for complaining about violations. This format is Form 483. FDA's Form 483, "is issued by one or more FDA investigators at the conclusion of a site inspection, and usually is not reviewed by a compliance officer, district director, or an official in FDA's headquarters before it is issued. An FDA Warning Letter, on the other hand, is issued by a district director or headquarters official of similar seniority, and only after review by FDA's Office of Chief Counsel" (14).

FDA provides the following outline regarding the timeline of FDA inspections and duties of FDA inspectors (15). Typically, the FDA inspector makes a comparison, and compares what is set forth in the Sponsor's submissions to the FDA with documents that are possessed by the investigator, such as case report forms:

> When the inspection occurs as a result of FDA's receipt of a marketing application/submission, it will include a comparison of the data submitted by the sponsor to FDA with source documents at the clinical investigator's site ... and case report forms (CRFs) in the clinical investigator's files ... [i]f it is a ... surveillance inspection of an on-going study, data comparison will generally involve only source documents and case report forms ... [s]ource documents may include office records, hospital records, laboratory reports, records of consultations, etc.

One of FDA's Warning Letters provides guidance for responding to a Form FDA 483. The guidance states that the Sponsor should not merely assert that corrective actions will be taken, but should detail the corrective steps that will be taken. In the FDA's words, "Your firm's response stated that procedures will be put into place to ensure compliance with the FDA regulations in the future. We acknowledge your firm's assurance that corrective actions will be taken. However, we note that the response did not contain a detailed outline of procedures or processes that would be implemented to prevent the future occurrence of these observations" (16). This Warning Letter includes an exemplary account of correcting a procedural issue. The example is from a chronic problem of dosing errors of a pediatric drug. The remedial steps taken by the Sponsor were to suspend enrolment at various study sites pending retraining of personnel, reassessing the ability of personnel to follow the Clinical Study Protocol, and increasing monitoring of drug accountability to 100% for all study sites (17).

Most Warning Letters are preceded by a Form 483 notice (18). Copies of issued Form 483 notices can be acquired by the public, but requests must be made via the Freedom of Information Act Office. This Office will cooperate and provide these documents, but only

[14]Cooper, RM and Fleder, JR. Responding to a form 483 warning letter: a practical guide. Food Drug Law J. 2005;60:479–93.

[15]Inspections, Compliance, Enforcement, and Criminal Investigations (April 15, 2015) U.S. Food and Drug Administration. Accessed by author from FDA website on July 3, 2015.

[16]Warning Letter No. 10-HFD-45-04-01 (April 9, 2010) from Dr Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.

[17]Warning Letter No. 10-HFD-45-04-01 (April 9, 2010) from Dr Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.

[18]On July 9, 2015, this author conducted searches, demonstrating that most Warning Letters are preceded by a Form 483. These searches were: "institutional review board" (167 hits), "institutional review board" + 483 (163 hits); "consent form" (128 hits), "consent form" + 483 (125 hits); "adverse events" (277 hits), "adverse events" + 483 (204 hits); and "protocol deviations" (50 hits), "protocol deviations" + 483 (50 hits).