From: OC GCP Questions
To: [redacted]
Subject: RE: Question on BA/BE Studies Exempt from IND Safety Reporting to the IRB
Date: Tuesday, June 02, 2015 9:40:00 AM

Dear [redacted] -

Thank you for your question. If I understand your question correctly, I believe you are asking for clarification as to whether serious AEs (regardless of causality) observed during the conduct of an *in vitro* bioavailability (BA) or bioequivalence (BEQ) study are required to be reported to the IRB by the investigator. In general, any AE observed in a BA or BEQ study that is considered to be an unanticipated problem involving risk to human subjects or others must be reported to the IRB.

As you noted, the FDA regulations found at 21 CFR 320.31(d)(3) require that the person conducting the study, including any contract research organization, must notify FDA and all participating investigators of any serious AE, as defined in 312.32(a). You are correct that these regulations do not specifically address safety reporting by investigators to the IRB for BA/BEQ studies, but then neither do the regulations for IND safety reporting.

The regulations at 21 CFR 320.31(d)(2) require that a BA or BEQ study in humans be conducted in compliance with 21 CFR 50 (informed consent) and 56 (IRB). As you know, the IRB regulations at 21 CFR 56.108(b)(1) require the IRB to follow written procedures for reporting of any unanticipated problems involving risk to human subjects or others to the IRB, appropriate institutional officials, and the FDA. FDA also has Guidance for Clinical Investigators, Sponsors, and IRBs titled, "*Adverse Event Reporting to IRBs - Improving Human Subject Protection*" (see http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126572.pdf). This guidance is intended to assist the research community in interpreting requirements for submitting reports of unanticipated problems, including certain AE reports, to the IRB.

Some AEs are considered to be unanticipated problems and therefore require reporting to the IRB. The IRB's written procedures should include operational details that outline what constitutes an unanticipated problem involving risk to subjects or others, including those AEs that require reporting to the IRB as an unanticipated problem. IRBs should also consider making their written procedures available to investigators to ensure investigators are aware of the IRB's requirements, and to facilitate investigator compliance with the IRB's requirements.

The preamble to the final rule for IND safety reporting requirements for human drug and biological products and safety reporting for requirements for BA/BEQ studies (found at Federal Register /Vol. 75, No. 188 /Wednesday, September 29, 2010 /Rules and Regulations - see http://www.gpo.gov/fdsys/pkg/FR-2010-09-29/pdf/2010-24296.pdf) provides some explanation of FDA's thinking in addressing reports to investigators and IRBs. Please refer to section P, Comment 39 found on page 59955 of the FRN, copied here for reference:

> **P. Reports to Investigators and IRBs**
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> **(Comment 39)** Some comments stated that although the IRB's charge is to have written procedures for reporting ''any unanticipated problems involving risks to human subjects or others,'' the proposed rule is silent about sending any information to IRBs. These comments recommended that the agency provide guidance to sponsors, manufacturers, investigators, and IRBs that clearly delineates the responsibilities of reporting SADRs to the IRB. One comment requested that FDA require that the IRB receive from the sponsor the same expedited reports that the sponsor sends to FDA and all participating investigators (under proposed § 312.32(c)(1)). Other comments pointed out that IRBs are currently overwhelmed with IND safety reports and recommended that sponsors provide IRBs with routine timely aggregated reports of listings of adverse events instead of individual reports. Another comment suggested that investigators be permitted to provide these line-listings to their IRBs in lieu of individual reports. One comment urged FDA to adopt the CIOMS VI recommendations for IRB notification.
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> **(Response)** The agency concurs with the overall sentiments expressed by the comments and has provided recommendations for reporting adverse event information to IRBs in our ''Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting - Improving Human Subject Protection.'' We also expect that the more useful individual reports submitted by sponsors to FDA and investigators will translate into more useful information being provided by investigators to their IRBs. In addition, the agency may consider revisions to investigator reporting requirements to IRBs in a separate rulemaking initiative.

As noted in the preamble to the final rule and also in FDA's guidance on "*Safety Reporting Requirements for INDs and BA/BE Studies*", the occurrence of serious AEs is very unusual in a BA or BEQ study because the number of subjects enrolled in the study is small, the subjects are usually healthy volunteers, and drug exposure is typically brief. However, FDA occasionally receives safety-

related information associated with these types of studies, which could reflect either a problem with the drug product being evaluated or with the study design being used. For these reasons, the occurrence of any serious AE is of interest. The agency continues to believe that receiving reports from these trials is important for human subject protection and, therefore, has revised § 320.31(d)(3) to require that any serious AE be reported to FDA and all participating investigators, instead of any serious and unexpected SADR.

Because the agency continues to believe that receiving reports from these trials is important for human subject protection, IRB's should consider requiring notification from their investigators of such reports (i.e., when the IRB develops their written procedures on unanticipated problems, they should consider whether any serious AEs on a BA/BEQ study belong in the subset of AEs that qualify as an unanticipated problem requiring reporting to the IRB).

As you noted, the Compliance Program Guidance Manual for IRB inspections (referred to as BIMO in your question) as written could be misconstrued to imply that there is an expectation for IRB written procedures to include a requirement to receive notification of serious AEs from BA/BEQ studies, but the sentence you refer to in the CPGM says *should*, not *must*. The use of the word *should* means that something is suggested or recommended, but not required.

In summary, IRBs are required to follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials and the FDA of any unanticipated problems involving risk to human subjects or others (21 CFR 56.108(b)(1). In general, any AE from any study involving human subjects that is considered to be an unanticipated problem involving risk to human subjects or others must be reported to the IRB in accordance with the IRB's written procedures.

I hope this information is useful. If you need further information and/or have additional questions, please feel free to contact us at the official GCP mailbox, gcp.questions@fda.hhs.gov. You may also find it useful to access the set of redacted GCP e-mails found at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriestoFDAonGoodClinicalPractice/default.htm since we find that many questions and concerns are repeated over time.

Best Regards,

Janet

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Office of Special Medical Programs, Food and Drug Administration

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From: [redacted]
Sent: Wednesday, May 27, 2015 5:41 PM
To: OC GCP Questions
Subject: Question on BA/BE Studies Exempt from IND Safety Reporting to the IRB

Upon my review of the FDA BIMO for IRBs, I need assistance in determining whether or not investigators conducting BA or BE studies that are exempt from an IND are required by the FDA to report serious AEs (**regardless of causation**) **to the IRB**. (Investigators are required to report these events to the Sponsor and FDA).

The BIMO (dated 11/28/11) states, "Determine if the IRB has written procedures in place for clinical investigator **reporting of AEs** to the IRB (21 CFR 56.108(b)). The written procedures should **also** address how **unanticipated problems** are reported to the **IRB**, appropriate institutional officials, and FDA." This is in our procedures; **however**, the BIMO goes on to say, "The **written procedures should include reporting of serious AEs observed during the conduct of an in vitro bioavailability or bioequivalence study** in humans (21 CFR 320.31(d)(3)) that is exempt from the IND requirements under Part 312 (21 CFR 320.31(d))." It is this last statement that we need clarification on.

The FDA Guidance document, "Safety Reporting Requirements for INDs and BA/BE Studies" December 2012, explains unanticipated problems being reportable to the IRB. It also describes reporting requirements for BA/BE studies; however, I do not see anywhere where it states these should be reported to the IRB. The requirement, "The person conducting a BA or BE study, including any contract research organization, must **notify FDA and all participating investigators of any serious adverse event** observed during the conduct of the study, **regardless of whether the event is considered drug related**, as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence (21 CFR 320.31(d)(3)). This includes, for example, serious adverse events

listed in the reference product's approved labeling, the investigator brochure, and protocol. Serious adverse events, whether observed in the investigational drug group or in the approved drug group (e.g. reference listed drug), must be reported (21 CFR 320.31(d)(3)).”

Based on the above, we believe the requirement to report **serious AEs** (regardless of whether the event is considered drug related) observed during the conduct of an **in vitro BA or BE study in humans that is exempt from an IND** is from the Clinical Investigator/Sponsor to the FDA and **not** to the IRB. Please confirm or explain precisely what the reporting requirement to the IRB is for these studies and where that is stated in the regulations or how it can be surmised from them and/or precisely what you are looking for in the IRB's written procedures.

Thanks in advance for your assistance.