- *Subgroups*. The clinical trial design included subgroups taking the form of overseas study subjects. The reviewer rationalized the use of data from the overseas study subjects, that is, why data from these subjects were likely to be applicable to potential patients in the United States.
- *Dosing*. The reviewer noticed a trend in efficacy, as disclosed in one of the Kaplan–Meier plots, perceived that the plot indicated that a more frequent dose would have greater efficacy, and recommended further analysis of data on the more frequent dose.

d. Infectious Diseases, as Exemplified by Hepatitis C Virus

This is from FDA's review of *sofosbuvir*, a drug used for treating hepatitis C virus. The information is from NDA 204671, September 6, 2013 on the FDA's website.

1. Further Studies of HCV Genotype 3

The reviewer reiterated the established fact that hepatitis C virus occurs in various genotypes, and provided comments on two of these genotypes. Regarding genotype 2, the reviewer stated that the 12-week treatment for HCV genotype 2 is satisfactory, and that the Sponsor had no plans to change the package label's current writing about the 12-week treatment for HCV genotype 2. Regarding another genotype (HCV genotype 3), the reviewer stated that the Sponsor had agreed with FDA's recommendation to test longer duration treatment (16 weeks) of patients infected with HCV genotype 3.

2. Further Studies on Subgroup of Subjects With Renal Impairment

Regarding the subgroup of study subjects with renal impairment, the reviewer reiterated the fact that the Sponsor had agreed to design and conduct an additional clinical trial, on HCV-infected subjects with renal impairment.

3. Observations About Baseline Characteristics

The reviewer also provided a table of all of the baseline characteristics of the study subjects, for example, the genotype of the virus, whether the subject had cirrhosis, the baseline titer of the virus, and whether the subject had received prior treatment against the virus. Regarding the baseline characteristics, the reviewer stated that, "[t]here were no notable imbalances between the two treatment groups for the baseline characteristics."

4. Association of Adverse Events With Study Drug

In comments about adverse events, the reviewer stated that the adverse events were not likely related to the study drug. For example, regarding allergies (blotchy rash and difficulty in breathing), the reviewer stated that these adverse events occurred "several weeks after initiation of study drug." Also, the reviewer referred to "the resolution of the event with continuation of study drug." Regarding the adverse event of eczema and swelling of the legs, the reviewer pointed out that these adverse events occurred, "4 weeks after the completion of study treatment." Further criteria for assessing whether an adverse event was caused by a study drug are revealed, in this textbook, on the account of the Naranjo algorithm (144,145).

[144]Kane-Gill SL, et al. Comparison of three pharmacovigilance algorithms in the ICU setting: a retrospective and prospective evaluation of ADRs. Drug Saf. 2012;35:645–53.

[145]Son YM, et al. Causality assessment of cutaneous adverse drug reactions. Ann. Dermatol. 2011;23:432–8.