From: Woollen, Stan - OC
Sent: Tuesday, June 14, 2005 5:24 PM
To: [purged]
Subject: FDA 483/Warning letter questions

Dear Ms. [purged],

Your letter below was forwarded to our office for response. I'll try to address each of your questions:

Q. 1Are all FDA 483s followed by a Warning Letter? (It is my understanding that FDA 483s are issued immediately after an inspection and that they are not necessarily followed by a Warning Letter.)

A. Your understanding is correct. Warning letters are only issued after agency review of all information pertinent to the findings of the inspection. This information includes the 483, inspection report (EIR) and any other information such as a response to the 483. Warning letters are reserved for the more significant cases of noncompliance where the final compliance classification is Official Action Indicated (OAI). Many inspections result in a 483 but do not result in a Warning letter.

Q.2. Are all Warning Letters in response to FDA 483s? (I have found many Warning Letters (mostly from DDMAC)regarding labeling and promotional material, which I believe are not included in FDA 483 violations.)

A. Ordinarily Warning letters follow an inspection at which a 483 is issued. However, the agency has in house review functions, such as DDMAC's, in which a review of labeling for example can result in a Warning letter. Not all inspections result in a 483. see A1 and http://www.fda.gov/foi/warning.htm

Q3. Is it possible to obtain information on the total number of FDA 483s given to specific sponsors, clinical investigators and contract research organizations?

A3. Let me first begin by saying that the total number of 483s issued is really not very meaningful in trying to assess overall compliance of an industy sector. Please see the answer to your fourth question below.

That said, with respect to obtaining information on the total number of 483s issued to specific sponsors and CROs, I am not aware of listings of sponsor or CRO inspections which would provide the information you are seeking. In general, you would need to make an FOI request asking for the 483 in question for the specific firms in question and would have to tally the

numbers. You'll need to identify the firm name and inspection date. Before you make such a request, please visit our FOI web page http://www.fda.gov/foi/foia2.htmfor for more information on how to get information through FOI

Regarding 483s for clinical investigators (CI) studying drugs and biologics, the job is easier. There are lists of CIs who have been inspected by FDA. You can find CBER's clinical investigators inspection list at:
http://www.fda.gov/cber/compl/clininvlist.htm
You can find CDER's list at:
http://www.accessdata.fda.gov/scripts/cder/cliil/
In each of these lists you will notice a final classification of NAI,VAI,or OAI. You generally can assume that a 483 was issued for any inspection with a classification of VAI or OAI. 483s may have been issued for a NAI inspection but this is the exception rather than the rule.

The list referenced above do not include inspections of clinical investigators conducting device or veterinary studies.

Q3a(I have found comparable information for Warning Letters in the FOI Reading Room - is this a complete list of all FDA issued Warning Letters?)

A 3a. The Warning letters posted are all those which are publicly available as described on the web page. Please be sure to remember that a 483 does not equal Warning letter (see answer 1).

Q3b Is it possible to limit both of these searches to just GCP violations?

A3b.The CI inspection lists include clinical investigators only. To search the Warning letters I suggest you search by subject. For GCP inspections, search on each of the following "clinical investigator" "Institutional Review Board","Sponsor".

4. Is there a better regulatory mechanism (other than FDA 483s and Warning Letters) that could be used to measure clinical trial quality and compliance with GCP?

A. Yes there are better measures than a 483 alone.
First, the 483 should not be used alone in judging GCP compliance. The 483 is a list of the inspector's observations which in the inspector's judgment represent deviations from the regulations

which are significant. The decision as to whether a 483 observation is indeed a regulatory deviation is an agency decision made after review of all the facts as reported and documented in the EIR and from other sources such as correspondence from the inspected party. After each inspection, the Center, with responsibility for the inspection, will issue a post inspection correspondence which communicates the agency's final decision on the compliance status of the site inspected. The Center will assign a final compliance classification as either OAI,VAI,or NAI. These classifications are listed in the inspection lists I mentioned above in A3.

In general, when we here in FDA look at compliance data, we generally determine the percent of inspections which fall into one of these three compliance classifications. Some Centers also track specific deviations. For example, you will notice in the CI list for CDER, there are deviation codes by each inspection indicating the nature of problems found. From these lists you can develop your own compliance metrics just as we do. I've attached some of this data as a power point slide to illustrate.

Warning letters are a form of post inspection correspondence, but they are only sent to the firms that are seriously noncompliant. Fortunately this is only a small percentage of all firms inspected.

I hope this information is helpful. If you need additional information, please feel free to contact us through our GCP questions e-mail box at gcpquestions@oc.fda.gov.

Stan W. Woollen
Associate Director for Bioresearch Monitoring
Good Clinical Practice Programs
OSHC, Office of the Commissioner

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.

CImetrics.ppt

---Original Message-----
From: [purged]
Sent: Tuesday, June 14, 2005 9:19 AM
To: james.mccormack@fda.gov
Subject: FDA 483/Warning Letter Questions

Dear Dr. McCormack,

I am a research assistant with the [purged]. I am currently working on a project dealing with the quality of clinical trials and compliance with GCP. I have a few questions regarding FDA Warning Letters and 483 forms that I hope you will be able to answer:

1. Are all FDA 483s followed by a Warning Letter? (It is my understanding that FDA 483s are issued immediately after an inspection and that they are not necessarily followed by a Warning Letter.)

2. Are all Warning Letters in response to FDA 483s? (I have found many Warning Letters (mostly from DDMAC) regarding labeling and promotional material, which I believe are not included in FDA 483 violations.)

3. Is it possible to obtain information on the total number of FDA 483s given to specific sponsors, clinical

investigators and contract research organizations? (I have found comparable information for Warning Letters in the FOI Reading Room - is this a complete list of all FDA issued Warning Letters?) Is it possible to limit both of these searches to just GCP violations?

4. Is there a better regulatory mechanism (other than FDA 483s and Warning Letters) that could be used to measure clinical trial quality and compliance with GCP?

I greatly appreciate your help in clarifying these questions or forwarding them on to someone who can. Thank you so much for your time.

Sincerely,

[purged]