that sampling be continued for at least 80% of the area under the curve (AUC) (153).

The following bulletpoints summarize FDA's comments for the antihepatitis C virus drug, sofosbuvir:

- *Longer duration tests on some study subjects.* The reviewer referred to the Sponsor's agreement to conduct a longer duration study of patients infected with HCV genotype 3.
- *Subgroup of subjects with renal impairment.* The reviewer referred to the Sponsor's agreement to design and conduct clinical studies on the possible influence of the study drug on subjects with impaired kidney function.
- *Baseline characteristics.* The reviewer agreed that the baseline characteristics in the various subgroups of study subjects were reasonably balanced.
- *Association of adverse events and study drug.* The reviewer provided reasons why the adverse events were not likely caused by the study drug.
- *In vitro drug–drug interaction tests.* The reviewer complained about the analysis of the results from the drug–drug interaction test, namely, that the analysis had failed to comply with the recommendations in the FDA's Guidance for Industry.

XXII. PROCESSES OF ADMINISTRING CLINICAL TRIALS

Dilts, Sandler, and coworkers (154,155,156) published a number of articles on the daunting task of administering a clinical trial. These authors describe the various concurrent timelines that need to be administered, and reveal how communications with regulatory agencies, ethics committees, and so on, fit into these timelines. In particular, these authors warn about a managerial problem called a circular mismatch loop. An example is where the Sponsor cannot collect information from an outside agency, unless the Sponsor first approves of the clinical trial—but where the Sponsor cannot approve of the trial, unless it first gets the information from the agency. Steensma (157) provides examples of circular mismatch in clinical trials, where changes in the Clinical Study Protocol, "can upset trial development homeostasis, creating endless loops or Catch-22s that then require special intervention to resolve. Committee A may need the approval of Committee B to move a protocol forward to Committee C, but Committee B may be silent because it is waiting on something from Committee A … some protocols have been delayed because study sponsors are reluctant to sign contracts until IRBs approve the protocol, yet some IRBs have been hesitant to approve protocols until contract language is agreed."

[153]European Medicines Agency. Guideline on the investigation of bioequivalance; January 2010 (27 pp.).

[154]Dilts DM, Sandler AB. Invisible barriers to clinical trials: the impact of structural, infrastructural, and procedural barriers to opening oncology clinical trials. J. Clin. Oncol. 2006;24:4545–52.

[155]Dilts DM, Sandler AB, Cheng SK, et al. Steps and time to process clinical trials at the Cancer Therapy Evaluation Program. J. Clin. Oncol. 2009;27:1761–6.

[156]Dilts DM, Sandler A, Cheng S, et al. Development of clinical trials in a cooperative group setting: the eastern cooperative oncology group. Clin. Cancer Res. 2008;14:3427–33.

[157]Steensma DP. The ordinary miracle of cancer clinical trials. J. Clin. Oncol. 2009;27:1737–9.