From: OC GCP Questions
To: [redacted]
Subject: Questions about observations and warning letters
Date: Monday, April 30, 2018 11:20:00 AM
Attachments: [redacted]

Good morning –

Warning letters are only issued after agency review of all information pertinent to the findings of an FDA 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.

Establishment Inspection Report (EIR) classifications from FDA's inspectional compliance program as follows.

NAI - No Action Indicated -- No objectionable conditions or practices were found during an inspection (or the objectionable conditions found do not justify further regulatory action);

VAI - Voluntary Action Indicated -- Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action; and

OAI - Official Action Indicated - Regulatory and/or administrative actions will be recommended. Generally a Warning Letter would be issued usually within 4 months from the time the inspection ends. Although this timeframe might vary a bit. An OAI recommendation is appropriate when regulatory violation(s) uncovered is/are significant/serious and/or numerous, and the scope, severity, or pattern of violations(s) are numerous.

See guidance below for Inspections of Clinical Investigators.
www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf

See Clinical Investigator Compliance Program.
www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm

Please see the WL website. Warning Letters which is searchable via several terms, including the name of the party receiving the letter. While it is possible for an inspection to be classified OAI and the inspected party not to receive a WL, it is highly unlikely.

There are lists of CIs who have been inspected by FDA. 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 no action indicated 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 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.

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.

Warning letters are a form of post inspection correspondence, but they are only sent to the firms that are seriously noncompliant. There is no set number of violations for Warning Letters. Fortunately this is only a small percentage of all firms inspected.

Please see the link below that gives you inspectional findings by year. Clinical Trials and Human Subject Protection > BIMO Inspection Metrics

I cannot comment on GMP inspections.

I hope this information is helpful.

Kind regards,

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Office of Good Clinical Practice
Office of the Commissioner, FDA

U.S. FOOD & DRUG ADMINISTRATION

From: [redacted]
Sent: Monday, April 30, 2018 9:59 AM
To: OC GCP Questions <gcpquestions@fda.hhs.gov>
Subject: Questions about observations and warning letters

Dear Mr./Ms.

Good morning, and thanks for your time!

I have been struggling to get the answers for the below questions, and very much appreciate your help on this.

1.Does the GCP inspection observations have the equal severity? If not, what categories are they assigned(critical, major, minor?)? Would you please give more information on this? How about GMP part? Thanks!

2. I can't locate that how many violations will lead to a warning letter (criteria to issue a warning letter), do we have a recommended number, for instance more than 5 major

deficiencies or 1 critical observation will cause warning letters. How about GMP field?

Thank you very much for your help!

Best regards

[redacted]