Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

Frequently Asked Questions About Medical Devices

Additional copies are available from:

Good Clinical Practice Program, HF-34
Office of Science & Health Coordination, Office of the Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) (301)-827-3340
http://www.fda.gov/oc/gcp/guidance.html

or

Division of Small Manufacturers, International, and Consumer Assistance, HFZ-220
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive
Rockville, MD 20850
Tel: 1-800-638-2041
www.fda.gov/cdrh

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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

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. Significant 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.)

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 dist

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

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.