subgroup analysis. The goal of stratification is to ensure that equal numbers of subjects having a particular characteristic are randomized to the study drug arm and to the control arm, during the process of randomization. The fact that subjects were stratified according to a given factor does imply that this factor was a subgroup of the study subjects, but it is not necessarily the case that the Sponsor conducted any analysis of the efficacy and safety results, according to this subgroup.

b. Where Subjects Are Stratified According to a Certain Factor, It Is Not Necessarily the Case That Subgroup Analysis of Efficacy and Safety Take into Account That Factor

In a clinical trial on *cetuximab* for colorectal cancer, all of the subjects were stratified according to study site, meaning that, for each site, the study design ensured that equal numbers were apportioned into the study drug arm and control arm. This information is from BLA 125084, on March 2015 of FDA's website. The Sponsor refrained from conducting any subgroup analysis based on study site. The reason for not doing subgroup analysis based on the study site was that a large number of sites were used, and that only a small number of subjects were enrolled at each site. The reviewer commented on the fact that subgroup analysis did not take into account the study sites, writing that, "[w]hile the analysis excluded study center … a stratification variable for randomization … this was acceptable because the **large number of centers would create many small or unfilled cells**."

c. Subgroup Analysis According to Biomarkers

The following subgroup analysis resulted in a recommendation that drug dosing levels be lower for one particular subgroup of patients. Also, the subgroup analysis addressed the number of dose modifications that were made during the course of the clinical trial. Moreover, the subgroup analysis resulted in a warning on the package insert of the marketed product.

This concerns a clinical trial for *lenalidomide* (Revlimid®), for treating anemia in patients with a type of cancer, myelodysplastic syndromes (MDS). The information is from the *Medical Review* for NDA 21880 from November 2013 of FDA's website. This concerns subgroups with and without an abnormality in chromosome 5. The abnormality was "deletion 5q." Regarding this deletion, "loss of all or part of the long arm of chromosome 5, del(5q), is a hallmark of myelodysplastic syndrome" (164).

Sallman et al. (165) commented on hematological disorders that are associated with this deletion, writing that, "[m]yelodysplastic syndromes … represent a hematologically diverse group of myeloid neoplasms, however, one subtype characterized by an isolated deletion of chromosome 5q [del(5q)] is pathologically and clinically distinct. Patients with del(5q) … [have] hypoplastic anemia and unique sensitivity to treatment with lenalidomide."

The clinical trials that were used in support of this submission to FDA included subjects with and without the deletion. According to the *Medical Review*, for one of the clinical trials, "[a] total of 45 subjects were enrolled … with or without an associated del 5." For another of

[164]Liu TX, et al. Evolutionary conservation of zebrafish linkage group 14 with frequently deleted regions of human chromosome 5 in myeloid malignancies. Proc. Natl. Acad. Sci. 2002;99:6136–41.

[165]Sallman DA, et al. PP2A: the Achiles heal in MDS with 5q deletion. Front. Oncol. 2014;4:264 (7 pages).