**From:** Hommel, Carolyn - OC on behalf of OC GCP Questions
**Sent:** Friday, May 05, 2006 9:42 AM
**To:** [Redacted]
**Subject:** RE: Industry Practice of Authorizing Exemptions to Protocol Inclusion/Exclusion Criteria

Dear [Redacted]:

I apologize for the delay in responding to your e-mail. After consulting with other FDA offices, I can provide you with the following information:

As you know, 21 CFR 56.108(a) requires IRBs to follow written procedures "...(3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to human subjects."

In addition, 21 CFR 312.66 states, "...The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity...and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects."

Per 21 CFR 312.53(c)(1)(vi)(a), the investigator also gives his/her commitment to the sponsor, "...to conduct the study(ies) in accordance with the relevant current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects..."

In general, all protocol exceptions must be approved by both the sponsor and the IRB, and appropriately documented, before they are implemented. If a protocol exception has been approved by both the sponsor and the IRB, and appropriately documented, then it generally would not appear on the 483.

Having said that, I would point out that there may be instances in which one or more exceptions may be cited anyway, depending on the number of exceptions involved and the clinical/medical significance of the criterion/criteria for which the exception or exceptions were granted. We also note that numerous ad hoc changes to a study protocol, in effect, would undermine the purpose of IRB review and approval. The IRB needs to be involved, as does the sponsor, prior to making any change, unless it's an emergency situation requiring immediate action.

Furthermore, if numerous exceptions to the protocol are allowed, it may also undermine the study, and, potentially, the usefulness of the data in supporting determinations of safety and/or efficacy. If it appears that such waiver requests from one or more study sites are justified, the sponsor should develop an

amendment to the protocol in this regard (see 21 CFR 312.30, generally) so that all sites will function in the same way and the data will be consistent across sites. If it appears that such waiver requests are seemingly routinely granted, it may be worth exploring with the sponsor to determine if the sponsor has requested a protocol amendment.

Bottom-line, if the change has been approved by the sponsor and IRB, or it's to eliminate immediate hazards, whether it is a single occasion or just a few, it probably will not appear on the 483, though it should still be discussed and included in the establishment inspection report (EIR).

I hope this is helpful.

Sincerely,

Carolyn Hommel
Consumer Safety Officer
Good Clinical Practice Program
Office of Science and Health Coordination
Office of the Commissioner
U.S. Food and Drug Administration (HF-34)
5600 Fishers Lane, Room 9C24
Rockville, MD 20857

Note new e-mail address: Carolyn.Hommel@fda.hhs.gov

Phone: 301/827-3340
Fax: 301/827-1169

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.

---

**From:** [Redacted]
**Sent:** Monday, March 20, 2006 7:38 AM
**To:** OC GCP Questions
**Subject:** Industry Practice of Authorizing Exemptions to Protocol Inclusion/Exclusion Criteria

Recently I have seen what appears to be an increase in the FDA Form 483 findings being issued related to protocol deviations including the citing of investigators that have documentation that the sponsor approved an exemption to a inclusion criteria prior to enrolling the subject. It has been common in the industry for investigators to contact the sponsor when they have potential subjects that they want to enroll in the study but do not meet the protocol stated inclusion or exclusion criteria. The investigator obtains documentation from the sponsor to allow the subject to be enrolled in the study.

Also at a recent meeting a speaker from the FDA stated they they still consider pre-approved protocol exemptions to still be protocol deviations and felt that they should be listed as an inspection finding.

We are having many questions from our sponsors regarding this subject and I would appreciate knowing the agency policy position regarding pre-approved protocol exemptions.

Thank you for your time and consideration on this subject.

[Redacted]