e. Protocol Violations That Can Separate Subjects in the ITT Population From Those in the PP Population, and That Can Also Result in a Refuse to File Notice

Clinical trials typically involve protocol violations that are low in number or severity, and merely compel the conclusion that data from the violating subjects can be included in ITT analysis, but not used for PP analysis. But protocol violations that are great in number, and that are severe, may have an additional consequence of a *Refuse to File* (RTF) notice.

The following is from a clinical trial on cetuximab, an antibody drug against cancer. As part of the study design, *cetuximab* was used in combination with another drug, *irinotecan*. The information is from BLA 125084, available at March 2015 of the FDA's website.

The *Medical Review* focuses on an earlier clinical trial, the 9923 trial, which the FDA called a "supporting trial," and a later clinical trial, the 62202-007 trial, which the FDA called the "pivotal trial." The earlier trial had major protocol deviations that were so severe and great in number, that the FDA issued a *Refuse to File* notice. The later trial also had some major and minor protocol deviations, but these did not dissuade the FDA from granting approval to the drug. The locations, in the *Medical Review*, of the FDA's comments, are identified in footnote (110).

1. The Earlier (No. 9923) "Supporting" Clinical Trial, Which Resulted in the FDA Issuing a Refuse to File

This discloses the protocol violations of the earlier of two clinical trials that were part of BLA 12504 for *cetuximab* (Erbitux®). This also includes the unfavorable comments from the FDA reviewer.

The *Medical Review* divided the Protocol violations into those that were Protocol Eligibility Violations and Protocol Deviations During the Study. These are shown in Tables 8.2 and 8.3.

TABLE 8.2 Protocol Eligibility Violations

	Percent of Patients
INCLUSION CRITERION	
Bidimensionally measurable disease; index lesions not previously irradiated	2.9
Signed informed consent after enrollment	2.9
Hematological function	4.3
Hepatic function	25.9
Renal function	6.5
EXCLUSION CRITERION	
Prior murine Ab or cetuximab therapy	1.4
Surgery within 1 month of study entry	1.4
Chemotherapy for colorectal cancer between irinotecan regimen and enrollment	0.7
History of clinical significant cardiac disease, arrhythmias, or conduction abnormalities	0.7

[110]Study 62202-007, the later trial which the FDA called "pivotal," is described on pages 36–50 of the first 50-page pdf file and on pages 1–13 of the second 50-page pdf file. Study 9932, which the FDA called "supporting," and which inspired the FDA to issue a Refuse to File, is described on pages 19–20 of the second 50-page pdf file, that is part of the FDA's Medical Review. This Medical Review has three pdf files.