Excerpts from FDA's *Medical Reviews* are worthy of reiteration in this textbook, because they disclose the nature of the FDA's feedback at the time that approval is granted, and because they demonstrate the practical application of concepts taught in earlier chapters in this textbook.

b. Oncology

This is from the *Medical Review* of *ibrutinib*, used to treat a type of hematological cancer. The information is from NDA 205552, from Nov. 2013 of the FDA's website. The FDA reviewer made the following recommendation:

> This reviewer recommends accelerated approval for this new drug application (NDA). The Applicant has demonstrated the efficacy of patients with mantle cell lymphoma (MCL) who have been previously treated.

1. Need for Pharmacovigilance on Blood Clotting Adverse Events

In comments on risks and benefits, the reviewer made note of the risk for SAEs, writing that, "hemorrhagic adverse reactions occurred in about half (48%) of the trial population," and commented on how the Sponsor proposed to address this safety issue, writing that, "Applicant has pharmacovigilance plans in place to further characterize hemorrhagic events … confirmatory trials are ongoing to better define the benefit–risk profile."

2. Need for Sponsor to Correlate an Older Test with a Newer Test

The reviewer referred to a revised version of the criteria for assessing efficacy of the drug, writing that the present NDA "represents the first regulatory application" of the revised criteria. The revised version of the criteria is simply called "2007 Response Criteria." The reviewer noted that the new criteria incorporate a new type of test, namely, *fludeoxyglucose positron emission tomography* (FDG-PET) scans. The reviewer suggested that the Sponsor collect information on whether this new test provides data that are consistent with a test (computed tomography) used in the older set of criteria. The reviewer expressly requested that, "A longer duration of follow-up is needed to further characterize the correlation of on-treatment FDG-PET scans with long-term outcome."

3. Requirement for In Vitro Experiments on Drug's Influence on Blood Clotting

In addition to requesting information serving to validate the new test (FDG-PET), the reviewer recommended that the Sponsor conduct in vitro laboratory experiments relating to drug safety. To this end, the reviewer asked for experiments on the influence of the study drug (ibrutinib) on platelets, writing that the Sponsor should, "[d]etermine the effect of a broad range of concentrations of ibrutinib on the potential to inhibit platelet function." This recommendation was made, because of the high rate of bleeding in the study subjects.

4. Requirement for Clinical Trial Designed to Assess Relation of Study Drug to Adverse Event of Renal Failure

Further concerning drug safety, the reviewer referred to the adverse event of renal failure in some of the study subjects, and recommended that the Sponsor conduct an entirely new clinical trial to determine whether the study drug contributes to renal failure. The reviewer commented that the present study (subject of the Approval Letter) was only a single-arm study and thus was not designed to be sensitive to determine whether adverse events were caused by the study drug. At the time of the *Medical Review*, the most plausible reason for the renal failure was the extreme old age of all of the study subjects. Thus the reviewer was interested in the possible influence of the study drug (independent of old