- Registry;
- Postmarketing clinical studies.

The following narrative begins with the BLA submission, dated June 30, 2009. FDA agreed to give the standard 10-month review, that is, regarding safety, efficacy, pharmacokinetics, and manufacturing. During this 10-month period, FDA held an Advisory Committee meeting (March 1, 2010) in order to get independent opinions from outside experts. The Advisory Committee voted to approve the drug, but the vote was not unanimous. After the Advisory Committee's meeting and vote, FDA declined to approve the drug, the reasons being mainly because of problems with manufacturing the drug. The Sponsor then submitted additional information, and the FDA determined that all of the issues were adequately addressed, and the drug was approved on June 15, 2011.

At the time of FDA approval, FDA also imposed the requirement that the Sponsor prepare a REMS. The goal of this REMS was to ensure that the benefits of the approved drug outweighed the risks of the disease. FDA determined that a REMS was needed to ensure that physicians and patients were aware of the serious risks of the diseases (posttransplant lymphoproliferative disorder), and how to mitigate those risks. FDA also imposed the requirement for postmarketing clinical studies. The goal of these studies was to provide an estimate of the prevalence of the disease in clinical practice, where the information was deposited in a registry called, "ENLIST." The goal of another of the postmarketing studies was to analyze patterns of use of the approved drug, that is, as used in routine clinical practice.

XX. FDA APPROVAL LETTER

This documents one element of the feedback from the FDA, when it approves an NDA or BLA, namely the approval letter. The example is from the approval letter for *ibrutinib* for the indication of mantle cell lymphoma, a type of hematological cancer. The NDA had been submitted on June 28, 2013, and the date of the approval was Nov. 13, 2013.

The approval letter illustrates these concepts:

- *Accelerated approval*. The study on ibrutinib was conducted under a provision by the FDA for accelerated approval under 21 CFR §314.500. A Sponsor can submit a NDA or BLA under the accelerated approval program, where approval is based on data from a *surrogate endpoint*. In other words, the approval is based on data from an endpoint that is different from actual recovery from the disease. The FDA's *Guidance for Industry Expedited Programs for Serious Conditions* details the requirements, where a Sponsor wishes to submit its NDA or BLA in the accelerated approval program. The requirement for use of a *surrogate endpoint* is reproduced in footnotes (135,136). In commentary on the FDA's accelerated approval program, Dr Richard Pazdur and coworkers outlined the use of *surrogate endpoints* versus the "gold standard" endpoint of survival, and details regarding the successes and failures of postmarketing data

[135]"a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

[136]U.S. Department of Health and Human Services. Food and Drug Administration Guidance for Industry. Guidance for Industry Expedited Programs for Serious Conditions; May 2014 (36 pp.).