III. MOA AND SURROGATE ENDPOINTS

Where a surrogate endpoint is to be used as part of the basis for regulatory approval, the investigator will likely need to provide evidence that the surrogate is related to the clinical endpoint. If the surrogate endpoint is low-density lipoprotein cholesterol (LDL-cholesterol) and if the clinical endpoint is heart attack, the principal investigator or medical writer will need to draft arguments that rely on the mechanisms of action, to argue that drugs that reduce LDL-cholesterol are likely also to reduce the incidence of heart attacks.

Where a clinical trial includes a surrogate endpoint such as a biomarker, the investigator provides the biochemical or physiological mechanisms that connect the surrogate endpoint with the clinical endpoint. The Prentice criteria (8,9) set forth criteria for determining if a proposed surrogate endpoint is relevant to a clinical endpoint. The Prentice criteria are discussed in this textbook in the chapter on biomarkers. The fact that the FDA accepts data on surrogate endpoints as part of the basis for regulatory approval is established by the relevant statutes, for example 21 USC 356 (10) and by the relative administrative law, for example 21 CFR 314.510.

IV. MOA AND EXPECTED ADVERSE DRUG REACTIONS

Knowledge of the MOA can provide insight into the expected adverse drug reactions (11). For example, if it is established that Drug A, which inhibits Biochemical Pathway A, results in a certain type of adverse drug reaction, and if the study drug also inhibits Biochemical Pathway A, then it might be useful for the package insert for the study drug to disclose these expected adverse drug reactions. The package inserts that come with marketed drugs may include a warning regarding a class of drugs with a common mechanism of action. According to the FDA's Guidance for Industry (12) on drug labeling, the package insert should disclose expected adverse drug reactions, where these are based only on expectations (not on actual observations). This warning should be included in the package insert, providing that the expected adverse drug reaction

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

[9] 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.

[10] 21 USC 356, in effect as of January 24, 2002.

[11] Wilke RA, Lin DW, Roden DM, et al. Identifying genetic risk factors for serious adverse drug reactions: current progress and challenges. *Nat Rev Drug Discov*. 2007;6:904–916.

[12] U.S. Dept. of Health and Human Services, Food and Drug Administration. Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format (January 2006);11 pages.