c. Criteria for surrogate markers

The following material addresses surrogate markers, as well as markers that do not meet the stringent requirements of surrogates. According to Prentice (21,22) a valid surrogate is one that correlates with the true clinical outcome and fully captures the net effect of drug treatment. The term *surrogate* refers to a biological parameter, such as tumor shrinkage, cholesterol levels, blood pressure, bloodstream virus levels, or serum levels of a tumor antigen, which can replace the true clinical outcome, and contribute to convincing a regulatory agency to approve the study drug. Regarding these particular examples, tumor shrinkage can be a surrogate for total elimination of cancer, lowered cholesterol can be a surrogate for reduction in heart attack rate, lowered blood pressure can be a surrogate for reduced heart attack rate, reduced virus levels can be a surrogate for total cure from the virus, and reduced tumor antigen can be a surrogate for total cure from the cancer.

Fleming and DeMets (23) and Molenberghs et al. (24) warn that merely establishing a *correlation* between the proposed surrogate and the clinical endpoint is not sufficient to establish the parameter as an acceptable surrogate. What is also needed is that the proposed surrogate endpoint be validated, that is, experimentally tested using appropriate statistical methods. "From a regulatory perspective, a biomarker is not considered an acceptable surrogate endpoint for a determination of efficacy of a new drug unless it has been empirically shown to function as a valid indicator of clinical benefit" (25).

Fleming and DeMets (26) provided an insightful set of factors that may prevent a proposed surrogate, including proposed surrogates that are biomarkers, from being established as a valid surrogate. These factors are as follows:

1. The surrogate is not in the causal pathway of the disease process.
2. Of several causal pathways of disease, the study drug affects only the pathway mediated through the surrogate, and does not affect other pathways that can cause the disease.
3. The surrogate is not in the pathway of the drug's effect.
4. The study drug has mechanisms of action that are independent of the disease process.

[21] Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med*. 1996;125:605–613.

[22] Gill S, Sargent D. End points for adjuvant therapy trials: has the time come to accept disease-free survival as a surrogate end point for overall survival? *Oncologist*. 2006;11:624–629.

[23] Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med*. 1996;125:605–613.

[24] Molenberghs G, Buyse M, Burzykowski T. *The Evaluation of Surrogate Endpoints*. New York, NY: Springer; 2005;9.

[25] Molenberghs G, Buyse M, Burzykowski T. *The Evaluation of Surrogate Endpoints*. New York, NY: Springer; 2005;7.

[26] Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med*. 1996;125:605–613.