to the sponsor. In accordance with the regulations at Part 812, the study may not start until both FDA and the IRB have given their approval.

Note: A conditional approval letter from FDA allows the study to begin if the study is approved by the IRB, but requires the sponsor to provide additional clarifying information in order to obtain full approval for the study.

IRBs do not have to make the SR or NSR determination if FDA has already made the risk determination. Most often, clinical investigators submit SR device investigations for IRB review after the study has already received IDE approval from FDA. IRBs may ensure that SR device investigations have an FDA-approved IDE by asking the clinical investigator to request from the sponsor a copy of FDA's IDE approval letter.

An IRB may be asked to review an SR device study before the sponsor receives FDA approval of an IDE submission. Under this circumstance, IRBs should be aware that because it is possible that FDA may not approve the IDE or may request significant changes to the research protocol, the IRB may need to re-evaluate the study after FDA reviews the application. If an IRB approves the significant risk device study before FDA approves the IDE, there may be more of a risk that clinical investigators will mistakenly enroll subjects before the study should be started (i.e, before FDA approves the IDE.)

B. Non-Significant Risk Device Studies

An NSR device is an investigational device that does not meet the definition of a significant risk device. If an IRB finds that an investigational medical device study poses a NSR, the sponsor does not need to submit an IDE to FDA before starting the study. If the IRB determines that the proposed study is an NSR study, the IRB may proceed to review the study under 21 CFR 56.109 and 21 CFR 56.111. FDA considers an NSR device study to have an approved IDE after IRB approval and when sponsors meet the abbreviated requirements at 21 CFR 812.2(b). Consequently, in most cases, FDA is not aware of non-significant risk device studies.

As stated above, if FDA has already made the risk determination, the IRB does not need to duplicate this effort. If, however, FDA has not made the risk determination or the IRB disagrees with the NSR determination made by a sponsor, then the IRB must notify the investigator and, where appropriate, the sponsor, that the study involves a significant risk device (21 CFR 812.66). If a sponsor or an IRB needs help in making the SR/NSR determination, it may ask for a written determination from FDA.[3]

The IRB should consider the following in determining whether a device study poses a SR or NSR:

- the sponsor's description of why the study is not SR
- whether the proposed NSR research study meets the definition of "significant risk" (see above)
- the proposed use of the device as well as any protocol related procedures and tests, not just the device (test article) alone. (This process is different from the IRB review process found at 21 CFR 56.111(a)(2)).)
- additional information from the sponsor, if needed.

[3] See the guidance memorandum entitled, "Procedures for Handling Inquiries Regarding the Need for an Investigational Device Exemptions Application for Research Involving Medical Devices" at www.fda.gov/cdrh/ode/blue-ide-d01-1.html

C. Exempt Studies

In accordance with 21 CFR 812.2(b), sponsors and investigators of certain studies are exempt from the requirements of 21 CFR Part 812, with the exception of §812.119 (disqualification of a clinical investigator). Examples of exempt studies are consumer preference testing, testing of a device modification, or testing of two or more devices in commercial distribution if the testing does not collect safety or effectiveness data, or put subjects at risk.[4]

Studies of an already cleared medical device in which the device is used or investigated in accordance with the indications in the cleared labeling are exempt from Part 812.[5] Note: Studies of a cleared device *for a new use* must comply with the human subject protection (informed consent and additional safeguards for children in research), IRB, and IDE regulations. Similarly, studies of a PMA approved device are exempt from the IDE requirements if the device is being studied for the indications in the approved labeling.

In addition, diagnostic device studies (e.g., *in vitro* diagnostic studies) are exempt from the requirements of 21 CFR Part 812 under certain circumstances. The study is exempt as long as the sponsor complies with the requirements at 21 CFR 809.10(c) for labeling, and if the testing: (i) is noninvasive; (ii) does not require an invasive sampling procedure that presents significant risk; (iii) does not by design or intention introduce energy into a subject; and (iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. 21 CFR 812.2(c)(3).

13. Are IDE exempt studies subject to the requirements for informed consent and IRB review and approval under Parts 50 and 56?

If an exempt study is being conducted to collect data to support either a clinical investigation or a marketing application, then the study must comply with 21 CFR Part 50 and should comply with 21 CFR Part 56. 21 CFR 50.1(a), 21 CFR 50.20, 21 CFR 56.101(a), 21 CFR 56.103.

14. Does FDA require IRB review and approval of off-label <u>use</u> of a legally marketed device?

No, when a physician uses a legally marketed device outside its labeling to treat a patient and no research is being done, IRB review is not required. Note: Although not required by FDA, an IRB may still decide on its own initiative to review such use. Yes, when the off-label use of a legally marketed device is part of a research study collecting safety and effectiveness data involving human subjects, IRB review and approval is required (21 CFR 812.2(a)).

[4] See 21 CFR 812.2(c)(4).
[5] See 21 CFR 812.2(c)(1) and (2).

For additional information on the off-label use of devices, see the FDA Information Sheet guidance, " 'Off-label' and Investigational Use of Marketed Drugs, Biologics and Medical Devices."[6]

15. Must an IRB review a study conducted after submission of a (510(k)) to FDA but prior to FDA's decision on that submission?

Yes. During FDA's review of the premarket notification submission, the device remains an investigational product. Therefore, the human subject protection (informed consent and additional safeguards for children in research), IRB, and IDE regulations apply. The device may not be distributed, except for investigational use, unless FDA clears the device for marketing.

16. Can a physician use an unapproved device in an emergency?

In general, an unapproved medical device may be used only on human subjects when the device is under clinical investigation and when used by investigators participating in a clinical trial. Section 561 of the Act, however, recognizes that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient or to prevent irreversible morbidity when there exists no other alternative therapy. For investigational devices under an IDE, the IDE regulation permits deviations from the investigational plan without prior approval when necessary to protect the life or physical well-being of a subject in an emergency. (See 21 CFR 812.35(a)). A physician may treat a patient with an unapproved medical device in an emergency situation if he/she concludes that:

- The patient has a life-threatening condition that needs immediate treatment;[7]
- No generally acceptable alternative treatment for the condition exists; and
- Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

FDA expects the physician to make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. In the event that a device is used in circumstances meeting the criteria listed above, the physician should follow as many of the patient protection procedures listed below as possible:

- Informed consent from the patient or a legal representative;
- Clearance from the institution as specified by their policies;

[6] This guidance can be found at: www.fda.gov/oc/ohrt/irbs/offlabel.html

[7] FDA considers "life-threatening condition" to include serious diseases or conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity.

- Concurrence of the IRB chairperson;
- An assessment from a physician who is not participating in the study; and
- Authorization from the IDE sponsor, if an IDE exists for the device.

While prior approval for shipment or emergency use of the investigational device is not required, the use must be reported to FDA by the IDE sponsor within 5 working days from the time the sponsor learns of the use. 21 CFR 812.35(a)(2) and 812.150(a)(4). The report should contain a summary of the conditions constituting the emergency, patient outcome information, and the patient protection measures that were followed. If no IDE exists, the physician should follow the above procedures and report the emergency use to CDRH or CBER.

For additional information on the procedures physicians and IRBs should follow in an emergency use situation, please see Chapter III Expanded Access to Unapproved Devices of the guidance entitled, "IDE Policies and Procedures."[8]

17. What if the situation is not an emergency? Can a patient with a serious illness or condition have access to an investigational device outside a study?

Yes, FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious or life-threatening condition (hereinafter referred to as "compassionate use"). Unlike emergency use of an unapproved device discussed above, prior FDA approval is needed before compassionate use occurs. Section 561(b) of the act and 21 CFR 812.35. In order to obtain agency approval, the sponsor should submit an IDE supplement requesting approval for a protocol deviation under section 812.35(a) in order to treat the patient. The IDE supplement should include:

- A description of the patient's condition and the circumstances necessitating treatment;
- A discussion of why alternatives 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;
- An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient; and
- The patient protection measures listed above that will be followed.

[8] This guidance may be found at: www.fda.gov/cdrh/ode/idepolcy.html

The patient identified in the supplement should not be treated with the device until FDA approves its use under the proposed circumstances. In reviewing this type of request, FDA will consider the above information as well as whether the preliminary evidence of safety and effectiveness justifies such use and whether such use would interfere with the conduct of a clinical trial to support marketing approval.

If the request is approved, the attending physician should devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient should be monitored to detect any possible problems arising from the use of the device. Following the compassionate use of the device, a follow-up report should be submitted to FDA in which summary information regarding patient outcome is presented. If any problems occurred as a result of device use, they should be discussed in the supplement and reported to the reviewing IRB as soon as possible.

Additional information on the procedures physicians and IRBs should follow in compassionate use situations may be found in Chapter III Expanded Access to Unapproved Devices of the guidance entitled, "IDE Policies and Procedures." [9]

18. What is the definition of a custom device?

To be considered a custom device, the device must meet all of the following criteria, which are described in section 520(b) of the act and at 21 CFR 812.3(b):

(1) It necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist;
(2) The device is not generally available to, or generally used by, other physicians or dentists;
(3) It is not generally available in finished form for purchase or for dispensing upon prescription;
(4) It is not offered for commercial distribution through labeling or advertising; and
(5) It is intended for use by an individual patient named in the order form of a 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 (such as a particular operating tool).

19. Does an IRB need to review custom use?

FDA regulations do not require review and approval for custom device use. However, FDA recommends that as many of the patient protection measures listed in paragraph 16 be followed as possible. IRBs should be familiar with the regulatory requirements for custom devices

[9] This guidance may be found at: www.fda.gov/cdrh/ode/idepolcy.html

because physicians or institutions may seek information from the IRB about the use of a custom device in patients at their healthcare facility. IRBs may develop procedures for the use of custom devices to ensure that patient protection measures are thoughtfully carried out.