ibrutinib on the potential to inhibit platelet function by conducting in vitro studies … [e]valuation should include samples from subjects with and without concomitant conditions associated with platelet dysfunction, e.g., severe renal dysfunction, use of a concomitant anticoagulant, and use of aspirin.

You will conduct this study according to the following schedule:

Final Protocol Submission: 12/2014
Study Completion: 06/2016
Final Report Submission: 12/2016

Conduct an assessment and an analysis of data from clinical trials and all post-marketing sources in order to characterize the risk of serious bleeding in patients treated with … ibrutinib … [t]he risks of special interest are major hemorrhagic events. This enhanced pharmacovigilance study will include … continue … for a period of four years … [with a] Final Report Submission: 11/2018.

Sincerely, Richard Pazdur, M.D.

XXI. FDA FEEDBACK AT TIME OF ISSUE OF THE FDA APPROVAL LETTER

a. Introduction

At the time FDA issues the Approval Letter, FDA reviewers also provide their reasons for approving the drug, as set forth on the package label, in the format of the following documents. These documents can be found, on FDA's website, by following the footnoted instructions (140). Any given review may contain comments from different FDA employees (141). These reviews include:

- *Medical Review* or *Clinical Review*;
- *Pharmacology Review*;
- *Microbiology Review*;
- *Statistical Review*.

The following compares the writing and analysis that was submitted by the Sponsor, and the writing found in the Reviews that are prepared and published by the FDA. FDA reviewers use both Sponsor's analysis and the FDA's independent analyses in their reviews. In many cases, the FDA checks the data provided by the Sponsor.

In preparing the reviews, FDA officials use primary data acquired from the Sponsor, and then use the data to create tables and graphs. Thus, the majority of tables and graphs are prepared by an FDA reviewer. Some of the material in FDA's reviews may take the form of text that is copied and pasted from documents provided by the Sponsor (142). If the FDA get the same information in the FDA's own analysis, the FDA may simply recreate the tables and writing provided by the Sponsor (143).

The following provides excerpts from the *Medical Reviews* that accompanied FDA's Approval Letter for a selection of drugs. These drugs, which track the content of this textbook, are from *oncology*, autoimmune diseases, as exemplified by *multiple sclerosis*, and infectious diseases, as exemplified by *hepatitis C virus*.

[140]On the FDA website, under Drugs, first click, "Search Drug Approvals by Month Using Drugs@FDA." Then, click "Approval History, Letters, Reviews, and Related Documents." Finally, click on "Review."

[141]"Note that there may be differences among reviewers since the FDA review divisions and teams operate slightly differently from one another." Response by RL, Drug Information Specialist, Division of Drug Information, Center for Drug Evaluation and Research, FDA. E-mail response dated March 2, 2015.

[142]Kind advise from Dr Patrick Archdeacon, MD, FDA, CDER, in e-mail dated March 5, 2015.

[143]The author is grateful to Dr Michelle Eby, PharmD, of FDA, CDER for providing this advice, in an e-mail of March 3, 2015.