> [a]pproval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit … [p]ostmarketing studies would usually be studies already underway … [t]he applicant shall carry out any such studies with due diligence.

c. FDA's Decision-Making Process in Approving a Drug, Where the Drug Had Been Subjected to a Clinical Trial That Took Advantage of the Accelerated Approval Pathway

This concerns panitumumab for treating colorectal cancer. The information is from the *Medical Review* for BLA 125147, from March 2015 of the FDA's website. The FDA reviewer disclosed the reason for the FDA's approval, stating that, "[t]he recommendation for accelerated approval is based on demonstration of … progression-free survival (PFS) … which is a surrogate endpoint reasonably likely to predict … survival." The study drug arm received panitumumab, while the control arm received no drug, but instead only received best supportive care. Efficacy was clearly demonstrated by the PFS endpoint, where the mean PFS was 96.4 days for the study drug arm and only 59.7 days for the control arm.

The FDA reviewer commented on the fact that overall survival was measured, but that this endpoint demonstrated lack of efficacy. In the words of the FDA reviewer, "[t]he trial failed to show evidence of an impact on overall survival. This may be a result of a large number of patients from the best supportive care crossing over to the active treatment arm within a short period of time on study … about 50% crossed over within 8 weeks."

As stated above, where a Sponsor requests the accelerated approval pathway, and where the results of the clinical trial are sufficiently persuasive to convince FDA to grant approval to the drug, the Sponsor is committed to conduct a subsequent clinical trial where the primary endpoint is overall survival. To this point, the FDA reviewer stated that, the Sponsor "has committed to conduct a randomized trial [where] … [t]he primary endpoint of this trial is overall survival and the trial is intended to verify the benefit of" the study drug. FDA's Approval Letter, after its review of the trial that used the accelerated approval pathway, reiterated this commitment, stating that:

> [a]pproval under these regulations requires … that you conduct adequate and well-controlled studies to verify and describe … increased survival … [i]f postmarketing studies fail to verify the clinical benefit … we may, following a hearing … withdraw or modify approval.

XVII. REFUSE TO FILE

a. Purpose of a Refuse to File Notice

The topic of a *Refuse to File* (RTF) notice was introduced earlier in this book in the descriptions of animal models. *Refuse to File*, which has a basis in 21 CFR §314.101(d), can be applied against a New Drug Application (NDA) and against a Biological License Application (BLA). According to FDA's *Manual of Policies and Procedures*, a *Refuse to File* under is a:

> tool to help CDER [or CBER] avoid unnecessary review of incomplete applications … [i]ncomplete applications can lead to multiple-cycle reviews and inefficient use of CDER resources. CDER also believes an RTF action can allow an applicant to begin repair of critical deficiencies in the application far sooner than if these were identified much later … and may lead to more rapid approval of safe and effective drug products (122)

[122]U.S. Department of Health and Human Services. Food and Drug Administration Manual of Policies and Procedures. Good Review Practice: Refuse to File; October 11, 2013. (22 pp.).