How Broad Is (Should Be) the Kit Producer's Responsibility for Supplying "Normal" Values?

To the Editor:

Due to the widespread use of kits stimulated by the reagent complexity of enzyme assays and radioimmunoassays, and the use of semiautomated and automated instrument systems, the responsibility for establishing the range of normal values needs some assessment. The commonly touted notion that each laboratory must determine its own normal values has been used as a "cop-out" by kit manufacturers. Review of expected normal values stated in kit enclosures, especially in the field of endocrinology by radioimmunoassay, reveals grossly inadequate documentation. Therefore, the following comments are offered.

1. Normal values (the range of normal values including 95% of the population) are said to vary from laboratory to laboratory, and many believe that this variation is due to biological differences related to climatic, ethnic, geographic, dietary, diurnal sampling variations, and other variables.

2. More likely, the variations in normal values are due to: (a) differences in methods—modified methods—measuring different things; (b) differences in standards—accuracy-control variables; and (c) differences in precision from laboratory to laboratory.

3. With a commercial kit, the factors in paragraph 2 should be standardized and what should be left as an explanation of variations in normal values is biological differences. The fact that commercial kits can achieve uniform data from one laboratory to another is a very favorable plus for commercial kits.

4. Therefore, it seems mandatory for all kit manufacturers to document normal range studies for their product; to ascertain diurnal, seasonal, age, geographic, ethnic, and other biological variables if they are significant.

5. Within a given area where normal values have been authenticated by the kit manufacturer, the kit user should be able to utilize the established normal values. By using simple verification protocol, and by continued monitoring of the distribution of values from patients' specimens the laboratory should provide a high order of confidence in its normal values with minimal cost. This procedure should also enhance confidence in the reliability of the method used.

6. Experiences with the clinical reliability of the method such as expected diagnostic abnormal findings should also be documented when feasible, or deemed clinically necessary.

Therefore, in conclusion:

The commonly stated theme "each laboratory should determine its own normal values" should be replaced with, "the kit manufacturer is responsible for determining normal values along with providing reliable standards and accuracy controls for their product." They should also provide data concerning the diagnostic reliability of abnormal findings.

A manufacturer should not be permitted to distribute its kit unless adequate normal values are documented; this requires resources not available to each laboratory user of the kit; the manufacturer would have to arrange for capable health-care facilities to perform the normal values studies with their kit, which will also provide an overall assessment of the reliability of the kit. From a medical usefulness criteria viewpoint, documentation of expected diagnostic abnormal values could also be provided in the same studies.

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Ed. note: If I may be permitted a general observation: Years of experience in both industry and academe have convinced me that commercial product-development laboratories often do more research on their products than the consumer gives them credit for, and that they are delighted to have the consumer bring problems such as this to their attention.

A reputable kit supplier was chosen, more or less at random, and asked to try to respond for the industry. This response follows, and gives insight into the travails and dilemmas of the manufacturer. May the reader's tolerance be increased.

To the Editor:

We have read Dr. Schoen's letter with great interest. As we understand it, he proposes the establishment of what Galen and Gambino (1) term "referent values" for clinical laboratory tests, rather than normal-range values. In Galen and Gambino's sense, referent values allow the end user of laboratory results to distinguish not only the diseased from the healthy, but a population with one disease from a population with another disease. Dr. Schoen clearly feels that it is the responsibility of reagent manufacturers to provide such values.

The Federal regulations governing the labeling of diagnostic products require that each manufacturer provide, in the instructions accompanying his product, a section on "expected values." This can be interpreted to mean normal range information of one or another type. Therefore, it is legally impossible for manufacturers to completely "cop out" of providing normal-range information. However, there is no requirement that the manufacturer conduct his own studies, and all too often in the past the values given have been resurrected from some ancient, if respected, source in the literature. At best these data may be shaky, at the worst out-rightly dangerous. Fortunately, most responsible reagent manufacturers do provide data based on actual experience with their reagent. In view of what Dr. Schoen suggests, these data probably do appear "grossly inadequate," and even when experimentally derived data are provided, most manufacturers also include a cautionary phrase suggesting that normal ranges should be checked in each individual laboratory. By this we intend to mean that the values be re-examined and expanded by a verification protocol such as the one which Dr. Schoen suggests.

We have had some interesting experiences with the normal range data we have provided to our customers. It seems the laboratory world is divided into three populations:

- A group that uses the figures we provide in the way that they are intended—that is, as a starting point for working with their own patient population and verification in their own laboratory.