enables the Sponsor to remove them from the trial, prior to initiating boceprevir.
- *Identify study subjects who cannot tolerate interferon.* Yet another advantage, is that the run-in period allows the Sponsor to identify subjects who cannot tolerate the interferon or ribavirin, that is, who respond with severe adverse drug reactions. Identifying these subjects enables the Sponsor to remove them from the trial.

It is interesting to note that features of this run-in period were eventually incorporated in the package insert. The package insert is the sheet of paper, included inside boxes that contain drugs, that provides instructions and warnings, regarding drug use. The package insert for *boceprevir* (Victrelis®), included the following instructions for administration (54). Although the package insert stated that, "VICTRELIS must be administered in combination with peginterferon alfa and ribavirin," it went on to state that dose recommendations are different for some subgroups. For patients with cirrhosis, the package insert recommended that "[p]atients with. . .cirrhosis should receive 4 weeks peginterferon alfa and ribavirin followed by 44 weeks of VICTRELIS." In short, the package insert included directions for drug administration that, in effect, included the run-in period.

b. Cysteamine Bitartrate for Nephropathic Cystinosis

The study drug is a timed-release formulation of *cysteamine bitartrate*, to be taken once every 12 h. The information is from the FDA's review of NDA 203389, which can be found on April 2013 of the FDA's website. The study drug and the active control drug were both cysteamine bitartrate, where the study drug (Procysbi®) was a timed-release formulation for taking once every 12 h, and the control drug (Cystagon®) was a formulation that needed to be taken once every 6 h.

The goal of the run-in period was to ensure that all study subjects comply with the inclusion criteria.

The inclusion criteria required that the subjects be taking Cystagon, that white blood cell levels of cystine have a level of under 2 nanomoles of half-cystine per milligram of protein, and that the subjects be able to swallow the capsule. As stated in the FDA's *Medical Review*, the inclusion criteria required:

1. Male and female nephropathic cystinosis patients on a stable Cystagon regimen (ie, able to maintain WBC cystine level <2 nmol ½ cystine/mg protein).
2. Able to swallow intact Cystagon capsule.

Please note that Clinical Study Protocols for most or all FDA-regulated clinical trials have a list of inclusion and exclusion criteria, for determining which subjects can be admitted to the trial.

In detail, the inclusion criteria for the Procysbi clinical trial required that all subjects be taking the active comparator (Cystagon), for a 2-week run-in period prior to randomization. Immediately after the run-in period, the subjects were randomized to receive the study drug (Procybi), or to continue receiving the comparator drug (Cystagon). The importance of the run-in period was the very real possibility that the study subjects would not be able to swallow the Cystagon capsules. The FDA reviewer described the "formulation issues (inability of children to swallow over-encapsulated capsules) and the inability to mask the sulfurous smell of drug metabolites that are excreted via the lungs." Thus, as is the case with a number of other clinical trials, the run-in period for this clinical trial was to ensure that the subjects could comply with the study design, and actually consume the drugs.

[54]Package insert for, VICTRELIS™ (boceprevir) Capsules. Merck & Co., Inc.; May 2011 (26 pp.).