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Calibration curves and linearity. Data for these studies should be subjected to linear regression analysis (if a linear response is obtained) and should include the slope, intercept, standard error of estimate (standard deviation about the regression line), and the standard deviations of the slope and intercept. Standard deviations of repeated points may be included. In preparing radioimmunoassay calibration curves, authors may use any objective, statistically valid method, but specify the method used (see, e.g., 6).

Precision. Studies must include estimates of “within-run” and “total” standard deviations. Each should be determined at low, normal, and above-normal concentrations with use of specimens that are in an appropriate biological matrix. One method of estimating both within-run and total standard deviation is the analysis of variance experiment described in NCCLS EP5-T[7], which calls for two replicates per specimen per run and two runs per day for 20 days. This permits separate separation of between-day and between-run, within-day standard deviations, as well as within-run and total standard deviations. For acceptable alternatives that include only one run per day, see the cited document.

Accuracy. (a) Analytical recovery studies involve analyses after known amounts of analyte are added to the biological fluid on which the determination will be performed. Recovery of added analyte should be calculated. (b) Interference studies should be performed to assess the effects of common interferents, e.g., lipids, hemoglobin, bilirubin, and components of uremic plasma. Exogenous materials such as commonly used or commonly coadministered drugs that might interfere with the determination should also be tested for interferences. (c) Comparison-of-methods studies should compare results by the new or proposed method with those by a reference-quality method or other generally accepted analytical method for which assay performance is documented [8, 9]. It is desirable to test 100 to 200 different samples from patients who have been selected to include a wide variety of pathological conditions and to present a range of values for the analyte that includes those likely to be encountered in routine application. Appropriate statistical evaluation of the data typically requires regression analysis with slopes and intercepts (and their standard deviations) and standard errors of estimates. The correlation coefficient has limited utility.

Analytical sensitivity and detection limit. These terms are commonly confused. The International Union of Pure and Applied Chemistry defines analytical sensitivity as the ability of an analytical procedure to produce a change in signal for a defined change of the quantity (i.e., the slope of the calibration curve). Detection limit (or limit of detection) is defined as the lowest concentration or quantity of an analyte that can be detected with reasonable certainty for a given analytical procedure. The operational definition of this limit must be supplied by the author: e.g., the concentration at a specified signal-to-noise ratio or the concentration corresponding to a signal 3 SD above the mean for a calibrator that is free of analyte.

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Evaluation of diagnostic accuracy. In clinical studies, simple testing of the significance of differences between mean values of patients’ groups (e.g., by Student’s t-test) provides insufficient information to assess diagnostic accuracy. Scatter plots of data, calculations of diagnostic sensitivities and specificities, and use of approaches such as receiver-operating characteristic (ROC) curves [15], cumulative distribution analyses [16], likelihood ratios [17], and discriminant analysis [18] provide information that is appropriate to specific situations. Discussions of predictive values in illustrative settings may be useful additions to assess the potential clinical utility of tests with known accuracy.

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15. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine [Review]. Clin Chem 1993:39:561–77. Note that in Figs. 4–12 in this paper, the labels for the x-axis at the top and bottom are reversed. The (correct) dual labeling of the x-axis solves the problem of whether to plot specificity or 1 – specificity on the x-axis.