g. Subgroup Analysis Provides Prognostic Factors

In a clinical trial of gastrointestinal (GI) cancer, Van Glabbeke et al. (160) defined several subgroups, including:

- Age
- Gender
- Primary site of disease (abdominal, stomach, small bowel)
- Prior treatments for GI cancer (surgery, radiotherapy, and chemotherapy)
- Size of lesions (diameter of the largest lesion) at the time of trial inclusion
- Baseline hematologic and biologic parameters (white blood cells, granulocytes, platelets, hemoglobin, creatinine, bilirubin, and albumin).

A goal of the clinical trial was to identify subgroups where the drug was less effective. Low efficacy was evident where, during chemotherapy, tumor size or number increased early on, that is, during the first 3 months of chemotherapy. The study determined a subgroup where the drug was less effective. This was the subgroup of patients with *high granulocyte count at baseline*. Based on this finding, the authors recommended increasing the amount of dose of the drug (imatinib) for this particular subgroup, as follows. "In particular, imatinib resistance can be delayed by increasing the initial dose in patients with high granulocyte counts" (161).

h. Recommending Dropping One Subgroup from the Trial, Rather Than Stopping the Entire Trial

Where one particular subgroup in a trial is experiencing severe adverse drug reactions, such as death, the investigator can drop that particular subgroup from the trial (162). Dropping one subgroup from a trial is preferable to stopping the entire trial. Hence, in configuring the subgroups in the study population, the investigator or medical writer should contemplate various risk factors that might be expected in the study population, and for each risk factor, and include in the Clinical Study Protocol criteria that can be used to identify subjects as high, moderate, and low risk. An example of dropping one particular subgroup from a clinical trial can be found in a study of emphysema (163). Further information on dropping a subgroup from a clinical trial appears in this textbook, in the Drug Safety chapter, Chapter 25.

V. FDA's DECISION-MAKING PROCESSES IN EVALUATING STRATIFICATION AND SUBGROUPS

a. Introduction

FDA's comments in its *Medical Reviews* provide guidance for stratification and for

[160]Van Glabbeke M, Verweij J, Casali PG, et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organisation for Research and Treatment of Cancer–Italian Sarcoma Group–Australasian Gastrointestinal Trials Group study. J. Clin. Oncol. 2005;23:5795–804.

[161]Van Glabbeke M, Verweij J, Casali PG, et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organisation for Research and Treatment of Cancer–Italian Sarcoma Group–Australasian Gastrointestinal Trials Group study. J. Clin. Oncol. 2005;23:5795–804.

[162]DeMets DL, Furberg CD, Friedman LM. Data Monitoring in Clinical Trials. New York, NY: Springer; 2006.

[163]National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. N. Engl. J. Med. 2001;345:1075–83.