The Honorable Leonard Lance
House of Representatives
Washington, D.C. 20515-3007

Dear Mr. Lance:

Thank you for your letter dated May 29, 2014, on behalf of a constituent, regarding the submission of clinical trial results under section 801 of the Food and Drug Administration Amendment Act of 2007 (FDAAA).

Section 801 of FDAAA requires the submission of results for certain trials that meet the statutory definition of an “applicable clinical trial.” As you note, FDAAA requires submission of results for applicable clinical trials of drugs, biological products, and devices, where the drugs, biological products, and devices are approved or cleared by the Food and Drug Administration (FDA) and the trial either was initiated after, or was ongoing 90 days after, the enactment of FDAAA. In general, results from such trials must be submitted 12 months after the applicable clinical trial’s completion date. However, submission of results can be delayed if the manufacturer certifies that it has filed, or will file within one year, a marketing application with FDA for the use studied in the clinical trial. Depending on the circumstances, results reporting may not be required for up to three years after the completion date of the clinical trial. In addition, FDAAA also allows for the Director of the National Institutes of Health (NIH) to extend the deadline for submission of clinical trial information if the responsible party shows good cause for an extension.

We have restated each of your questions below in bold, followed by our responses. We have combined our responses to questions 2 and 3, as they are related.

1. Please describe the Agency’s interpretation of Title VIII of the Food and Drug Administration Amendments Act (FDAAA) of 2007, specifically in regard to the requirement for public and private entities to submit clinical trial data.

FDAAA requires responsible parties to register certain applicable clinical trials on ClinicalTrials.gov and submit certain information for those trials. “Applicable clinical trial” is defined in the statute. For certain applicable clinical trials of approved drugs, biological products, and devices, responsible parties also are required to submit results information to the ClinicalTrials.gov databank. The timing for submitting results information depends on several factors, including the primary completion date of the trial and whether the manufacturer has requested a delay in the submission deadline. The statutory provisions do not differentiate between public and private entities with regard to the requirements to submit clinical trial...
information. NIH’s ClinicalTrials.gov website provides information on the statutory requirements to assist responsible parties in understanding their responsibilities under FDAAA.¹

Section 801 of FDAAA directed FDA to update its regulations to require that informed consent documents include a statement about the ClinicalTrials.gov requirements. We revised our regulations related to informed consent in a final rule published in 2011. The preamble to the final rule outlined our interpretation of this specific FDAAA provision and we also issued guidance related to this informed consent requirement.² FDAAA also requires that certain drug, biologic product, and device applications and submissions to FDA be accompanied by a certification that all applicable FDAAA requirements have been met. We created Form FDA 3674 for submitters to certify FDAAA compliance and provided guidance regarding this required submission to FDA.³ FDA’s web site has a page describing the Agency’s role in connection with clinical trials.gov. See, http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/FDAsRoleClinicalTrials.govInformation/default.htm.

2. and 3. Are government entities such as the National Institutes of Health (NIH) and Food and Drug Administration (FDA) in violation of federal law as a result of not submitting the results of their clinical trial data? Are private companies in violation of federal law as a result of not submitting the results of their clinical trial data? What has been the compliance rate of private drug sponsors compared to government and academic drug sponsors?

As we stated above, the statutory provisions do not differentiate between public and private entities with regard to the requirements to submit clinical trial information, including the requirements for results submission. The failure to submit required clinical trial information is a prohibited act under section 301(jj) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(jj)). In order to determine whether a responsible party (either a government entity or a private company) is in violation of federal law, a number of factors would have to be reviewed and a significant amount of data, some not posted publicly on ClinicalTrials.gov, would have to be assessed. Because FDAAA includes a requirement to undertake rulemaking, discussed below in response to question 5, implementing the statutory provisions, a number of requirements will not be in place until that rulemaking is completed; in the absence of a final rule, enforcement is challenging.

Determining the compliance rate for clinical trial results submission is difficult. The information changes daily and the databank includes a significant number of trials that either are not subject to the results submission requirements, or are not subject to FDAAA at all. Currently existing data fields do not always provide the precise information needed to determine compliance. Identifying which trials registered on the ClinicalTrials.gov databank meet the definition of an applicable clinical trial requires assessing whether the particular trials involve FDA-regulated

¹ http://clinicaltrials.gov/ct2/manage-recs/fdaaa
³ This guidance may be found at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM164819.pdf.
products, what the phases are of the trials (for drugs and biological products), whether the trials are considered controlled trials, and whether, for device studies, the trials are studying a health outcome. In addition, the results submission date is determined by both the completion date of an applicable clinical trial—which may not be described in a manner consistent with FDAAA requirements—and whether the FDA-regulated product is approved, which usually requires relying on and analyzing information from other sources, including FDA databases. As noted above, even if it may appear from the database that results are required for a particular applicable clinical trial, the deadline for submitting the results information may be delayed if, for example, a manufacturer submitted a certification of delay.

FDA is aware of certain published analyses of ClinicalTrials.gov data describing the lack of results reporting for clinical trials, such as that published by Prayle in 2012. FDAAA conducted a preliminary analysis of the data used for the article. Although Prayle concluded that 77.9% of trials were missing results information, we found that, when taking the factors described above into consideration, the percentage of trials that appeared to be missing results was lower: 34.6% as of the date of the Prayle data pull, and as of May 2012, 21.1%. FDA believes that, while analyses such as Prayle’s have the ability to identify trials that may be out of compliance, such analyses may overestimate the number of trials lacking results, because they do not necessarily take into consideration one or more of the key factors noted above. Furthermore, as discussed above, specific determinations of noncompliance can be made only after examining all of the particular elements of each trial in question and evaluating a significant amount of information, not all of which is posted on ClinicalTrials.gov. We agree that 21.1% needs to be reduced, and there have been and continue to be outreach efforts aimed at submitters who appear to be noncompliant.

4. If public and/or private entities are in violation of federal law, have any monetary penalties been issued? If so, what is the amount of the fines? If not, why have no penalties been issued?

To date, there have been no civil monetary penalties assessed for noncompliance with the requirements of section 801 of FDAAA. There are a number of enforcement tools available to FDA under FDAAA. For example, FDA has been able to achieve voluntary compliance in certain cases where we have identified apparent noncompliance and brought that to the attention of the responsible party. These interactions have increased awareness and resulted in compliance, without the need to assess civil monetary penalties. Significant efforts also have been devoted to providing assistance to stakeholders and to clarify the requirements of the statute, in order to encourage compliance. The NIH rulemaking will help clarify reporting responsibilities under FDAAA and we anticipate it will help achieve greater compliance by the affected parties.

5. In a March 12, 2014 letter from NIH, Donald A.B. Lindberg, MD stated, “implementing a law as complex as FDAAA takes time. NIH has worked closely with FDA to address the implementation and enforcement of all registration and results reporting provisions and to complete the Notice of Proposed Rulemaking (NPRM), the next step in completing the implementation of this law. We anticipate that, when the regulations are in place, the

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clinical community will be equipped to comply with the requirements, and the FDA will be able to enforce them more fully.” When do you expect the NPRM to be completed? When will the final regulations be promulgated and implemented?

NIH is the lead for the NPRM and would be in the best position to discuss a timeline for its publication and any final rulemaking. The NPRM is currently under review by the Office of Management and Budget (OMB) and is listed on OMB’s public calendar.

FDA continues working on various transparency initiatives, including our work with NIH on ClinicalTrials.gov. See:

http://www.fda.gov/AboutFDA/Transparency/OpenGovernment/default.htm (availability of certain FDA data sets, e.g. certain recalls)

http://www.fda.gov/AboutFDA/Transparency/TransparencyReports/ucm393798.htm (access to compliance and enforcement data)

http://www.fda.gov/AboutFDA/Transparency/track/default.htm (program performance)

Thank you, again, for contacting us regarding this important matter. Please let us know if you have any additional questions.

Sincerely,

Karen Meister
Supervisory Congressional Affairs Specialist