drug combination has a poor safety profile. In contrast, therapy with ibrutib is relatively nontoxic (181).

Ibrutinib is also effective for treating another type of cancer, CLL. CLL is the most common leukemia in adults (182). A subgroup of CLL patients is characterized by the chromosomal deletion, 17p13.1. This subgroup of CLL patients fails to respond to older forms of chemotherapy, such as the combination of fludarabine and anti-CD20 antibody, or the combination of fludarabine, cyclophosphamide, and anti-CD20. In other words, this subgroup responds poorly to chemoimmunotherapy. In contrast, response to ibrutinib appears to be independent of whether the patient has, or does not have, the 17p13.1 deletion (183). To summarize, the above commentary illustrates the value of subgroup analysis that involves biomarkers, such as chromosomal abnormalities and genetic mutations.

VIII. SUMMARY

Drugs are generally classified as small molecules and biologicals. Because a chemistry background is needed in order to write FDA-submissions, this chapter includes a brief account of the concepts of hydrophilic and hydrophobic, a generic diagram of an antibody, a picture of a polypeptide chain with all of its amino acids, and a table of the 20 classical amino acids.

Further regarding animal models, data on efficacy and safety, as acquired from animal models, are used by a Sponsor for submitting to the FDA by way of the IND application. The goal of the IND is to acquire permission to initiate clinical trials in human subjects. Data from animal models are also used to support the warnings statement appearing on package labels of drugs. The FDA states that the warning can, in part, be based on animal data, in its writing that, "[a]nimal data raise substantial concern about the potential occurrence of the adverse reaction in humans (eg, animal data demonstrating that a drug has teratogenic effects" (184).

Hence, animal data are used prior to engaging any communications with the FDA, as well as in the final stages of the drug-approval process when the package label is being perfected.

During the course of drug development, animals are used to establish the mechanisms of action of the disease and of the drug. As the degree of engagement with the FDA increases, there is an increase in the need to comply with regulations regarding the use of animals. These regulations include those set forth by Good Laboratory Practices (GLP), as well as the need to follow validated Standard Operating Procedures (SOPs).

[181]Wang ML, Rule S, Martin M, et al. Targeting BTK with ibrutinib relapsed or refractory mantle-cell lymphoma. New Engl. J. Med. 2003;369:507–16.

[182]Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. New Engl. J. Med. 2013;369:32–42.

[183]Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. New Engl. J. Med. 2013;369:32–42.

[184]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Warnings and precautions, contraindications, and warning sections of labeling for human prescription drug and biological products—content and format; October 2011 (13 pp.).