e. FDA's Decision-Making Process in Utilizing SNP Biomarkers in the FDA's Approval of Telaprevir

Background information on SNPs from one of FDA's *Medical Reviews*, and from the published literature, is disclosed above. What follows is actual data from a clinical trial that led to the approval of a drug for HCV.

The drug was telaprevir, in combination with two other drugs, ribavirin and pegylated interferon-alpha2a. The goal of the study was to assess use of the *IL-28B* genotype for predicting SVR. SVR is defined above.

The clinical trial is from NDA 201917, and the *Medical Review* is available from May 2011 of FDA's website. The FDA reviewer observed that, after the clinical trial was started, researchers discovered various SNPs occurring near the *IL-28B* gene in patients with chronic HCV. The genotypes, that is, mutations in the chromosomal DNA, took the following three forms: C/C, C/T, and T/T.

The FDA reviewer noted that the Sponsor wanted to stratify the subjects who were enrolled in the trial, but it was too late for a conventional stratification. As such, the Sponsor implemented a work-around, and by way of Consent Forms, obtained consent to identify the genotypes of the enrolled subjects. This illustrates the concepts of:

- Stratification by SNP genotype;
- Correlating SNP genotype with favorable response to the drug;
- Obtaining permission to conduct additional tests on study subjects, once the clinical trial is underway;
- Stratifying subjects according to being treatment-naive or treatment-experienced;
- Critique from the FDA reviewer.

The FDA reviewer wrote:

> In 2009, numerous publications described a novel association between single nucleotide polymorphisms (SNPs) near the interleukin (IL) 28B gene locus and response to treatment in subjects with CHC [chronic hepatitis C] … the investigators identified a particular SNP (rs12979860) strongly determined the outcome of HCV therapy. Three genotypes were identified: C/C, C/T and T/T. The discovery of the IL28B SNPs occurred after the Phase 3 trials had been fully enrolled and mostly completed. As such, it was not possible for the Applicant to stratify subjects at enrollment based on the IL28B genotype. Specific consent for genotyping for rs12979860 was obtained.

The FDA reviewer commented on the applicability of using SNPs in predicting outcome for treatment-naive subjects and treatment-specific subjects:

> **Treatment naïve C/C subjects** appeared to respond favorably to PR [active control] alone, although SVR [sustained virologic response] rates were higher for all of the telaprevir-containing regimens in this subgroup. C/T carriers had lower response rates than C/C carriers in all treatment arms … [i]n **treatment experienced subjects**, telaprevir appeared to benefit subjects of all genotypes by increasing SVR rates by 50–60% for each genotype compared to Pbo/PR [active control].

The reviewer's criticism was that, "[t]he above data must be interpreted with caution because … the data were not collected and analyzed prospectively."

VII. VALIDATING BIOMARKERS

FDA's Guidance for Industry states that, "[f]or pivotal studies that require regulatory action for approval or labeling … the bioanalytical methods should be fully validated" (209).

[209]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Bioanalytical method validation; 2013 (28 pp.).