II. FDA'S DECISION-MAKING PROCESSES IN EVALUATING RUN-IN PERIOD

When the FDA grants approval for a drug, it published *Medical Reviews*, *Pharmacology Reviews*, and other reviews. FDA's comments in these reviews provide an intimate picture of FDA's decision-making process. This concerns the run-in period of the study design from the FDA's reviews of clinical trials on boceprevir, omalizumab, and cysteamine bitartrate. The comments in the FDA's reviews provide insights into the rationales for including a run-in period as part of the study design.

a. Boceprevir for Hepatitis C Virus

The study drug was boceprevir. In the clinical trial, boceprevir was administered in combination with ribavir and pegylated interferon-2A. The information is from the FDA's review of NDA 202258, which can be found on May 2011 of the FDA's website.

The study drug arm received all three drugs, while the control arm received ribavir and pegylated interferon-2A. Subjects in the control arm received an active control, that is, a drug (or drug combination) that was already established to have efficacy in treating the disease. DiNubile (52) discusses some aspects of using a study design that includes an active control arm. In using an active control, the Sponsor needs to take care in assigning subjects to each arm. Care must be taken so that the likelihood for safety issues is equal, a priori, for subjects receiving the study drug and for subjects receiving the active control (the comparator drug). An active control arm is also used, as part of the study design, when use of a placebo arm would be unethical (53).

In the clinical trial on boceprevir, the run-in period lasted 4 weeks, and in this period all subjects in the study drug arm and the active control arm received the combination of ribavir and pegylated interferon-2A. (Boceprevir was not given.) Then, after the 4-week run-in period, boceprevir was added to the study drug arm. According to the FDA reviewer, this run-in period had the following advantages:

- *Reduced possibility of drug resistance.* The 4-week run-in period reduced the viral load in all subjects, thus decreasing the likelihood of the viruses developing resistance upon exposure to boceprevir. In other words, the fewer viruses that are exposed to boceprevir, at the time that administration of boceprevir begins, the lesser is the likelihood that resistance to this drug will develop.
- *Ensuring that all three drugs are simultaneously active.* The run-in period enables the immune system to adjust to the immune stimulant, pegylated interferon-2A. The immune system's response, which has various components, to this drug may take days or weeks to develop maximally. If no run-in period was used, and if all three drugs were simultaneous administered from the very beginning, only the boceprevir and ribavirin would be exerting their full influence against the virus.
- *Identify study subjects who do not respond to interferon.* An additional advantage of the run-in period, is that it enables the Sponsor to identify study subjects with immune systems that fail to respond to interferon. Identifying these particular study subjects

[52]DiNubile MH. Double-blind active-control trials: beware the comparator you keep. Clin. Infectious Dis. 2008;47:1064–7.

[53]Kaul S, Diamond CA. Good enough: a primer on the analysis and interpretation of noninferiority trials. Ann. Intern. Med. 2006;145:62–9.