VII. FDA WARNING LETTERS

a. Blinding Oversights During a Clinical Trial

FDA's Warning Letters provide guidance for selected features of clinical trials, most frequently, about the need to adhere to instructions in the Clinical Study Protocol, and to the responsibilities of the Institutional Review Board (IRB). The following Warning Letter concerns one of the instructions in a Protocol, that relating to blinding. The letter referred to 21 CFR §312.50, and complained about failure to follow instructions regarding the need for nurses to be blinded as to the treatment versus control (59):

> [s]tudy monitors failed to ensure that planned study blinding procedures were correctly followed for Study [redacted] at Site #063. This study was to be conducted in a double-blind fashion. According to the Protocol … "the unblinded pharmacist will be responsible for preparing the study medication for each subject in such a way that investigators and staff remain blinded to the medication being administered" … study nurses, rather than the unblinded pharmacist, were responsible for completing drug dissolution and reconstitution, as well as administering study drug infusions and caring for the subjects. Therefore, nursing personnel caring for subjects … were not blinded to study treatment, as specified by the protocol.

The letter further complained that, "nursing notes were viewed by clinical investigators at the site. Although it appears that the nurses used correction fluid to cover writing, in some cases the covered writing could still be read."

b. Sponsor Made Claims About the Study Drug in Advertisements, but the Advertisements Contained Information From Poorly Designed Clinical Trials That Were Not Blinded

In addition to regulating the design and conduct of clinical trials, the FDA also regulates the information on package labels of the marketed drug, as well as any promotions and advertisements. The following Warning Letter complained about a promotion that was considered to be misleading, because the promotion made use of poorly designed clinical trials that were not blinded. The drug was *dexmethylphenidate* (Focalin XR®) for treating hyperactivity in children (60). Please note the letter's use of the term "open-label" to refer to clinical trials that lack blinding. The letter complained that (61):

> [t]he slide deck presents numerous claims about the long-term effectiveness and safety of Focalin XR … [t]hese presentations misleadingly imply that Focalin XR is effective for long-term use when this has not been demonstrated by substantial evidence or substantial clinical experience … [i]n fact, no well-controlled trial supports long-term effectiveness, and the reference in slides 25–27 refers to an **open-label**, not concurrently controlled study that would not be considered substantial evidence of long-term effectiveness.

The Warning Letter specifically addressed the fact that, in general, subjective data must be acquired or captured using a blinded trial design. By subjective data, what is meant is data on feelings and emotions of the study subjects. This type of data is usually captured

[59]Warning Letter No. 09-HFD-45-0702. From Dr. Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration; August 10, 2009.

[60]Seif E, Carlson J. The prevalance of medication use in head start preschool sample. Dialog 2015;17:83–98.

[61]Warning letter to Sue Duvall (no letter no.). From Robert Dean, Division of Drug Marketing, Advertising, and Communications, U.S. Food and Drug Administration; September 25, 2008.