

Industry Leader

The Role Of The Clinical Lab In Detecting Adverse Events

There are numerous factors which bear an influence on data interpretation, such as recent alcohol intake, exercise, ethnic origin, circadian and seasonal variation, and nutritional supplement drug-interaction. Considerable emphasis should also be placed on the preanalytical factors during phlebotomy.

Laboratories specializing in services to the pharmaceutical industry accumulate high volumes of data, and on statistical analyses interesting differences can emerge. Using serum calcium as an example, significant differences between male and female reference ranges are apparent due to gender differences in the levels of protein to which calcium is largely bound.

Clinical laboratories have an advantage since their databases can hold information from all investigators taking part in a study. Toxicity to drugs in phase III studies may not be apparent to individual investigators as only one or two patients in their group may show minor changes. Therefore, the clinical laboratory should take responsibility for monitoring the database in order to provide possible early warning of drug toxicity. It is important not to underestimate the potential toxicity of new chemical entities. Taking hepatotoxicity as an example, Lee (2003) reported that drug-induced liver injury has become the leading cause for acute liver failure in patients referred for liver transplantation in the United States, and Temple and Himmel (2002) commented that drug-induced liver injury is the most frequent single reason for removing approved drugs from the market. Add potential problems related to nephrotoxicity and haematological changes, then critical assessment

of sensitive laboratory markers becomes essential.

POPULATION-BASED STATISTICS NOT THE ANSWER

Population-based statistics relative to reference ranges are of value; however, of greater importance is any change an individual subject displays from their baseline data. In clinical studies, we are looking at safety tests to monitor potential toxicities, and it is apparent that the use of the broad-spectrum population-based reference range does not offer the most sensitive assessment. What then is the alternative? For many years in diagnostic pathology, we have employed the smallest significant difference (SSD) or the reference change value (RCV) for assessing variation in results from the same individual on different occasions.

An original publication in the *British Medical Journal* in 1989 discussing the interpretation of laboratory results drew attention to the use of intrasubject variation and its relevance in clinical decision making (Fraser and Fogarty, 1989), and the value of this measurement in clinical trial safety profiles was reported by Craig (1994), (2004). The use of this parameter thus treats the individual as their own reference point and offers greater sensitivity than broad-spectrum reference ranges.

Fraser (1993) showed that the average within-subject variation in healthy elderly people and younger adults is similar and that there is no apparent variation with different ethnic groups. Thus it is possible to build a significant database on biological variation. The SSD combines the intraindividual variation of any biological measurement, supplemented by the analytical variation of the particular test and is essentially the likely total error surrounding any measurement.

However, there are two further issues



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in relation to the testing. The first being that in many protocols, too many tests are included, many of which duplicate biological functional information, and the greater the number of tests undertaken, the greater chance there will be of attaining results outside the reference range. In this respect, tests such as MCH (mean corpuscular hemoglobin), total protein, urea, chloride and bicarbonate added little, if anything, to the standard safety profile data. The second matter questions whether the correct tests are being applied. Laboratories now have a large range of sensitive procedures to look critically at possible toxicity changes, and many of these are being overlooked. Further, the laboratories are more aware of samples requirements, stability, and the limitations of the analytical methods. In conclusion, there is the need for active participation of the laboratory at the protocol design stage, for the laboratory to monitor patient data on an ongoing basis during the trial, and for greater laboratory safety testing once the drug is marketed. ●