

CONSIDERATION OF INVESTIGATIONAL DEVICE EXEMPTIONS

The Food and Drug Administration regulations permit a device to be shipped only if it has a marketing permit. Shipment of a device without a marketing permit is not allowed unless that device is exempt from the permit requirements by means of an Investigational Device Exemption (IDE).

The FDA regulation about IDEs is located in 21 CFR 812. This regulation also specifies several exemptions from the IDE rules such as consumer preference testing and testing of a non-invasive diagnostic device where the usual procedure is also used as a back-up. These are exemptions from the IDE requirements; they are *not* exemptions from Part 56 (IRB review) or from Part 50 (informed consent requirement).

There are two types of IDE. First, the sponsor may apply directly to the FDA. Second, the FDA will consider an "abbreviated IDE" to have been granted should an Institutional Review Board (IRB) give approval to the investigation under Part 56, *and* make a decision that it agrees with a sponsor's contention that the device is a "non-significant risk device." (812.2b)

The regulation defines a "significant risk device" in 21 CFR 812.3(m). The FDA Information Sheet of October 1, 1995 defines it as "a study of a device" that meets one of the following criteria.

1. is intended as an implant
AND presents a potential for serious risk to the health, safety, or welfare of a subject;
2. 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;
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;
4. *or* otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The difference between the two definitions is critical as the first evaluates the risks of the device and the latter interpretation evaluates the risks derived from all of the procedures in the study of the device.

The Information Sheets also suggest that the IRB should consider the NSR/SR question (Part 812.2) first and the protocol approval question (parts 56 and 50) second.

The following are the guidelines of the IRC IRB for making decisions regarding the significance of the risk of devices.

REASONING:

In order to reach a consensus on the IRB review guidelines for making SR/NSR decisions, the IRB has agreed on several policies and presumptions.

- 1. The IRB depends upon the sponsor to make an initial determination of the regulatory status of the device, to state that determination clearly and to provide justification for that position.**

The IRB does not have the sponsor's knowledge of the device's development or of the regulatory status vis-a-vis the FDA. Therefore, it is a sponsor's duty to determine their marketing strategy and their decisions about the regulatory status of the device.

- 2. The IRB will not routinely ask for outside expert consultation**

Both Congress and the FDA understood the diverse membership and lack of specific expertise on IRBs when they assigned IRBs the NSR review task. FDA should recognize that most IRBs do not have the expertise to render peer review of the quality given by FDA panels.

- 3. The IRB will consider the IDE question to be separate from the question of protocol approval and will render two separate decisions.**

The criteria for IRB approval and for NSR/SR decisions are quite different and use several different definitions of risk. Each risk definition requires a different analysis and has a different outcome.

The risks considered under part 56.111(a) must be minimized and those in (b) include all of the risks in a study and are judged in relation to the benefits of the study. The risk in 50.25(a)(2) is simply to be explained. The risks in 812.(3)(m) are those of the device.

This policy could lead to approval of a protocol and a SR decision or to an NSR decision and disapproval of the protocol.

- 4. The IRB will consider the incremental risk posed to a subject by the device or the changed device over the risks of the device or procedure that would be posed to a patient by the standard or usual device or procedure.**

Although it is reasonable to think that the FDA could not have wished an absolute criterion to be used since this would seem to be self-defeating, the October 1995 Information Sheets state,

"The amount of potential reduced or increased risk associated with the investigational pacemaker should only be considered (in relation to possible decreased or increased benefits) when assessing whether the study can be approved."

The intent of Congress was to allow a method of review that would speed the device approval process *without adding undue risk to subjects*. An absolute criterion evaluates the risks against a null background without comparison to existing (FDA cleared) devices or procedures or the harms that might befall the patient during ordinary care. It therefore yields a much higher risk analysis which means almost all devices are SR and must go to FDA.

- 5. The IRB will not consider the risks that might occur through negligent use of the device.**

Following release of a device, the FDA has no ability to control the skill of the device user. Therefore, analysis of risk in a trial must rely on the risks posed by the device as it would be used normally rather than as it might be misused. (For example, if surgery is involved, the evaluation will not include the skill of the surgeon beyond the skill usually required in practice.)

6. The risk to be considered in review of the study are all risks; those reviewed for the NSR determination are those presented by the device used in the way it will be used in the confines of that study.

Using this criteria the IRB satisfies both the regulatory definition which asks for evaluation of the device and the FDA interpretation which asks for evaluation of the device study.

CRITERIA FOR IRC IRB DECISIONS ABOUT SIGNIFICANCE OF RISK:

The questions involved in an IRB NSR decision are:

- 1) what are the possible harms to subjects in this study and which of those are potentially caused by the device as it is to be used in the context of the proposed study
- 2) how frequently might those harms occur in the population described in the protocol, and
- 3) how serious are those harms?

To reach their decision:

1. The IRB will review the statements from the applicant concerning regulatory status and regulatory requests.
2. The IRB will render two decisions: one concerning approval of the investigational protocol and one concerning whether the device as used in the context of the study poses a significant or non-significant risk. A decision approving a protocol is not a decision relative to NSR or SR.
3. The IRB will consider all of the risks of the device as compared to similar devices already approved for use. That is, the IRB will consider the increment in risk over the prevailing risks the subject might experience.
4. In general the IRB will consider the risks of the device itself rather than those risks plus those from all ancillary procedures. An exception will be made if a procedure is done solely due to the investigational nature of the device.
5. The IRB will consider risks posed by possible device malfunctions; it will not generally consider risks posed by negligent use.
6. As a general rule, a device causing systemic effects will be considered as significant risk device.
7. The IRB decision about the significance of the risk of the device will be limited to the device's use in the context of the approved protocol and by the investigator(s) named. That is, the NSR decision is not transferable to any other situation or protocol.
8. The IRB will not consider an absence of data to dictate a decision of significant risk. That is, the first ever use of a device will not necessarily be thought to be a significant risk just because of the lack of clinical information on it.
8. The IRB STRONGLY SUGGESTS that a sponsor notify the FDA of any decision that a device poses a non-significant risk.

NSR APPLICATION PROCEDURES AND REQUIREMENTS:

The NSR application must be separate and distinct from the protocol. It is usually submitted as an appendix. The review question and decision criteria are different and require a separate and distinct appraisal and decision.

The questions are (1) what are the possible harms caused by the the device as it is to be used in the context of the proposed study (2) how frequently might those harms occur in the population described in the protocol, and (3) how serious are those harms?

The applicant should submit an appendix to the submitted protocol. This appendix should accomplish several goals:

1. It should describe the proposed device clearly enough so that there is not likely to be any future confusion about which model of which device was considered. If possible there should be a version or model number used.
2. It should contend that the device does not pose significant risk to the health, safety, or welfare of subjects, and
3. To allow evaluation of the risk, the sponsor should submit all relevant positive or negative information about all prior investigations with the device, AND with similar devices. The document, "Report of Prior Investigations" is usually submitted in support of an investigational protocol and is appropriate.
4. It should include sufficient evidence to support that claim to allow the IRB members to reach the same conclusion.
5. The IRB letter will indicate that a named device, was reviewed, that it was found to pose non-significant risk as it is to be used in the context of the particular study, and that a number has been assigned.

IMPORTANT -- PLEASE NOTE:

As there is the possibility that FDA will not agree with an IRB's decision, and that this difference of opinion will not be known until the time a PMA is submitted, it is strongly suggested that sponsors notify FDA of the NSR decision before making any large investment of time and money.