Biomarker validation encompasses a number of activities (210). First, *analytical validity* refers to the accuracy, reliability, and reproducibility of the test that detects and quantifies a given biomarker. Second, *biologic validity* refers to establishing that expression of a biomarker is associated with a particular nonclinical endpoint, that is, an endpoint measured in studies with animals or by way of in vitro cell culture. Third, *clinical validity* refers to the demonstration that expression of a biomarker correlates with a clinical endpoint. McShane and Hayes (211) observed that establishing reliability and accuracy of a biomarker used in the prognosis of a disease, or for predicting efficacy of a drug, can be difficult in documenting that the drug has efficacy. FDA has issued a number of guidance documents that relate to biomarkers (as cited in 212,213,214). For example, FDA states that the Sponsor should include analytical assay validation reports, with information on, "strengths and limitations of the submitted data," "atypical parameters that define when and how the biomarker should be used," and "if the biomarker is used to select or exclude study subjects, to optimize doses, to monitor drug safety" (215).

Regarding *clinical validity* of a biomarker, Scher et al. (216) state that a clinically qualified biomarker is one for which sufficient evidence has been generated for FDA acceptance for use in regulatory submissions, and that FDA has separate criteria for evaluating biomarkers that are prognostic biomarkers or predictive biomarkers. Scher et al. (217) also refer to validity of biomarkers that are measured in the timeframe *after* a drug is administered (rather than *before*), where the biomarker correlates with clinical efficacy.

Validation of an in vitro diagnostic test can involve tests on the reproducibility of test results, where data are acquired from the same test conducted at different study sites, different reagent lots, different operators, and for the same test repeated on different days. Validation studies of these types are typically required by the FDA, where a new type of

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