Measurement 50 (2014) 175–185

Contents lists available at ScienceDirect

Measurement

journal homepage: www.elsevier.com/locate/measurement

Modeling, analysis and optimization of calibration uncertainty in clinical laboratories

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ARTICLE INFO

Article history:
Received 23 May 2013
Received in revised form 17 December 2013
Accepted 23 December 2013
Available online 8 January 2014

Keywords:
Calibration correlation analysis
Optimal calibrator selection
Clinical laboratory measurements
Serum triglycerides

ABSTRACT

Uncertainty in the calibration of a clinical laboratory measurement process has a significant effect on the uncertainty of the measurement result. We develop a mathematical model of the analytical stage of the measurement of serum triglyceride concentration in the clinical laboratory, and use the Monte Carlo method to estimate the net uncertainty associated with this model. We then use the model to study the effect of instrument calibration on the uncertainty of the laboratory measurement result. The effect of the correlation between the parameters of the linear calibration function on the measurement result is quantified using the model. In addition, the effect of the choice of calibrator concentration levels on the measurement result distribution is studied using the model, by studying the effect of the value or the position of the calibrator concentration, and the difference or the distance between calibrator concentrations, on the uncertainty of the measurement result.

1. Introduction and literature review

Clinical laboratory testing plays a crucial role in the medical decision making process, and statements of uncertainty about the measurement result, also referred to as the *measurand*, are necessary in order to ascertain the quality of the clinical laboratory measurement process. Calibration of the instrument used to analyze patient samples is a vital part of the laboratory measurement process. In a measurement process with an indirect measurand – a process wherein the instrument measures a related property of the analyte instead of directly measuring the quantity of analyte – the purpose of calibration is twofold: (a) it establishes the values of the parameters of the function that converts the value of the measured property into the amount of the analyte, and (b) it identifies and facilitates removal of any systematic shifts in the location of the distribution of the measurement result. However, due to the presence of sources of variation within the various components of the measurement system, the calibration process also introduces uncertainty into the measurement process. In this paper, we use the measurement of triglyceride concentration in human blood serum to illustrate the effect of instrument calibration on the distribution of the measurement result. This is accomplished by developing a mathematical model of the serum triglyceride assay analysis procedure, and using the Monte Carlo method to estimate the uncertainty associated with such a model with stochastic parameters. The simulation model is then used to study two aspects of the effect of calibration on the measurand distribution: one, the correlation introduced between calibration function parameters when the parameters are estimated from the same set of data points is quantified, and the effect of this correlation on the mean and standard deviation of the measurand distribution is quantified. The implications of this correlation introduced by the calibration process for clinical laboratory operating policy are also

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http://dx.doi.org/10.1016/j.measurement.2013.12.027

explored. Secondly, the effect of calibrator concentration levels on the measurand distribution is quantified, and the simulation model is utilized to choose the combination of calibrator concentration levels that minimizes the total error at medical decision points as well as across a set of possible patient sample concentration levels. This study was carried out in collaboration with Roche Diagnostics based in Indianapolis, IN (USA) and the Mayo Clinic at Rochester, MN (USA).

A clinical laboratory measurement process can generally be divided into three stages: first, the pre-analytical stage, which involves activities such as patient sample collection, sample preparation, handling and storage; second, the analytical stage, wherein the sample is analyzed on the instrument; and finally, the post-analytical stage, which involves recording and reporting the measurement result. In this study, the analytical stage of the laboratory measurement process is modeled, as identifying and characterizing the variation of the numerous sources of uncertainty within the pre-analytical stage requires a separate study in its own right [23], and is therefore beyond the scope of this paper.

The concept of uncertainty and general principles for the development of uncertainty models were first introduced in the ISO/BIPM/OIML/IUPAC Guide to the Expression of Uncertainty in Measurement in 1993 [4] and revised in its subsequent editions and companion publications [10,12]. The term uncertainty associated with the quantity to be measured refers to a parameter used to characterize the dispersion of values that can be attributed to the measurand [4]. This concept of uncertainty is used to characterize the variation in the components and parameters of the system. In this paper, any component that is subject to variation is described by a probability distribution with the expected value or mean and the standard deviation as parameters. While the parameter used to represent uncertainty in this study is the standard deviation, we also study the effect of calibration on the location or mean of the measurand distribution in order to provide a complete description of the effect of calibration on the measurand distribution.

There have been several attempts to model specific analytical laboratory measurement processes [13,8,17,21,20], and some attempts to estimate the measurement uncertainty associated with serum cholesterol and other lipid panel laboratory measurement processes [9,14,6,23]; however, there seems to be very limited literature dealing with the estimation of the measurement uncertainty associated with serum triglyceride assays [26]. Kallner and Waldenstrom [13] develop a model that uses the law of propagation of uncertainty to estimate the uncertainty associated with the measurement of blood glucose in human serum, and include pre-analytical uncertainty in the model. They find that the instrument is the largest contributor to the measurement uncertainty, and this is consistent with the findings of Linko et al. [17] and Ramamohan et al. [22]. Linko et al. develop models of the serum glucose and the serum calcium assays and automate the estimation of the uncertainty using the law of the propagation. Their work stresses that a significant amount of the information required to build an uncertainty model can be obtained from internal quality control processes. Fuentes-Arderiu et al. [9] compare the measurement uncertainty associated with the direct plasma low-density lipoprotein (LDL) cholesterol method of measurement with that estimated indirectly via the Friedewald equation. However, the methods involved in the estimation of measurement uncertainty described in Fuentes-Arderiu et al. [9] involve either direct estimation from laboratory test results or the use of the Friedewald equation. The methodology used by Kouri et al. [14] and Chen et al. [6] to estimate measurement uncertainty for the serum cholesterol assay involved the use of the rules of uncertainty propagation described in the GUM [4] and the EURACHEM/CITAC Guide [7]. Sundvall et al. [26] utilize the data from external quality assessments to estimate the systematic error associated with the serum triglyceride assay. In this paper, a mathematical model of the serum triglyceride laboratory assay analysis procedure is developed and the Monte Carlo method is used to estimate the uncertainty associated with such a mathematical model.

However, the concept of modeling analytical methods in chemical laboratories from a systems engineering perspective has previously been suggested by Aronsson et al. [2], and Krouwer [16]. Aronsson et al. [2] perform a systems analysis using a simulation procedure to evaluate the influence of various systematic and random errors that are characteristic of the analytical procedure, and conclude that the simulation procedure is a valuable tool for minimizing the effect of these factors. In this paper, the different stages of the serum triglyceride assay analysis procedure from collecting the patient sample to reporting the results are conceptualized as a self-contained system. The input to the system – represented by the patient sample – is processed by the system components, and a property of the sample is quantified and expressed as the output quantity, represented by the result of the measurement process. The principal components of the serum triglyceride laboratory measurement process are identified as being the following: the patient sample, the calibrators, the measuring instrument and the reagents. In addition, the assay analysis procedure is divided into two phases: the calibration phase, wherein the parameters of the calibration function relating the measured property and the quantity of interest or measurand are estimated; and the measurement phase, wherein the patient sample with unknown triglyceride concentration is analyzed by the calibrated instrument.

The Monte Carlo method is used to characterize the long-term behavior of the system under conditions of uncertainty in its components. As stated in the GUM Annex 1 [11], the law of uncertainty propagation proposed in the GUM becomes unsuitable in the following situations: (a) the mathematical model involved is non-linear in nature; (b) the behavior of the measurand of the system is not Gaussian in nature; and (c) estimating the degrees of freedom for the sources of uncertainty is not possible, especially for Type B characterizations [4], which involve non-statistical characterizations of the variation of a parameter. The third case is particularly relevant here, as the statistical characterization (Type A) of the various sources of uncertainty using relevant data is often not