**From:** OC GCP Questions
**To:** [redacted]
**Subject:** Question of Site to Site IP transfer
**Date:** Thursday, August 23, 2018 9:04:00 AM
**Attachments:** [redacted]

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Good morning --

As stated in my first email, documentation of the unused product should be completed and the unused IP should be returned to the sponsor. 21 CFR 312.53(b) stated "*Control of drug.* A sponsor shall ship investigational new drugs only to investigators participating in the investigation." It is recommended that the unused IP be shipped back to the sponsor and the sponsor can ship it to the second site. This will assure proper documentation and recordkeeping of the IP.

Kind regards,

Doreen M. Kezer, MSN
Senior Health Policy Analyst
Office of Good Clinical Practice
Office of the Commissioner, FDA

U.S. FOOD & DRUG ADMINISTRATION

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:** Thursday, August 23, 2018 3:24 AM
**To:** OC GCP Questions <gcpquestions@fda.hhs.gov>; OC GCP Questions <gcpquestions@fda.hhs.gov>
**Subject:** Re: Question of Site to Site IP transfer

Dear Team,

Good morning..!

Thank you very much for your prompt response.

Can you please clarify - FDA view on below specific question.

What is FDA's Guidance on the transfer of unused Investigational Product (IP) (within Expiry period) from one site to another site by a sponsor in a Phase II/III multi-centric randomized clinical trial?

There is a specific case, where a sponsor wishes to transfer unused IP (within Expiry period) from one site to another site due to inevitable circumstances. The transferred unused IP to another site will be administered to new subjects getting enrolled at the new site.

Is above process followed by a sponsor acceptable to the FDA?

Thank you.

With Regards

[redacted]

On Wed, Aug 22, 2018 at 9:30 PM OC GCP Questions <gcpquestions@fda.hhs.gov> wrote:

> Good morning –
>
> For questions 1 and 2 –
>
> I can point you to the ICH E6(R2): Good Clinical Practice: Consolidated Guidance https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf, which is official guidance recognized by FDA, does address storage temperatures in the following sections
>
> 5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.
>
> 5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).
>
> The manufacturer/sponsor of the investigational product generally determines (via controlled studies) the appropriate storage conditions for the investigational product. The study protocol usually states the conditions/controls under which the investigational product should be stored in an effort to preserve the quality, strength, purity and identity of the product. If excursions are permissible, this should be described in the study protocol.
>
> FDA's regulations on records about disposition of the investigational drug state, "An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 312.59."
>
> 312.59 states -- The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug in accordance with 312.57.
>
> 312.61 states -- Control of the investigational drug.
> An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.
>
> 21 CFR 312. 62(a) pertains to disposition of drug at the clinical site and states, " An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under sec. 312.59". The regulation seems to imply that that clinical investigator should maintain records showing disposition of the drug returned to the sponsor. These records would typically include records of shipment of unused supplies back to the sponsor. Such records could include for example, common carrier shipping records, a drug log or other inventory records such as memos to the file. The clinical investigator only has to keep a record showing the drug was returned. There is no explicit regulatory requirement that the clinical investigator must confirm receipt by the sponsor and keep a record of this at the clinical site. Logically, the sponsor should have a record of the return as explained above and required under 312.57. This would seem to address the concern that there is some record to confirm final receipt of drug returned from the sites.
>
> 312.69 states -- Handling of controlled substances.
> If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.
>
> As you can see, the regulations are very general to allow sponsors and study sites the necessary flexibility to account for the supplies of investigational product that were received, administered, returned, and the final disposition (e.g., destruction) of any unused investigational articles. Please note that the records maintained at the site need to be adequate to show "disposition of the drug, including dates, quantity, and use by subjects.

FDA experience is that only the CI of record can receive the investigational product (must be shipped to him/her at the specific site address). All this being said, the disposition (shipment) of the drug should be outlined in the protocol or the Investigator Brochure. Also, please contact your study sponsor for specific questions regarding shipment. Documentation of the unused product should be completed and the unused IP should be returned to the sponsor.

See below for question 3.

I hope this information is helpful.

Kind regards,

Doreen M. Kezer, MSN
Senior Health Policy Analyst
Office of Good Clinical Practice
Office of the Commissioner, FDA

[redacted]

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**From:** [redacted]
**Sent:** Wednesday, August 22, 2018 8:05 AM
**To:** OC GCP Questions <gcpquestions@fda.hhs.gov>
**Subject:** Question of Site to Site IP transfer

Dear Team,

Please provide clarity on below questions of multicentric IND clinical Trial (Phase II /Phase III).

1. USFDA allows Investigational product (IP) transfer from one investigator site to another investigator site of multicentric IND clinical Trial. (Phase II /Phase III)? If yes, then what is USFDA requirement for same? (See above)

2. Is it acceptable to USFDA to record IP storage condition (Temperature) once in a day or we have to record it for 24hrs (Min/Max temperature recording) at the investigator site? (See above) The IP storage conditions should be outlined in the protocol.

3. Sponsor - CRA/Monitor and Project Manager should be kept blinded to Double blind study?

Below is general information regarding monitoring and blinding.

Generally, the study site monitor and/or PM does not need to be aware of study arm assignments in order to fulfill site monitoring responsibilities Although the site monitor does not have a role in study outcome assessment, he/she will be interacting with the site staff. There is the potential that information may unintentionally be revealed that could break the blind for study staff. In order to avoid such a possibility, individuals whose roles do not require knowledge of study arm assignments should be kept blinded. If a monitor discovers findings where unblinding may be needed, he/she should contact the sponsor who would determine how to proceed with those findings while maintaining the study's integrity.

Again, unblinding can compromise the integrity of a study. Sponsors often use blinding and randomization to help minimize bias in the conduct of a study. Prematurely breaking the blind in a study

has the potential to bias the study and would not be in keeping with Good Clinical Practice. FDA's various guidance documents repeatedly warn (generally) against inadvertently breaking the blind of a study; it sort of goes without saying that intentionally doing so is a poor practice, particularly if breaking the blind is not specified in the study protocol.

Again citing ICH E-6(R2) --

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e g , accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s)

Thank you.

Regards
[redacted]