- Bilirubin either not normal and not <1.5 xuln: 3 (0.9%)
- Surgery or radiation within 4 weeks prior to study entry: 1 (0.3%)

2. Post randomization violation
   - >7 days between randomization and start of treatment: 14 (4.3%)"

Regarding the *minor protocol violations*, the reviewer wrote that, "[t]hese minor violations did not impact on efficacy or safety analysis and were similar in both arms." Regarding the *major protocol violations*, the FDA reviewer commented that, "[t]he number of patients with major violations was small and did not impact the efficacy or safety analysis."

f. Refuse to File—Example of Cetuximab

FDA describes the *Refuse to File* notice in its Good Review Practice document (112). In a narrative on the FDA's *Refuse to File* notices, including the *Refuse to File* that was issued for the cetuximab (Erbitux) BLA, Scheindlin (113) wrote:

> Review of the NDA is done by an interdisciplinary group of scientists ... including pharmacologists, physicians, statisticians, pharmacists, and chemists. The first step is a cursory yet complete scan of the application, to see if all the "pieces" mandated by the regulations are there. If the NDA is deemed incomplete at this stage, the FDA may refuse to file it ... [t]he deficiency may be relatively minor, in which case the firm is able to make corrections quickly; or it may involve a major flaw, causing repercussions ... [o]nce the filing hurdle is cleared, the substantive review of the NDA begins.

One of the FDA's reviews, the *Administrative Documents* review, published with the approval of cetuximab, includes a memo mentioning the *Refuse to File*.

In the memo, the FDA reviewer stated that, "[t]he review team identified ... deviations from Good Clinical Practices ... of the clinical protocols, missing data and inconsistencies in reported data for efficacy and adverse events ... inadequate justification for the proposed dose and schedule ... [t]he totality of the deficiencies rendered the application unacceptable for filing and a *Refuse to File* letter was issued."

In the *Statistical Review*, the FDA reviewer commented on the scope of a *Refuse to File*, and expressed hope that the Sponsor could correct the deficiencies set forth in the *Refuse to File*. The reviewer stated that it, "may be relatively minor, in which case the firm is able to make corrections quickly, or it may involve a major flaw ... as ... for example [was the case with] Erbitux®."

To conclude, the *Medical Review* and other reviews that were published at the time of FDA approval, provide concrete data regarding protocol violations that occur at a relatively minor frequency, and where the only consequence is that the subjects with the violations are excluded from any PP analysis. Also, these Reviews provide clear-cut information, as to the nature and frequency of protocol violations that might inspire the FDA to issue a *Refuse to File*. Moreover, the Review provides an exemplary account of violations that are protocol eligibility violations, and those that are protocol deviations that occur during the study. Additionally, the BLA is a good example of the fact that most NDAs and BLAs are based on data from two or more clinical trials, not just one.

[112]U.S. Dept. of Health and Human Services. Food and Drug Administration. Manual of Policies and Procedures. Good Review Practice: Refuse to File; October 11, 2013 (21 pp.).

[113]Scheindlin S. Demystifying the New Drug Application. Mol. Interv. 2004;4:188–91.