The FDA reviewer referred to placebo effects, writing that, "[p]lacebo effect may vary among subgroups as well as among studies." The reviewer referred to various clinical studies that were numbered, study 1201 [−3.2], study 2201 [−6.5], study 2203 [−8.4], study 2204 [−7.0], and study 2308 [−4.8]. The placebo effect on blood pressure is indicated by the bracketed number. The reviewer stated that, "[t]here do appear to be substantial differences in placebo effect by study."

In addition to pointing out differences in placebo effect in different studies, the reviewer referred to gender subgroups and racial subgroups. To these points, the reviewer wrote that, "[s]ome studies, but not all, show a substantial difference in placebo effect by gender." The FDA reviewer concluded that, "[h]ence it seems reasonable to me to do placebo correction by both study and gender." Regarding race, the FDA reviewer wrote, "[o]verall whites showed a higher placebo effect than blacks and Asians showed the lowest … estimates of placebo effects for blacks and Asians … were highly variable, likely the result of insufficient numbers of these racial groups."

Thus, for all data on the study drug's influence on blood pressure, the FDA reviewer made corrections for the placebo effects, prior to arriving at conclusions on efficacy.

f. Risks for Mistakes When Using the Double-Dummy Technique

This is from a clinical trial on *apixaban*, for preventing stroke and embolisms. The information is from NDA 202155, on March 2015 of the FDA's website.

The study drug arm received apixaban plus a dummy for the active control, warfarin. The control arm received the active comparator (warfarin) plus a dummy for the study drug.

A problem was that a small number of subjects were given two bottles, one containing apixaban and the other containing warfarin. Another problem was that some subjects were given two bottles, each containing a placebo, where the first bottle had the apixaban placebo and the second bottle had the warfarin placebo. The FDA reviewer commented that, "thus, medication errors could conceivably result in a patient concomitantly … two different active products (Warfarin and apixaban) … [or] … two placebos."

Fortunately for the Sponsor, few of these errors occurred, and the FDA concluded that, "the Applicant's response to our … letter … convinced us that the likelihood that the trial results were confounded by … medication errors was acceptably low." The take-home lesson is that medication errors are a real possibility for any clinical trial, where the risk for errors may increase with use of the double-dummy technique.

g. Need to Ensure That Study Subjects, as Well as Clinical Trial Personnel, Are Blinded as to Study Drug Versus Placebo

This is from a clinical trial on *apixaban*, for preventing stroke and embolisms, as described immediately above. The information is from the same NDA as described immediately above, namely, NDA 202155, on March 2015 of the FDA's website. The problem was a difference in size of the pill providing the study drug, and the pill providing the placebo version of that drug. Regarding the fact that the casual observer could have seen the difference between the drug and placebo, the FDA reviewer stated:

> Following a discussion of this issue with the Applicant, we received a submission that downplayed the importance of the **difference in thickness** between the **placebo** and **active 5 mg apixaban tablets**, but acknowledged its existence. The Applicant argued that individual patients would be exposed only to **active** or **placebo** … and would