From: OC GCP Questions
To: [redacted]
Subject: Request for your assistance re: PharmD qualifications to assess adverse events in a clinical study
Date: Monday, September 22, 2014 2:23:47 PM

Good afternoon –

As noted in FDA's Clinical Investigator Compliance Program, FDA expects the clinical investigator to assess adverse events and to determine if the event is related to the study drug. Please see the link below.

http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133773.pdf It states –

In section E, # 3 "Describe the nature and frequency of communications with the IRB. Determine whether the investigator submitted information promptly to the IRB, in compliance with the protocol and applicable regulations, of all deaths, serious adverse experiences, and unanticipated problems involving risk to human subjects."

In section F, b iii and iv -
All adverse events were documented and appropriately reported;
The clinical investigator assessed the severity of the adverse event and documented the relationship of the event to the test article, including any adverse event that was previously anticipated and documented by written information from the sponsor;

The investigator is required to report serious adverse events to the sponsor and must include an assessment of whether there is a reasonable possibility that the drug caused the event (21 CFR 312.64). The sponsor is required to report serious and unexpected suspected adverse reactions to FDA and all participating investigators (21 CFR 312.32(c)(1).

The investigator should follow the protocol regarding the format for reporting the investigator's causality assessment to the sponsor. The IND safety reporting draft guidance includes the following:

"The sponsor should decide how to capture the investigator's causality assessment (e.g., rating scale, yes/no response to a question such as, "Was there a reasonable possibility that the drug caused the adverse event?")."

Additionally, investigators are required to promptly report "to the IRB … all unanticipated problems involving risk to human subjects or others," (21 CFR 312.66). The term unanticipated problem used in the Adverse Event Reporting to IRBs guidance describes adverse events and other types of problems (i.e., adverse events are a subset of unanticipated problems) that investigators are required to report to IRBs.

For clinical investigations of drug and biological products conducted under an investigational new drug (IND) application, information about adverse events must be communicated among investigators, sponsors, and IRBs (ethics committee) as follows:

Sponsors are specifically required to notify all participating investigators (and FDA) in a written IND safety report "as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information" of "any adverse experience associated with the use of the drug that is both serious and unexpected" and "any finding from tests in laboratory animals that suggests a significant risk for human subjects" (§ 312.32(c)(1)(i)(A),(B)). And, more generally, sponsors are required to "keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use" (§ 312.55(b)).

Prior to initiation of a study at a site, information must be provided to the IRB (EC) for review. The IRB needs information on risks to subjects in order to allow the IRB to assure that these risks are reasonable in relation to the anticipated benefits (21 CFR § 56.111(a)(2). Such information would include adverse

events that have occurred with the use of the drug. As noted above, once the study is approved, investigators are responsible for reporting to the IRB unanticipated problems, which may include adverse events.

As you are probably aware, it is often several years after the close of a clinical study before a sponsor submits the results in support of a marketing application to FDA. In addition, there have been times when seemingly unrelated SAEs have been revealed as related to use of the drug when information across multiple sites is compiled, thus including larger numbers that can make rare events apparent.

Please see the links below for additional safety reporting requirements.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332846.pdf

Investigational New Drug (IND) Application > Final Rule: Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans

I hope this information was helpful. Please contact us at gcp.questions@fda.hhs.gov if you have further questions.

Kind regards,

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

From: [redacted]
Sent: Monday, September 22, 2014 8:20 AM
To: OC GCP Questions
Subject: Request for your assistance re: PharmD qualifications to assess adverse events in a clinical study

To Whom It May Concern:

I am an independent regulatory researcher and I would appreciate your assistance in clarifying whether a PharmD is considered medically qualified to assess adverse events and to determine if the event is related to the study drug.

Thank you very much for any feedback that you can provide.

Kind regards,
[Redacted]