k. Failure to Report Concomitant Treatments on the Case Report Form

The Warning Letter complained about failure of the Sponsor to record the use of a concomitant treatment, as was required by the Protocol. The treatment was a drug for neuropathic pain. The letter complained that (135):

> Subject # 3511-019's case report form (CRF) lacks information on the reported use of Cymbalta® and the clinical condition corresponding to the use of this medication … all treatments taken by subjects … at any time during the study, in addition to the investigational product, are regarded as **concomitant treatments** and must be documented on the appropriate pages of the CRF.

XIII. CLINICAL HOLD

This concerns the decision tree facing a Sponsor when the FDA issues a *Clinical Hold*. As documented in Chapter 33, excessive protocol violations can result in the FDA issuing a *Clinical Hold*. One of the requirements facing the Sponsor is that the Sponsor must inform the Institutional Review Board (IRB) of the fact of the *Clinical Hold*. This requirement is made evident from the following Warning Letter. The letter referred to 21 CFR §312.66 and complained that (136):

> You failed to promptly report to the IRB all changes to the research activity and failed to promptly report all unanticipated problems involving risk to human subjects … [y]ou failed to promptly notify the IRB that Study 2 was placed on clinical hold. In your absence, FDA notified [redacted]… that the study was placed on clinical hold, and FDA sent you a letter dated 10/17/03 listing the clinical hold issues. You did not inform the IRB about the clinical hold until 1/2/04, when you submitted a protocol amendment and revised consent form.

Another Warning Letter, which also concerned a *Clinical Hold*, revealed that the reason for the *Clinical Hold* was the issue of animal toxicity data. This particular Warning Letter is a "poster-boy" for major violations of the Code of Federal Regulations (CFR). The letter documents the following violations:

- The IRB warned the Sponsor that additional toxicity studies on animals were needed.
- Despite warning the Sponsor that more toxicity studies were needed, the IRB recommended that the Sponsor move forward with dosing in humans.
- The Sponsor began dosing human subjects, even though the Sponsor did not have an approved IND.
- The IRB failed to inform the FDA that the Sponsor was dosing human subjects, without any approved IND in place.

These violations are documented in the letter, which complained that (137):

> Minutes of the February 1, 2008 IRB meeting indicate that the IRB was aware that the clinical investigator had already dosed human subjects with the investigational drug … [d]espite knowledge that Dr. [redacted] was dosing human subjects without IRB approval, as required by 21 CFR 312.66, the IRB failed to report Dr. [redacted] noncompliance to the FDA pursuant to 21 CFR 56.108(b)(2) … [h]owever, in a letter dated February 15, 2008, the IRB

[135]Warning Letter No. 09-HFD-45-04-02 (April 20, 2009) from Dr Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.

[136]Warning Letter CBER-06-007 (July 10, 2006) from Mary A. Malarkey, Office of Compliance and Biologics Quality, CBER, U.S. Food and Drug Administration.

[137]Warning Letter No. 10-HFD-45-09-01 (October 5, 2009) from Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.