

## INFORMATION SHEETS

### Guidance for Institutional Review Boards and Clinical Investigators 1998 Update

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## Drugs and Biologics

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## Emergency Use of an Investigation Drug or Biologic

The emergency use of test articles frequently prompts questions from Institutional Review Boards (IRBs) and investigators. This information sheet addresses three areas of concern: emergency Investigational New Drug (IND) requirements; IRB procedures; and informed consent requirements.

### Obtaining an Emergency IND

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means [21 CFR 312.36].

## FDA Contacts for Obtaining an Emergency IND

Product	Office/Division to Contact
<i>The grayed-out information in this chart is no longer accurate. <a href="#">Get current information.</a></i>	
drug products	[Redacted] (HFD-210) [Redacted]
biological blood products	Office of Blood Research and Review (HFM-300) 301-827-3518
biological vaccine products	Office of Vaccines Research [Redacted] [Redacted] (HFM-400) [Redacted]
[Redacted]	[Redacted]
On nights and weekends	[Redacted] (HFC-160) 301-443-1240

### Emergency Exemption from Prospective IRB Approval

Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

**Life-threatening**, for the purposes of section 56.102(d), includes the scope of both life-threatening and severely debilitating, as defined below.

**Life-threatening** means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

**Severely debilitating** means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Institutional procedures may require that the IRB be notified prior to such use, however, this notification should not be construed as an IRB approval. Notification should be used by the IRB to initiate tracking to ensure that the investigator files a report within the five day time-frame required by 21 CFR 56.104(c). The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, "interim," "compassionate," "temporary" or other terms for an expedited approval process are not authorized. An IRB must either convene and give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, some IRBs have sent to the sponsor a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although, this is not an "IRB approval," the acknowledgment letter has been acceptable to manufacturers and has allowed the shipment to proceed.

This policy is undergoing review and is subject to change.

### **Exception From Informed Consent Requirement**

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFR 50.23(a)]:

- (1) The subject is confronted by a life-threatening situation necessitating the use of the test article.
- (2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- (3) Time is not sufficient to obtain consent from the subject's legal

representative.

(4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

### **Exception from Informed Consent for Planned Emergency Research**

The conduct of planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived, is provided by 21 CFR 50.24. The research plan must be approved in advance by FDA and the IRB, and publicly disclosed to the community in which the research will be conducted. Such studies are usually not eligible for the emergency approvals described above. The information sheet "Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble," is a compilation of the wording of 21 CFR 50.24 and pertinent portions of the preamble from the October 2, 1996 Federal Register.

*Also see these FDA Information Sheets:*

["Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble"](#)

["Emergency Use of Unapproved Medical Devices"](#)

["Treatment Use of Investigational Drugs"](#)

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### **Expanded Access of Investigational Drugs**

Investigational products are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an investigational new drug (IND) used for these purposes reflect the recognition by the Food and Drug Administration (FDA) that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval.

## OPEN LABEL PROTOCOL OR OPEN PROTOCOL IND

These are usually uncontrolled studies, carried out to obtain additional safety data (Phase 3 studies). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective Institutional Review Board (IRB) review and informed consent.

## TREATMENT IND

The treatment IND [21 CFR 312.34 and 312.35] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

There are four requirements that must be met before a treatment IND can be issued: 1) the drug is intended to treat a serious or immediately life-threatening disease; 2) there is no satisfactory alternative treatment available; 3) the drug is already under investigation, or trials have been completed; and 4) the trial sponsor is actively pursuing marketing approval.

Treatment IND studies require prospective IRB review and informed consent. A sponsor may apply for a waiver of local IRB review under a treatment IND if it can be shown to be in the best interest of the subjects, and if a satisfactory alternate mechanism for assuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the informed consent requirement. An IRB may still opt to review a study even if FDA has granted a waiver.

## GROUP C TREATMENT IND

The "Group C" treatment IND was established by agreement between FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. They can generally be administered by properly trained physicians without the need for specialized supportive care facilities. Group C drugs are distributed only by the National Institutes of Health under NCI protocols. Although treatment is the primary objective and patients treated under Group C guidelines are not part of a clinical trial, safety and effectiveness data are collected. Because administration of Group C drugs is

not done with research intent, FDA has generally granted a waiver from the IRB review requirements [21 CFR 56.105]. Even though FDA has granted a waiver for these drugs, an IRB may still choose to conduct a review under its policies and procedures. The usage of a Group C drug is described in its accompanying "Guideline Protocol" document. The Guideline Protocol contains an FDA-approved informed consent document which must be used if there has been no local IRB review.

### PARALLEL TRACK

The Agency's Parallel Track policy [57 FR 13250] permits wider access to promising new drugs for AIDS/HIV related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prospective IRB review and informed consent.

### EMERGENCY USE IND

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In such cases, FDA may authorize shipment of the drug for a specified use [21 CFR 312.36]. Such authorization is usually conditioned upon the sponsor filing an appropriate application as soon as practicable. Prospective IRB review is required unless the conditions for exemption are met [21 CFR 56.104(c) and 56.102(d)]. Informed consent is required unless the conditions for exception are met [21 CFR 50.23].

*Also see this FDA Information Sheet:*

["Emergency Use of an Investigational Drug or Biologic"](#)

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## **Waiver of IRB Requirements for Drug and Biologics Studies**

In accordance with 21 CFR 56.105, FDA may waive any of the requirements contained in the Institutional Review Board (IRB) regulations [21 CFR part 56] if requested by the sponsor or sponsor-investigator. A waiver can be granted for specific research activities or for classes of research activities otherwise covered by the IRB regulations. Note that the waiver provision does not apply to the informed consent requirements [21 CFR part 50]. An institution may still require IRB review on the local level even if a waiver from FDA is granted.

FDA uses the waiver provision only where it would be in the best interest of the subjects and where alternative mechanisms for assuring the protection of the subjects are adequate. Circumstances which FDA will consider for a waiver include "treatment INDs," i.e., the use of an investigational drug or biologic primarily for the treatment of a subject with a serious or immediately life-threatening disease for whom comparable or satisfactory alternate therapy is unavailable. [See 21 CFR 312.34.] The waiver provision is not needed for an emergency use because the regulations contain a provision for exemption from prospective IRB review in an emergency, provided that such use is reported to the IRB within 5 working days [21 CFR 56.104(c)].

FDA will handle waiver requests expeditiously. A request for waiver should contain the following information:

- (1) The specific requirement or requirements in the IRB regulations for which a waiver is requested.
- (2) The specific research activity for which the waiver will be applied and why this is a special situation.
- (3) Why a waiver would be in the interest of subjects.
- (4) What alternate mechanism(s) for assuring the protection of human subjects is available and would be utilized.
- (5) A copy of the proposed consent document.

The sponsor or sponsor-investigator should submit a request for a waiver associated with an IND to the Review Division in the Center for Drug Evaluation and Research (CDER) or to the Review Division in the Center for Biologic Evaluation and Research (CBER) responsible for reviewing the IND. If the identity of the responsible Review Division is unknown, the waiver request may be sent to:

**For DRUG PRODUCTS:**

Drug Information Branch (HFD-211)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857  
(301) 827- 4573

For a BIOLOGICAL BLOOD product, contact:  
Office of Blood Research and Review (HFM-300)  
Center for Biologic Evaluation and Research  
Food and Drug Administration  
1401 Rockville Pike  
Rockville, Maryland 20852  
301-827-3518

For a BIOLOGICAL VACCINE product, contact:  
Office of Vaccines Research and Review (HFM-400)  
Food and Drug Administration  
8800 Rockville Pike  
Bethesda, Maryland 20892-0001  
301-827-0648

For a BIOLOGICAL THERAPEUTIC product, contact:  
Office of Therapeutics Research and Review (HFM-500)  
Food and Drug Administration  
1451 Rockville Pike  
Rockville, Maryland 20852-1420  
301-594-2860

*Also see these FDA Information Sheets:*  
["Emergency Use of an Investigational Drug or Biologic"](#)  
["Treatment Use of Investigational Drugs"](#)

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## **Drug Study Designs**

Before a new drug or biologic can be marketed, its sponsor must show, through adequate and well-controlled clinical studies, that it is effective. A well-controlled study permits a comparison of subjects treated with the new agent with a suitable control population, so that the effect of the new agent can be determined and distinguished from other influences, such as spontaneous change, "placebo" effects, concomitant therapy, or observer expectations. FDA regulations [21 CFR 314.126] cite five different kinds of controls that can be useful in particular circumstances:

- (1) placebo concurrent control
- (2) dose-comparison concurrent control
- (3) no-treatment concurrent control
- (4) active-treatment concurrent control, and
- (5) historical control

No general preference is expressed for any one type, but the study design chosen must be adequate to the task. Thus, in discussing historical controls, the regulation notes that, because it is relatively difficult to be sure that historical control groups are comparable to the treated subjects with respect to variables that could effect outcome, use of historical control studies has been reserved for special circumstances, notably cases where the disease treated has high and predictable mortality (a large difference from this usual course would be easy to detect) and those in which the effect is self-evident (e.g., a general anesthetic).

Placebo control, no-treatment control (suitable where objective measurements are felt to make blinding unnecessary), and dose-comparison control studies are all study designs in which a difference is intended to be shown between the test article and some control. The alternative study design generally proposed to these kinds of studies is an active-treatment concurrent control in which a finding of no difference between the test article and the recognized effective agent (active-control) would be considered evidence of effectiveness of the new agent. There are circumstances in which this is a fully valid design. Active-controls are usually used in antibiotic trials, for example, because it is easy to tell the difference between antibiotics that have the expected effect on specific infections and those that do not. In many cases, however, the active-control design may be simply incapable of allowing any conclusion as to whether or not the test article is having an effect.

There are three principal difficulties in interpreting active-control trials. First, active-control trials are often too small to show that a clinically meaningful difference between the two treatments, if present, could have been detected with reasonable assurance; i.e., the trials have a high "beta-error." In part, this can be overcome by increasing sample size, but two other problems remain even if studies are large. One problem is that there are numerous ways of conducting a study that can obscure differences between treatments, such as poor diagnostic criteria, poor methods of measurement, poor compliance, medication errors, or poor training of observers. As a general statement, carelessness of all kinds will tend to obscure differences between treatments. Where the objective of a study is to show a difference, investigators have powerful stimuli toward assuring study excellence. Active-control studies, however, which are intended to show no significant difference between treatments, do not provide the same incentives toward study excellence, and it is difficult to detect or assess the kinds of poor study quality that can arise. The other problem is that a finding of no difference between a test article and an effective treatment may not be meaningful. Even where all the incentives toward study excellence are present, i.e., in placebo-controlled trials, effective drugs are not necessarily demonstrably effective (i.e., superior to placebo) every time they are studied. In the absence of a placebo group, a finding of no difference in an active-control study therefore can mean that both agents are effective, that neither agent was effective in that study, or that the study was simply unable to tell effective from ineffective agents. In other words, to draw the conclusion that the test article was effective, one has to know with assurance that the active-control would have shown superior results to a placebo, had a placebo group been included in the study.

For certain drug classes, such as analgesics, antidepressants or anti-anxiety drugs, failure to show superiority to placebo in a given study is common. This is also often seen with antihypertensives, anti-angina drugs, anti-heart failure treatments, antihistamines, and drugs for asthma prophylaxis. In these situations, active-control trials showing no difference between the new drug

and control are of little value as primary evidence of effectiveness and the active-control design (the study design most often proposed as an alternative to use of a placebo) is not credible.

In many situations, deciding whether an active-control design is likely to be a useful basis for providing data for marketing approval is a matter of judgment influenced by available evidence. If, for example, examination of prior studies of a proposed active-control reveals that the test article can very regularly (almost always) be distinguished from placebo in a particular setting (subject population, dose, and other defined parameters), an active-control design may be reasonable if it reproduces the setting in which the active-control has been regularly effective.

It is often possible to design a successful placebo-controlled trial that does not cause investigator discomfort nor raise ethical issues. Treatment periods can be kept short; early "escape" mechanisms can be built into the study so that subjects will not undergo prolonged placebo-treatment if they are not doing well. In some cases randomized placebo-controlled therapy withdrawal studies have been used to minimize exposure to placebo or unsuccessful therapy; in such studies apparent responders to a treatment in an open study are randomly assigned to continued treatment or to placebo. Subjects who fail (e.g., blood pressure rises, angina worsens) can be removed promptly, with such failure representing a study endpoint.

IRBs may face difficult issues in deciding on the acceptability of placebo-controlled and active-control trials. Placebo-controlled trials, regardless of any advantages in interpretation of results, are obviously not ethically acceptable where existing treatment is life-prolonging. A placebo-controlled study that exposes subjects to a documented serious risk is not acceptable, but it is critical to review the evidence that harm would result from denial of active treatment, because alternative study designs, especially active-control studies, may not be informative, exposing subjects to risk but without being able to collect useful information.

For additional information, contact:

For DRUG PRODUCTS:  
Drug Information Branch (HFD-211)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857  
(301) 827- 4573

For a BIOLOGICAL BLOOD product, contact:  
Office of Blood Research and Review (HFM-300)

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## **Evaluation of Gender Differences in Clinical Investigations**

### FDA Guideline

On July 22, 1993, the FDA published the Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, in the Federal Register [58 FR 39406]. The guideline was developed amidst growing concerns that the drug development process did not provide adequate information about the effects of drugs or biological products in women and a general consensus that women should be allowed to determine for themselves the appropriateness of participating in early clinical trials.

Many aspects of the guideline may be important to an Institutional Review Board (IRB) as part of its initial deliberations about protocols and ongoing surveillance of research. While the guideline specifically addresses drug and biologic testing, the Agency suggests that when reviewing medical device studies, IRBs consider whether the principles of the guideline apply to the device under investigation and, if so, whether to include these principles in their review of the protocol. IRBs should be aware that the FDA guideline represents current policy and describes the Agency's expectations regarding the inclusion of subjects in drug development.

The guideline presents the following critical changes that should be reflected in drug and biologic product protocols presented to IRBs:

- First, the guideline lifts a restriction on participation by most women with childbearing potential from entering Phase 1 and early Phase 2 trials, and now encourages their participation. FDA believes that early drug and biologic trials can be safely conducted in women even before completion of all animal reproduction studies through protocol designs that include monitoring for pregnancy as well as measures to prevent pregnancy during exposure to investigational agents. Pregnancy testing is recommended, and women must be counseled about the reliable use of contraception or abstinence from intercourse while participating in the clinical trial. The guideline does not, however, specify the type of contraception to be used because FDA believes that decisions of this nature are best left to the woman in consultation with her health care provider. It is important that investigators have access to gynecologic consultants who can provide information about contraceptives and advice for study participants.
- Second, the guideline states that sponsors should collect gender-related data during research and development and should analyze the data for gender effects in addition to other variables such as age and race. FDA requires sponsors to include a fair representation of both genders as participants in clinical trials so that clinically significant gender-related differences in response can be detected. The guideline also underscores the importance of collecting pharmacokinetics data on demographic differences beginning in the Phase 1 and 2 studies, so that relevant study designs are developed for later trials.
- In addition, the guideline identifies three specific pharmacokinetics issues to be considered when feasible: (1) effect of the stages of the menstrual cycle; (2) effect of exogenous hormonal therapy including oral contraceptives; and (3) effect of the drug or biologic on the pharmacokinetics of oral contraceptives.

### Informed Consent Issues

A critical responsibility of the investigator and the IRB has always included ensuring that there is an adequate informed consent process for study subjects. When preclinical teratology and reproductive toxicology studies are not completed prior to the initial studies in humans, male and female study subjects should be informed about lack of full characterization of the test article and the potential effects of the test agent on conception and fetal development. All study subjects should be provided with new pertinent information arising from preclinical studies as it becomes available, and informed consent documents should be updated when appropriate. Study subjects should also be informed about any new clinical data that emerge regarding general safety and effectiveness, including relevant gender effects.

## Summary

IRBs now have broader discretion to encourage the entry of a wide range of individuals into the early phases of clinical trials. FDA appreciates the cooperation of IRBs in assisting the Agency to foster changes in product development that will promote the overall health of all people. FDA urges IRBs not to needlessly exclude women or other groups.