Moreover, the Clinical Review may list major deviations from the Clinical Study Protocol, such as failures of study subjects to meet certain inclusion or exclusion criteria, failure to collect consent forms, and other irregularities. In addition, the Clinical Review may include recommendations for post-marketing surveillance, such as the requirement to monitor pregnant women for at least 6 months.

Often, the Clinical Review contains typed annotations from FDA reviewers. For example, where a Clinical Review disclosed that major deviations from the Clinical Study Protocol, such as the failure of one patient to meet an inclusion criterion (relating to a positive test of a biomarker), the reviewer typed:

> *Reviewer's Comment: The number of patients with major violations was small and did not impact the efficacy or safety analysis.*

Another reviewer's annotation concerned drug/drug interactions, involving the sponsor's drug and a second drug intended for co-administration:

> *Reviewer's Comments: In response to FDA request, the application addressed the issue whether cetuximab [sponsor's drug] was increasing or potentiating any of the adverse events associated with irinotecan [second drug]. Table 46 compares information about relevant adverse events associated with irinotecan…it does not appear that cetuximab or irinotecan worsen the toxicities associated with the other component of the combination.*

The Clinical Review may comment on the proposed packaged insert (or drug label). For example, one such comment read (105):

> *The initial proposed label by the applicant was long…negotiations between the agency [FDA] and the applicant focused on streamlining the label to provide specific information about the combination while retaining important risk information about each individual component of the therapy. A face-to-face meeting between the agency and the applicant occurred on May 5, 1998, at which time general agreement about the format and content of each section of the labeling was agreed upon. The final labeling submitted on May [sic, no date], 1998, adequately addressed the concerns raised by the…reviewers.*

Finally, the Clinical Review may contain a recommendation, such as the following. The particular recommendation that appears below is of a type favored and desired by patients and sponsor (106):

> *We recommend accelerated approval of ERBITUX for the following indications…ERBITUX monotherapy is indicated for the treatment of patients with…colorectal cancer.*

[105] United States Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Application No. STN/BLA 125084; Erbitux® (Cetuximab). All of the correspondence documents are incorporated by reference in the approval letter dated February 12, 2004.

[106] United States Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Application No. STN/BLA 125084; Erbitux® (Cetuximab). All of the correspondence documents are incorporated by reference in the approval letter dated February 12, 2004.