DEPARTMENT OF HEALTH & HUMAN SERVICES

JUL 27 2015

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Tim Murphy
Chairman
Committee on Energy and Commerce
Subcommittee on Oversight and Investigations
House of Representatives
Washington, D.C. 20515-6115

JUL 24 2015

Dear Mr. Chairman:

Thank you for your letter of May 27, 2015, relating to the Food and Drug Administration's (FDA or the Agency) issuance and posting of Untitled Letters.

We will be happy to provide you and your staff with a briefing, as requested, and in the meantime, have provided answers to your questions below.

1. **Do FDA centers use different criteria for issuing Untitled Letters? If yes, please identify and explain the criteria used by each center, and the rationale for FDA centers using different criteria. If no, please identify and explain the criteria used by all the FDA centers.**

Each FDA center follows the procedures specified in Chapter 4-2 of the Regulatory Procedures Manual (RPM), which provides guidance to personnel regarding the use and preparation of Untitled Letters. (*See* RPM, Chapter 4-2.) An Untitled Letter is correspondence with regulated industry that cites violations that do not meet the regulatory threshold for a Warning Letter. Untitled Letters should be clearly distinguishable from Warning Letters in their format and content. For example:

- The letter is not titled;
- The letter does not include a statement that FDA will advise other Federal agencies of the issuance of the letter so that they may take this information into account when considering the award of contracts;
- The letter does not include a warning statement that failure to take prompt correction may result in enforcement action;
- The letter does not evoke a mandated district follow-up; and
- The letter requests (rather than requires) a written response from the firm within a reasonable amount of time (e.g., "Please respond within 30 days"), unless more specific instructions are provided in a relevant compliance program.

These procedures guarantee a certain degree of uniformity in letters issued by the different product centers, while still permitting the centers to have specific procedures to address the particulars of the products they regulate.

Further, Exhibit 4-1 of the RPM provides procedures for clearing certain FDA Warning and Untitled Letters by the Office of the Chief Counsel (OCC) prior to their issuance. OCC reviews Untitled Letters that: (1) involve novel, controversial, or sensitive legal issues (all centers); (2) allege violation of the dietary supplement good manufacturing practice (GMP) regulations (Center for Food Safety and Applied Nutrition, or CFSAN); (3) allege violation of medical device advertising and promotion regulation, certain types of misbranding or unapproved device violations, or involve certain matters of bioresearch monitoring (Center for Devices and Radiological Health, or CDRH); (4) involve animal drug advertising and promotion or new animal drug compounding (Center for Veterinary Medicine, or CVM); (5) involve product jurisdiction or unregistered or unlicensed blood banks (Center for Biologics Evaluation and Research, or CBER); or (6) involve human drug compounding, unapproved new drugs (excepting health fraud cases), or over-the-counter drugs subject to final monographs (Center for Drug Evaluation and Research, or CDER).

The procedures in Exhibit 4-1 also provide time frames regarding OCC-cleared Untitled Letters, with the exception of direct reference Untitled Letters and Untitled Letters issued pursuant to a foreign inspection. The procedures state that FDA will strive to issue Untitled Letters within six months from the last day of the inspections, the date of sample analysis, or the date of collection of other evidence (exhibit 4-1, Section 6.1.3).

Program-specific guidance to staff related to the issuance of Untitled Letters can be found in compliance program guidance manuals (CPGMs). Each type of regulated product area has one or more CPGMs associated with the types of inspections the field conducts, e.g., sterile drug production, drug repackers and relabelers, compressed medical gases, etc. These compliance programs typically provide instructions to the field describing the types of observations which would meet the regulatory threshold for a Warning Letter. Compliance programs also may include instructions for the issuance of Untitled Letters under part five, which covers regulatory strategy and administrative matters.

2. **Please identify and explain the criteria used by each FDA center for posting or not posting an Untitled Letter, and how many days after the Untitled Letter is sent to the firm until the letter posted on the FDA website. Please also explain why FDA does not have consistent policies and practices among its centers for publishing Untitled Letters.**

The Agency issues Untitled Letters to communicate issues of concern regarding a firm's practices and/or products that do not merit a Warning Letter. Currently, FDA has Center-specific policies as to whether to post those Untitled Letters, except to the extent that it overlaps with the Agency's approach to proactive posting under the Freedom of Information Act (FOIA). The Agency's posting approach under FOIA requires the posting of any Agency record subject to the FOIA, such as an Untitled Letter if (1) the Agency has received three or more FOIA requests for a copy of the record, or (2) if the content relates to a matter of significant public interest and we expect to receive multiple FOIA requests for it. This approach is consistent with Federal law, Department of Justice Guidelines, President Obama's January 21, 2009, FOIA Memorandum, and Attorney General Holder's March 19, 2009, Memorandum (*see* 5 U.S.C. § 552(a)(2)(D)).

In addition to posting Untitled Letters, which are frequently requested or where such requests are anticipated, Centers may develop and implement approaches that provide a greater measure of transparency through proactive posting. In order to provide additional transparency to the public, the Agency has been encouraged to provide broader disclosure than legal requirements, when FDA Centers determine it is appropriate.
The six product Centers regulate commodities widely variable in terms of risk and vary in terms of availability of certain types of resources. Each Center determines its own relative factors of resources before determining its policy on proactive posting. The Centers further particularize their posting policies given in terms of factors, such as the need and likely value of deterrence.

CBER and CVM post all issued Untitled Letters, and both expect that posting these letters will deter other similar violations.
(*http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/complianceactivities/enforcement/untitledletters/default.htm*)

CDER developed its policy based on a broader-risk spectrum of issues applicable to drugs that makes a singular posting policy less effective. CDER routinely posts Untitled Letters related to advertising and promotional labeling. These violations are typically identified through evidence encountered outside of the inspectional process. Furthermore, CDER has posted Untitled Letters that document noncompliance with other standards (e.g., 21 CFR Part 320 (bioequivalence)) in anticipation of multiple FOIA requests for a copy of the record.

CDRH posts open letters to all manufacturers of certain types of medical devices, radiological health, or in vitro diagnostics, noting issues of concern.
(*http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm111104.htm*)

CFSAN posts all of the Untitled Letters it issues related to manufacturing controls or labeling requirements, or that are issued to Internet websites (cyber letters).
(*http://www.fda.gov/food/complianceenforcement/untitledletters/default.htm*)

Since its creation in 2009, FDA's Center for Tobacco Products (CTP) has issued and posted Warning Letters, but has not issued any Untitled Letters.

3. **Do any of the FDA centers use the number of Freedom of Information Act (FOIA) requests to FDA for Untitled Letters sent to a named firm as a basis for posting an Untitled Letter? If yes, what is the numerical threshold of FOIA requests used, and why does the FDA center have this practice?**

FOIA requires agencies to keep indexes of requests and records produced as a result of the requests and to publish them online. FDA's practice is to post records when we have received three FOIA requests for them. The Agency's FOIA policy applies to the Centers regarding requests made under FOIA.

4. **Regarding the FDA's posting on its website of Untitled Letters that are sent to publicly traded firms, could FDA's practice be modified to schedule the posting at times after the trading session has closed, i.e., after 4:00 p.m.? If not, why not?**

FDA follows a set schedule in posting Warning Letters and ordinarily does not seek to time their release based on market considerations. As noted above, the posting of Untitled Letters varies by Center. FDA does not ordinarily investigate or evaluate whether companies receiving a Warning Letter or Untitled Letter are traded on a U.S. or foreign exchange, either directly or through financial mechanisms such as American depository receipts that effectively allow a security to be traded on another exchange. FDA also has not evaluated whether posting Warning Letters or Untitled Letters in the evening would affect investors or regulated companies or whether any impact would occur in the same way on the following trading day. FDA does not believe the Agency has a special expertise or a mission to change its own processes to attempt to time impacts on the stock market and determine whether impacts are desirable. As a general matter, the Agency has sought to be more transparent about its processes where practicable.

5. **What is FDA's objective in sending Untitled Letters alleging violations found by a center (not the inspector) of which the firm was not notified during an inspection classified as No-Action-Indicated with no FDA Form 483 and not given an opportunity to correct and/or respond? How is this approach more efficient in gaining a firm's compliance than providing prior notice before issuing (or at least some reasonable period of time before posting) and giving the firm an opportunity to take corrective action? What evidence does FDA have that supports the superior efficiency of this approach?**

FDA's objective in sending an Untitled Letter is to communicate with the firm the Agency's assessment of violations by the firm that do not meet the regulatory threshold for a Warning Letter. Inspections are not the sole method by which FDA uncovers evidence of violations, and inspectional observations are not the sole method by which FDA provides notice to firms and provides the opportunity to respond. Regardless of the form in which initial notice is given, firms ordinarily have the opportunity to correct and respond to observations, and FDA considers such responses as part of the record for such a firm *(see* RPM 4-1-1 and Chapter 6).

6. **Do any of the FDA centers use Untitled Letters as a way to announce new regulatory approaches or policies? What due process or other legal considerations apply, if any, to Untitled Letters that state a firm is in violation based on a new application by FDA of regulatory standards without prior notice to regulated industry?**

As more fully explained in response to question number five, an Untitled Letter is intended to communicate to a firm, violations that do not rise to the threshold of a Warning Letter, but which do merit mention. Put another way, Untitled Letters themselves are a mechanism to communicate and to provide formal notice of a determination by FDA that a firm is in violation. However, FDA centers do not use Untitled Letters as a way to announce new regulatory approaches or policies.

In terms of announcing new regulatory policy, in accordance with Section 701(h) of the FD&C Act, 21 U.S.C. § 371(h), FDA established uniform procedures for issuing guidance documents. FDA's good guidance practice regulation, 21 C.F.R. § 10.115, implements Section 701(h). Section 10.115 establishes two types of guidance documents, Level 1 and Level 2. Level 1 guidances are those that: (1) set forth initial interpretations of statutory or regulatory

requirements, (2) set forth changes in interpretation or policy that are of more than a minor nature, (3) include complex scientific issues, or (4) cover highly controversial issues. Level 2 guidances, in contrast, set forth existing practices or minor changes in interpretation or policy.

7. How is FDA's approach more efficient than providing prior notice to the firm of the violation and the factual basis in support of FDA's conclusion of violation?

As described above, Untitled Letters are a form of correspondence or communication the Agency uses to inform firms of violations that do not rise to the level of regulatory significance, but for a variety of reasons, the Agency wants to have the firm address these concerns. For example, when CDRH cannot locate a company's authorization to market a device that is currently offered for sale in the commercial market, CDRH may issue an Untitled Letter to communicate the appearance of a violation and to ask the company to provide documentation of an active marketing authorization. Untitled Letters ordinarily provide the factual basis regarding the violation and serve to communicate a concern in a formal manner without committing the Agency to enforcement action if the violation is not corrected.

8. Does FDA have any awareness of the economic and legal sensitivities associated with posting Untitled Letters sent to publicly traded companies? How does FDA account for these sensitivities in its policies and practices in posting Untitled Letters?

See answer to question four above.

9. For each FDA center, what are examples of the "relatively minor violations" (per an FDA task force) that are the basis for Untitled Letters issued as a result of inspection?

Links to examples of Untitled Letters are set forth above. Also, as noted above, CBER and CVM post all of their Untitled Letters which can be viewed at *FDA.gov*. Examples of Untitled Letters issued as a result of inspection include the following:

Within CDER, an Untitled Letter is considered when there are not violations that meet the threshold of regulatory significance required for a Warning Letter. For foreign facilities, a violation may appear to lack regulatory significance due to the lack of recent involvement in U.S. commerce, if the establishment has not recently shipped active pharmaceutical ingredients and/or drug products to the United States.

Within CDRH, regulatory significance for a Warning Letter is established in the Compliance Program Guidance Manual – Program 7382.845 (*http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM244277.pdf*). Violations that do not meet the criteria of the CPMG are reviewed for an Untitled Letter communication or for a Voluntary Action Indicated (VAI) classification.

CFSAN issues Untitled Letters on a case-by-case basis. Some examples of concerns that did not meet the threshold of regulatory significance for a Warning Letter are as follows:

- BASF Corporation; UL issued 7/31/2014;

http://www.fda.gov/Food/ComplianceEnforcement/UntitledLetters/ucm409398.htm

- P. Jacquin et Fils; UL issued 3/29/2012;
http://www.fda.gov/Food/ComplianceEnforcement/UntitledLetters/ucm297975.htm

To date, CTP has not issued any Untitled Letters.

We would be happy to provide you or your staff with a briefing, as requested. To schedule a briefing, please contact Meghan Scott in FDA's Office of Legislation. She may be reached at 301-796-4675 or Meghan.Scott@fda.hhs.gov.

Thank you, again, for your interest in this matter.

Sincerely,

Thomas A. Kraus
Associate Commissioner for Legislation

cc:
The Honorable Fred Upton, Chairman
The Honorable Frank Pallone, Jr., Ranking Member
The Honorable Diana DeGette, Ranking Member