**From:** Lee, Bonnie on behalf of OC GCP Questions
**Sent:** Monday, June 12, 2006 11:55 AM
**To:** [Redacted]
**Subject:** RE: questions about single pt IND/emergency use

Dear [Redacted],

Assuming I am understanding your questions correctly, the answers are:

1. yes

2. yes

3. no, recipient of the test article is a subject with or without prior IRB review

4. no, in all cases, the data should be provided to the sponsor in order to allow the sponsor to evaluate all information on the use of the test article.

I hope this is helpful.

Sincerely,

Bonnie

Bonnie M. Lee
Associate Director for Human Subject Protection Policy
Good Clinical Practice Program, FDA

This communication does not constitute a written advisory opinion under 21 CFR 10.85, but rather is an informal communication under 21 CFR 10.85(k) which represents the best judgment of the employee providing it. This information does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

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**From:** [Redacted]
**Sent:** Friday, June 02, 2006 5:37 PM
**To:** OC GCP Questions
**Cc:** [Redacted]
**Subject:** RE: questions about single pt IND/emergency use

Ms. Lee,

Hello. Thank you for the information that you generously provided to me back in March. I appreciate your assistance. I just want to make sure that I have this straight.

1. So, b/c of the definition provided below, I should consider people who receive test articles through means of emergency use (whereby prospective IRB review and approval was obtained prior to use) and those who receive test articles through a single patient IND approval to be subjects, correct?

2. In addition, if the above is true, the Principal Investigator would be able to collect data on either scenario and transfer data to the sponsor for the purposes of research.

3. The only time that a person is not considered to be a subject through emergency use is if the test article was provided to the patient without prospective IRB review and approval (previous to use of the test article), correct? in which case the IRB would be informed by the PI of his or her use of the test article within 5 working days.

4. In the above case, the patient would not be considered to be a subject and therefore, data may not be collected or transferred to the sponsor (maker of drug) for purposes of the research, correct?

Thank you for your assistance in this matter. I thoroughly appreciate your time and effort.

[Redacted]

>>> "OC GCP Questions" <gcp.questions@fda.hhs.gov> 3/27/2006 11:29 AM >>>
Dear [Redacted],

Let me try to respond to each of your questions.

Emergency Use:
"Emergency use" is defined in the IRB regulations as "...the use of a test article on 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). One of the exemptions from the IRB review requirement is the "Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review." 21 CFR 56.104(c). The regulations define a human subject as "...an individual who is or becomes *a participant in research, either as a recipient of the test article or as a control*. A subject may be either a healthy individual or a patient." 21 CFR 56.102(e). Informed consent is required except as provided in life-threatening situations described in 21 CFR 50.23 (a last ditch effort to save the life of the subject) or 50.24 (emergency research). As "emergency use" is defined in part 56, by definition there is not sufficient time to obtain IRB review and approval. Again, by definition the recipient of the test article is a human subject. Further, because the statute provides that investigational products be used for the express purpose of assessing the safety and effectiveness of the product, data is to be collected and maintained as required by the respective FDA regulations (e.g., 21 CFR 312 or 812). The statutory citations are sections 505(i) and 520(g)(2)(A) of the Federal Food, Drug, and Cosmetic Act.

Although the emergency use provision in 56.104(c) requires prospective IRB review for "any subsequent use of the test article", we recognize that in certain situations this would be the wrong thing to do from an ethical perspective. "Subsequent use" would be any use of the test article in the same patient or a second patient that occurs more than 5 days after its initial emergency use. (Note: We recognize that there may be situations when the course of the emergency treatment will extent past 5 days (this is not considered a subsequent use). If there is a need to begin a new course of treatment in the same subject or extend emergency treatment to an additional subject, but the IRB is unable to meet to review the subsequent use within the 5 days, FDA may exercise its enforcement discretion.) That is, you don't let the second person die just because there was someone who came in the door before him or her. Rather, if you find that you now have a second person and may get more who need to obtain this particular product, it would seem wise to solicit a protocol and consent form that would describe the proposed use, who could administer the test article (e.g., physicians in the emergency department; or specific specialties; or specifically named individuals), etc., so that the IRB could review the protocol prospectively and not need to rely on the 56.104(c) exemption.

Single Patient INDs:
FDA has developed several mechanisms to expand access to promising therapeutic agents without compromising the protections given to subjects or the scientific integrity of product development and marketing approval processes. Let me briefly describe each mechanism:
*Open label or expanded access* protocols are usually uncontrolled studies, carried out to get added safety data (Phase 3 studies). See 21 CFR 312.21(c). They are typically used when the controlled trial has ended to allow the subjects and the controls in the trial to continue to receive the benefits of the investigational drug until FDA grants marketing approval. These studies require prospective Institutional Review Board (IRB) review and informed consent. See 21 CFR parts 50 and 56.
*Treatment INDs* provide eligible subjects with investigational drugs to treat serious and life-threatening illnesses for which there are no satisfactory alternative treatments [21 CFR §312.34 and 312.35]. FDA may approve a treatment IND after enough data are collected to show the drug may be effective for its intended use in its intended patient population and does not expose the patients to an unreasonable risk and significant additional risk of illness or injury. See 21 CFR §312.34(b)(3)(A) and (B). Treatment INDs also serve to expand the body of knowledge about the drug because they collect data related to safety and side effects. 21 CFR §312.34(a). Treatment IND studies require prospective IRB review and informed consent. See 21 CFR §312.34(c). A sponsor may apply for a waiver of IRB review under a treatment IND. The sponsor needs to show a waiver would be in the best interest of the subjects, and describe a satisfactory alternate mechanism for assuring the protection of human subjects that is available. See 21 CFR §312.10 and §56.105. An IRB may still opt to review a study even if FDA has granted a waiver. See 21 CFR §56.108(a) and §56.114. The agency, however, cannot waive the informed consent requirement. See 21 CFR §50.20.
*Emergency Use INDs:* An investigator may need an investigational drug or biologic to treat a patient in an emergency situation that does not allow time for submission of an IND application in accordance with 21 CFR §312.23 or §312.34. However, an IND is required for the emergency use of an unapproved investigational drug or biologic. If the patient does not meet the entrance criteria of an existing study protocol, the physician can contact the manufacturer to find out if the manufacturer can make the drug or biologic available for the emergency use. If the manufacturer agrees, the physician then contacts FDA. In such cases, FDA may allow shipment of the drug for a specified use [21 CFR §312.36]. FDA usually conditions such authorization on the sponsor/investigator filing an appropriate application as soon as practicable. FDA requires prospective IRB review unless the conditions for exemption are met. See 21 CFR §56.104(c) and §56.102(d). Additionally, informed consent is required unless the conditions for an exception to the requirement are met. See 21 CFR §50.23.

I assume, when you ask about Single Patient INDs, you are referring to emergency use INDs or possibly entry by a single patient into an expanded access protocol. Now, to your questions.

1. The sponsor ships the product conditioned, in part, on receiving data on the patient's/subject's experience. (See the discussion at the beginning of this email.)
2. The patients/subjects who receive a drug via a single patient IND are considered to be research subjects under FDA's regulations.

3. If the IRB receives additional requests involving the same drug for a single patient IND, but it is for a different patient, an additional single patient IND would need to be obtained to permit that person to receive the product. If the use was actually under an open label or expanded access protocol, and the patient met the entrance criteria, it may just be a matter of contacting the sponsor (or not) depending upon the protocol requirements in use. The "single patient" IND is named that for a reason. In some cases, the sponsor wants to limit access to the drug and will permit only a very few people to receive it.

It's hard to answer in the abstract, the last question in your email. Yes, if it is truly a single patient IND that you are reviewing, then you would need to review each case on its merits. If you have a standard protocol that describes the use, the investigators, etc., and this is really more of an expanded access protocol, you can review the protocol and conduct continuing review as you would for other studies.

I hope I haven't totally confused you. I hope this is helpful. If you have additional questions, please let me know.

Sincerely,

Bonnie

Bonnie M. Lee
Associate Director for Human Subject Protection Policy
Good Clinical Practice Program, FDA
Note new email address: Bonnie.Lee@FDA.HHS.GOV

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-----Original Message-----
**From:** [Redacted]
**Sent:** Tuesday, March 21, 2006 2:27 PM
**To:** OC GCP Questions
**Cc:** [Redacted]
**Subject:** questions about single pt IND/emergency use

Hello,

I would like to ask a question about the difference between emergency use and single patient INDs. I called the FDA regarding this issue and was told to email GCP about my question.

**Emergency Use –**

The way I understand emergency use is that - emergency use of a investigational drug, device, or biologic on a one time basis per institution

without IRB review and approval. It is always preferable for the IRB to review the emergency use previous to use, however the emergency use may proceed without IRB review and approval. Informed consent is required unless the situation is life-threatening. However, if there is not sufficient time to contact the IRB a written report should be submitted to the IRB within 5 business days on the emergency use, why it was necessary and the outcome. The patient is not considered to be a research subject and data may not be collected for the purposes of research.

1. Emergency use involving the drug, device or biologic should be used on a one time basis and requires formal study submission to the IRB for review in the instance that other scenarios involving the drug, device of biologic arise. Is this correct?

**Single Patient INDs –**

Single patient INDs are a means of providing eligible subjects (patients) with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. Single pt INDs do require informed consent and IRB review and approval prior to use. At my institution, we receive most of these requests as "compassionate use" whereby a specific patient meets the sponsor's guidelines for a "special exception protocol" or a "treatment use program".

1. My question is - can the sponsor request data related to the patient's experience with the drug received via a single patient IND for the purposes of research?

2. Are patients who receive drug via single pt INDs considered to be research subjects?

3. If the IRB receives additional requests involving the same drug for single pt IND but different patients meet the criteria -

Is there anything in the regulations which clarify if we receive the same request on a different patient and the patient meets the criteria - is formal IRB study submission required to the full board for review, because we have already approved the use of the drug once as a single pt IND and further requests require study submission. (I may be getting the "one time basis" confused with emergency use.)

It would seem that if different patients meet criteria for single pt use that the IRB would need to review each request on each patient on a case by case

scenario in order to determine if that pt meets the criteria for single pt use. Am I correct?

I appreciate your time in reviewing this information. We just want to be sure we are implementing the regulations correctly. Thank you for your assistance.

[Redacted]