From: OC GCP Questions
To: [redacted]
Subject: RE: FW: pharmaceutical company requirements for licensed MDs
Date: Monday, November 24, 2014 10:16:00 AM

Dear [redacted]-

Thanks for your latest question and your continued patience in my response. I consulted with other FDA offices (OSI and the Office of Hematology and Oncology Products) and have incorporated their feedback into this response.

As previously described, FDA's regulations regarding responsibilities of sponsors and investigators who participate in FDA-regulated drug studies can be found in 21 CFR 312 subpart D (see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.4). These regulations describe what responsibilities sponsors have, but the regulations are not specific about how the sponsor fulfills these responsibilities. When the regulations are silent, sponsors are free to develop their own procedures and practices as long as applicable regulatory requirements are met.

As you know, FDA's jurisdiction covers a wide range of products, including drugs, biologics and devices. Even within a particular product area (e.g., devices), there are devices that are considered to be minimal risk, those that are non-significant risk, and those that present a significant risk. Similarly, drug studies can present a varied range of risk. Therefore, the training, education, and experience required for sponsor personnel may necessarily, and appropriately, vary depending on the type of product, the indication, the study being conducted, and its associated risk. FDA's regulations are not explicit as to what constitutes adequate training, education and experience, nor do they outline specific qualifications, including whether such personnel must hold an active medical license. Moreover, sponsors have discretion in determining what qualifications are needed in certain positions based on the general recognition that this would include education, training and experience pertinent to the particular clinical study and its design and execution, as well as familiarity with human subject protection (HSP) regulations, recordkeeping, data integrity, and good clinical practice (GCP) standards and requirements. Whether or not certain sponsor personnel should hold an active medical license depends on the considerations outlined above and discussed below.

We recognize that, as you said, most, if not all, medically related fields have full time licensing bodies devoted to ensuring that MD/RN/NP etc. are "appropriately qualified". We generally find that personnel in certain positions within the sponsor company typically are medically trained, and sponsors may have their own company-specific job qualifications required for certain positions within their company, which may or may not require an individual to hold an active medical license. We note that assessing qualifications involves more than just looking to see that an individual holds an active medical license. Assessing qualifications also includes assessing, for example, ones knowledge in the field of study, ones training in this particular field of study, whether one has received training in research, the specific protocol, GCPs, study conduct, etc.

As stated above, and as is the case with most of the regulations, the regulations addressing sponsor and investigator responsibilities address what is required, but not how the requirements have to be met. For that reason, FDA cannot require that sponsors hire only personnel that hold active medical licenses. We have seen that some sponsor protocols detail the qualifications of certain sponsor staff, e.g., the Medical Monitor who will oversee the safety data at the sponsor company. If the protocol dictates the qualifications for specific personnel, then FDA can hold the sponsor responsible for ensuring these qualifications are met. If FDA finds that there may be concerns about the qualifications of any sponsor personnel (e.g., through an inspection, review of the safety information submitted to FDA, or a complaint), then FDA can gather additional information and consider whether further action is necessary.

Sponsor responsibilities to review safety information of ongoing investigations likely include the involvement of personnel with medical backgrounds and expertise. As described above, FDA's jurisdiction covers a wide range of studies that present a wide range of associated risks and, while the regulations are not explicit as to what constitutes adequate training, education, experience (including licensure) for sponsor personnel, the ICH GCP E6 Good Clinical Practice: Consolidated Guidance, (which is recognized as official FDA guidance – see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf) is more specific in section 5.3 which states:

> *5.3 Medical Expertise*
>
> *The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.*

Following the ICH GCP E6 guidance mentioned above, sponsors should designate appropriately qualified medical personnel for positions where medical expertise is necessary. This may or may not require an individual to hold an active medical license.

We hope this information is helpful in explaining that the answer to your question depends on a number of considerations that will vary across studies.

Best Regards,

Janet

Janet Donnelly, RAC, CIP
Policy Analyst, Office of Good Clinical Practice
Office of Special Medical Programs, Food and Drug Administration

represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: [redacted]
Sent: Friday, October 24, 2014 2:22 AM
To: OC GCP Questions
Subject: Re: FW: pharmaceutical company requirements for licensed MDs

Hi Janet

Thank you for the follow through.

I do not have a particular study or sponsor in mind, but must say that I found OSI's answer circular -- the guidelines say "appropriately qualified medical personnel" but there is nothing there on HOW someone can be said to be "appropriately qualified". Most, if not all, medically related fields have full time licensing bodies devoted to ensuring that MD/RN/NP etc are "appropriately qualified". If the FDA guidelines, and OSI implementation, does not formally require up to date licensure then HOW, pragmatically, can the FDA state that a pharmaceutical company's personnel are or are not "appropriately qualified medical personnel"? And how would a company judge to ensure they are following GCP?

If it helps, can OSI please answer this question for an oncology study and they are reviewing the sponsor at a routine sponsor audit (not the investigators at the sites)?

Thank you and kind regards,
[redacted]

On Tue, Oct 21, 2014 at 1:34 PM, OC GCP Questions <gcp.questions@fda.hhs.gov> wrote:
Dear [redacted]

Thanks again for your patience in our response. As I previously mentioned, I forwarded your latest questions to my colleagues in CDER's Office of Scientific Investigations (OSI). OSI shared with me the response received from the Enforcement Branch within OSI:

The details of "appropriate" qualifications would depend on the study details and requirements and any additional requirements that a sponsor may have in selecting investigators. "Medical personnel" does not necessarily mean a physician.

I recommend that if you have concerns about a particular individual at a sponsor company for a specific study that you discuss your concerns with that sponsor. Should you need to report a complaint related to FDA-regulated clinical trials, you can find information on our web site at http://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/complaintsrelatingtoclinicaltrials/default.htm.

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
Janet Donnelly, RAC, CIP
Policy Analyst, Office of Good Clinical Practice
Office of Special Medical Programs, Food and 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: OC GCP Questions
Sent: Tuesday, October 14, 2014 11:04 AM
To: [redacted]
Subject: RE: pharmaceutical company requirements for licensed MDs

Dear [redacted]-
I forwarded your latest questions to some of my colleagues in CDER and am still waiting to hear back from them. Thank you for your continued patience, and we hope to provide a response soon.

Best Regards,
Janet
Janet Donnelly, RAC, CIP
Policy Analyst, Office of Good Clinical Practice
Office of Special Medical Programs, Food and 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: Wednesday, October 01, 2014 12:50 PM

To: OC GCP Questions
Subject: Re: pharmaceutical company requirements for licensed MDs

Dear Ms. Donnelly

Thank you for your response. I am asking about the Sponsor requirements, not the site investigator requirements and the material you sent along was helpful.

I remain unclear however on how the FDA addresses/evaluates the requirement that "appropriately qualified medical personnel" (i.e., at time of Sponsor audit) oversee the data if the medical personnel are not licensed. Does a "medical personnel" mean a physician? If it is a physician (or other licensed medical professional such as a NP), how is "appropriately qualified" evaluated if a current license is not required (the licensing body being the guarantor of qualification)?

How would the FDA stop a company from hiring people with MDs from unvalidated online "universities" and labeling them "appropriately qualified"?

Licensing boards and medical specialty associations are now requiring recertification exams and proof of ongoing CME, recognizing that obtaining an MD at some point in the past is not sufficient to ensure patient safety. How does the FDA accomplish this for study oversight (or impose sanctions on companies that do not do this as part of their compliance activities) -- or does the FDA not consider that when auditing?

With thanks,

On Wed, Oct 1, 2014 at 9:19 AM, OC GCP Questions <gcp.questions@fda.hhs.gov> wrote:
Dear [redacted]-

Thank you for your question, which was forwarded to my office for a response. From the limited information provided, I am not sure whether you are asking if **the sponsor company** that initiates a clinical investigation must employ licensed physicians vs. whether **the investigator** who actually conducts a clinical investigation must be a licensed physician, so I've addressed both of these questions in that order below.

The FDA regulations regarding responsibilities of sponsors and investigators who participate in FDA-regulated drug studies can be found in 21 CFR 312 subpart D (see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.4).

Among the many responsibilities of sponsors outlined in these regulations, section 312.56(a) and (c) requires the following:

> *Sec. 312.56 Review of ongoing investigations.*
>
> *(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.*
>
> *(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under 312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with 312.33.*

Additionally, the regulations regarding IND safety reports, found at 21 CFR 312.32 (see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32), specifically section 312.32(b) states:

> *Sec. 312.32 IND safety reporting.*
>
> *(b) Review of safety information . The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.*

The ICH GCP E6 Good Clinical Practice: Consolidated Guidance, (which is recognized as official FDA guidance – see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf) also addresses sponsor responsibilities. Section 5.3 of this guidance specifically states:

> *5.3 Medical Expertise*
>
> *The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.*

Sections 5.4 (Trial Design) and 5.5 (Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee) of this guidance also discuss sponsor responsibilities to utilize appropriately qualified individuals throughout all stages of the trial process.

While the regulations don't specifically address whether or not a physician at a sponsor company must hold an active medical license, it is clear that in order to review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from

the investigators, the sponsor should designate qualified and appropriately trained staff to perform such tasks.

If you are asking whether an investigator must be a physician, FDA addresses this question in our guidance for sponsors, clinical investigators and IRBs titled, "Frequently Asked Questions – Statement of Investigator (Form FDA 1572)" – see http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm214282.pdf. Questions 4 and 5 in section I (General) read:

> *4. Must the investigator be a physician?*
>
> *The regulations do not require that the investigator be a physician. Sponsors are required to select only investigators qualified by training and experience as appropriate experts to investigate the drug (21 CFR 312.53(a)). In the event the clinical investigator is a non-physician, a qualified physician (or dentist, when appropriate) should be listed as a subinvestigator for the trial and should be responsible for all trial-related medical (or dental) decisions. (ICH E6 section 4.3.1;*
> *http //www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf).*
>
> *5. What are the minimum qualifications of an investigator?*
>
> *As stated in #4, the regulations require that sponsors select investigators who are qualified by training and experience as appropriate experts to investigate the drug. The regulations do not specify the minimum requirements nor do the regulations specify what qualifications an investigator must have in order to be considered qualified by training and experience to conduct a clinical investigation. Sponsors have discretion in determining what qualifications, training, and experience will be needed, based on the general recognition that this would include familiarity with human subject protection (HSP) regulations (i.e., 21 CFR Parts 50 and 56) and practices as well as good clinical practice (GCP) regulations (see 21 CFR Part 312) and standards (e.g., ICH E6) for the conduct of clinical studies.*

FDA performs on-site inspections of sponsors, contract research organizations and monitors as well as clinical investigators through our Bioresearch Monitoring (BIMO) Program. BIMO inspections include an assessment of compliance with FDA's regulations governing the conduct of clinical trials. FDA has developed Compliance Program Guidance Manuals (CPGMs) for each of the BIMO inspection types. These CPGMs were developed to provide uniform guidance and specific instructions for FDA inspections of regulated entities. If you are interested in reviewing the CPGMs for FDA inspections of Sponsors, Contract Research Organizations and Monitors and Clinical Investigators, you can access these documents at http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/ucm255614.htm.

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

Janet Donnelly, RAC, CIP
Policy Analyst, Office of Good Clinical Practice
Office of Special Medical Programs, Food and Drug Administration

From: [redacted]
Sent: Monday, September 22, 2014 8:58 PM
To: CDER DRUG INFO
Subject: pharmaceutical company requirements for licensed MDs

Hello

I am enquiring on whether companies that run and oversee drug development trials are required to have licensed MDs to oversee the trials/data. Specifically, if the drug development company is obligated to ensure patient safety via safety reviews of the ongoing clinical trials, do the physicians have to hold ***active medical licenses*** (and thus have proven continuing medical education and have a quality standard from the state licensing board to ensure they are properly trained physicians from an accredited medical school)?

If not, how does the FDA ensure that biopharmaceutical companies have qualified personnel overseeing the trials?

Thank you,