wrote the following to the clinical investigator, [redacted] M.D. "... additional toxicity studies on animals will need to be completed ... [o]n behalf of the Committee, you may go forward with the study and we look forward to your continued success in this area".

The Warning Letter then went on to complain that, "It is unclear why the IRB allowed the study to go forward in humans when additional toxicity studies in animals were requested. In addition, it is unclear why the IRB allowed Dr. [redacted] to continue ... the study when it appears that he initiated this research study, i.e., began dosing subjects, prior to obtaining IRB approval."

[T]he IRB sent a letter to ... the study sponsor ... regarding the status of the animal toxicity studies. The August 18, 2008 letter ... stated "At this time, I must remind you that human studies, according to the protocol, cannot proceed until your Investigative [Investigational, sic] New Drug (IND) Application is approved by the FDA." This letter to the sponsor appears to contradict the February 15, 2008 IRB letter sent to Dr. [redacted] in which the IRB permitted the study to go forward.

During the inspection in December 2008, you told the FDA investigator that you were unaware that this IND was on **clinical hold**. However, [redacted] responded to the IRB in a letter dated September 4, 2008, and referenced the **clinical hold** placed on the IND by FDA.

# XIV. CONCOMITANT MEDICATIONS

## a. Warning Letters About Concomitant Medications

A number of Warning Letters issued regarding concomitant medications concern failure to enter the medications on the case report form (138,139,140,141,142). These medications include acetaminophen and rosiglitazone.

Another Warning Letter complained about failure to comply with the exclusion criteria in the Clinical Study Protocol forbidding certain concomitant medications (143), "[p]rotocol ... specifically stated that subjects with current use of postmenopausal oral hormone replacement therapy were to be excluded from the clinical investigation ... [s]ubject #0011 was ... allowed to continue in the clinical investigation despite clinic records dated 8/8/06 and 1/24/07 documenting the use of the disallowed concomitant medication." The same type of violation was a complaint in other letters (144,145).

[138]Warning Letter No. 08-HFD-45-05-02 (May 28, 2008) from Dr Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.

[139]Warning Letter No. 10-HFD-45-03-02 (March 17, 2010) from Dr Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.

[140]Warning Letter No. 09-HFD-45-04-02 (June 18, 2009) from Dr Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.

[141]Warning Letter No. CBER-10-05 (March 11, 2010) from Mary A. Malarkey, Office of Compliance and Biologics Quality, CBER, U.S. Food and Drug Administration.

[142]Warning Letter No. CBER-07-008 (March 29, 2007) from Mary A. Malarkey, Office of Compliance and Biologics Quality, CBER, U.S. Food and Drug Administration.

[143]Warning Letter No. 10-HFD-45-11-01 (November 9, 2009) from Dr Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.

[144]Warning Letter No. 08-HFD-45-01-11 (March 19, 2008) from Dr Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.

[145]Warning Letter No. 05-HFD-45-102 (December 19, 2005) from Dr Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.