et al. (102), and Bilimoria et al. (103), endpoints were calculated from the *date of surgery*. In a clinical trial of esophageal surgery, Allum et al. (104) used a date occurring at *6 months after surgery* as the start date. Where date of surgery is used as the start date, this method for endpoint calculation (for the endpoint of DFS) prevents the particular inconsistency detailed earlier in this textbook in the chapter on disease-free survival.

IX. FDA'S DECISION-MAKING PROCESSES, RELATING TO ITT ANALYSIS AND PP ANALYSIS

a. Introduction

FDA's decision-making process, as it applies to ITT analysis and PP analysis is illustrated by quotations from FDA's *Medical Reviews*, *Statistical Reviews*, and other reviews published with the FDA's Approval Letter.

The following examples should be compared with the FDA's definition of per protocol analysis. To reiterate the definition, PP analysis is, "[t]he set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations" (105,106). Thus, it is the case that PP analysis requires that the subjects comply with the Clinical Study Protocol to the degree that effects of the drug are likely to have been exhibited.

The following narrative concerns violations of the Clinical Study Protocol, where the consequence is that the data from violating study subjects be used only for ITT analysis, and not for PP analysis.

The following examples are from two independent FDA submissions, one for cetuximab and the other for ibrutinib. FDA's reviews of NDA and BLA submissions can be acquired from FDA's website by the footnoted procedure (107).

b. FDA's Decision-Making Process for Clinical Trials on Antibiotics

For clinical trials on some types of infections, subjects are enrolled and randomized based on suspected infection, where confirmation of the infection of interest occurs several days after randomization. Hence, the use of modified ITT (mITT) or per protocol (PP) analysis makes more sense than ITT analysis,

[102]Colleoni M, Rotmensz N, Peruzzotti G, et al. Size of breast cancer metastases in axillary lymph nodes: clinical relevance of minimal lymph node involvement. J. Clin. Oncol. 2005;23:1379–89.

[103]Bilimoria KY, Bentrem DJ, Hansen NM, et al. Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. J. Clin. Oncol. 2009;27:2946–53.

[104]Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J. Clin. Oncol. 2009;27:5062–7.

[105]U.S. Dept. of Health and Human Services. Food and Drug Administration. Guidance for Industry. E9. Statistical principles for clinical trials; September 1998 (43 pp.).

[106]U.S. Dept. of Health and Human Services. Food and Drug Administration. Guidance for Industry. Coronary drug-eluting stents—nonclinical and clinical studies; May 2008 (84 pp.).

[107]On the FDA's website, under DRUGS, click on, "Search Drug Approvals by Month Using Drugs@FDA." Then, select the month and year. What is provided is the Approval Letter, Medical Review, Pharmacological Review, Statistical Review, and other reviews, that are published at the time FDA grants approval to a NDA or to a BLA.