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PRACTITIONER'S REPORT

Proficiency tests to evaluate commercially available IVD kits for glucose and cholesterol measurements

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Abstract The first proficiency testing round 630-IL-1002, was carried out with a Reference Material DMR-180a with reference values obtained by using gas chromatography isotope dilution mass spectrometry methods, in which glucose, cholesterol and creatinine were measured. The serum pool was obtained from blood donors and all the analytes were at the normal concentration in Mexican population. The laboratories participants used different field methods to measure the analytes. The Mexican compulsory standard NOM-064-SSA1-1993 "specifications for equipments in vitro diagnostic (IVD)" requests 5% precision and 5% maximum bias of the IVD equipments in the measurements of analytes like glucose and cholesterol. The results obtained by field laboratories in the proficiency testing round are compared to the reference value and uncertainty provided by the National Metrology Institute (CENAM). The quality of measurements is dependent not only on the laboratory competence but also on the methods used by those commercially available IVD kits. It is concluded that quality assessment of measurements in clinical laboratories should be critically evaluated by using stable and certified reference materials.

Keywords Glucose · Cholesterol · Serum · Proficiency test · Certified reference materials

Introduction

In Mexico, the clinical laboratories try to establish traceability in their measurements and they work for accreditation according to NMX-EC-17025-IMNC-2000 "General requirements for the technical competence by test and calibration laboratories", then they need to show traceability to the National Metrology Institute. By the time of the comparison the clinical laboratories quantify health status markers by using calibration curves prepared by commercially available standards (bovine for example) with no evidence of traceability to SI units and do not report measurement uncertainty, so, it was important to demonstrate that the use of certified reference materials (CRMs) could give support to metrological aspects in clinical area and proficiency test (PT) schemes.

A proficiency testing round was organized to measure glucose, cholesterol, creatinine and calcium in human serum. A CRM was used as a blind sample for the participants in the PT scheme. Four Mexican clinical associations that represent the clinical laboratories were invited to participate in the PT, and each of them invited 20 laboratories established in different parts of the country. Some public health laboratories were also invited in order to obtain representative samples of the clinical laboratories in the country. Forty-six laboratories from different regions of Mexico have reported results.

Whit this PT CENAM tried to identify the different analytical methods and IVD kits used in Mexico to measure the analytes mentioned above, in order to know their performance by measuring a certified reference material in it, trying to identify the sources of uncertainty and possible bias in the measurements. An additional intention was to form a network of laboratories for clinical measurements and to guarantee to the population a reliable clinical analysis service. According to the results found and presented in this paper, and considering the "guide of metrological traceability for clinical laboratories" [1] and ISO guide 17511 [2], it is required that the producers of the

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IVD kits provide to the field laboratories, standards for calibration and controls with traceability, in this way CENAM offers to collaborate with calibrator manufactures to integrate them into CTRM program to provide traceability in clinical measurements.

According to the Federal Law of Metrology and Standardization article 30, fraction III and V, and the Mutual Recognition Arrangement of the Comité International des Poids et Measures (CIPM) about the responsibility of the National Metrology Institutes (NMI's) related to quality, characterization and the values assigned to Certified Reference Materials, CENAM offers the program of Certified Traceable Reference Materials (CTRM) as a service whose main objective is to extent the availability of Reference Materials to establish the traceability of analytical measurements in field. The program is designed and implemented by the Centro Nacional de Metrología, CENAM [3], for the certification of Reference Materials (RM) developed and distributed or just distributed by the organizations and enterprises interested in offering RM with traceability to SI.

Methods

Sample preparation

The human serum material was collected from the blood donors in the transfusion center (Blood Bank) at Querétaro city taken into account all the requirements in written standards to be used as a reference material for measurement purposes. The CRM DMR-180a was prepared and certified at CENAM. To prepare the serum pool each serum donor tube was placed into a sterile glass, after that the pool, was stirred gently for 15 min. Then the gentamicine sulfate was added as an antibacterial agent and again stirred for 15 min. The pH was measured and finally the pool was filtered and ampouled in 2.0 ml glass ampoules. For each ampoule 1 ml of serum was dispensed with automatic pipette and the ampoule was sealed with flame. The samples were stored at −80 °C until use.

Value assignment

The analytes of interest were measured and certified by using GC-IDMS, the same methods were used to demonstrate the CENAM Calibration and Measurements Capabilities (CMC) for glucose reported at the BIPM web page [4]. On the other hand, this sample fulfills all the requirements for homogeneity and short and large term stability tests for a CRM according to the recommendations in the international written standards ISO guide 34 and ISO guide 35 [5, 6].

The CENAM metrologists implemented the primary methods (IDMS) to measure, certificate and value assignment of the glucose [7], cholesterol [8] and creatinine, for calcium a reference value was obtained by using HPLC.

The uncertainty estimation was done by following the ISO GUM [9], the expanded uncertainty reported here covers the uncertainty between bottle and short and large term stability. In this paper, only the results of glucose and cholesterol are reported. The certified value and their expanded uncertainties ($k = 2$) reported in the same units as the participants did in the PT: are as follow: glucose (90.8 ± 1.7) mg/dl, cholesterol (161.2 ± 2.7) mg/dl.

Organization of the comparison

Two ampoules of the CRM DMR-180a containing 1 ml of frozen human serum and the protocol of measurement were sent to each participating laboratory. The laboratories were requested to return the results of five measurements for each analyte in each ampoule 1 month later. The results were evaluated and discussed with the laboratories participants in the National Clinical Sectorial Seminar.

Results and discussion

Since the analytes certified in the CRM DMR-180a were measured by using reference measurement methods for well defined chemical entities as glucose and cholesterol, and that CENAM has demonstrated their CMC for these quantities, the provided values (certified values) traceable to the SI units were used to compare the laboratory/IVD performance against these reference values.

The field laboratories used, to measure the analytes of interest, the commercially available IVD kits, identified from A to G, in Fig. 1a and b, individual results are presented for each laboratory for one of the two samples measured for glucose and cholesterol, the solid line represents the certified value, dotted lines the expanded uncertainty ($k = 2$), and the dashed lines ±3 U, the measurement uncertainty bars presented for each lab correspond to the standard deviation of three measurements.

On the graph only the results reported for the measurement of cholesterol and glucose in 1 ampoule were plotted for a better visualization of these.

In Fig. 1a for glucose and b for cholesterol, it is observed a clear positive bias for most of the IVD kits used to measure, and the difference between laboratories are also shown by IVD kit. The largest intralaboratory variation (15%) in terms of relative standard deviation and the largest bias (42%) with respect to the reference value were reported for cholesterol, while those for glucose were 14 and 20%, respectively.

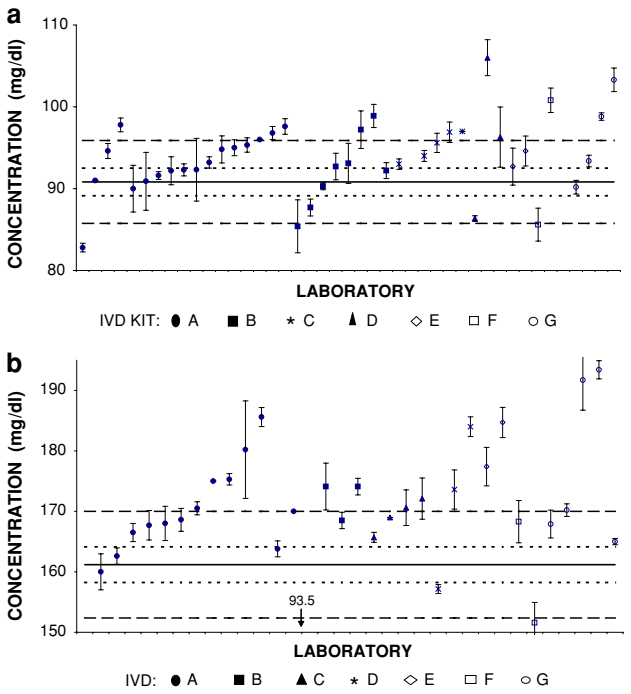

Fig. 1 Certified reference value (CRV) and the results obtained for the measurement of (**a**) glucose and (**b**) cholesterol for the different IVD Kits and laboratories

Thus, for the glucose measurement in 49% of the cases they reported at least for one of the two samples measured a value with bias to higher value from the reference value, and larger than 5% which is the criterion of Mexican standard.

From the laboratories that measured cholesterol, 19% reported one of the two measured values with a bias greater than 5% from the reference value, and 33% of the laboratories reported both values with a bias greater than 5% from the reference value. Thus in 51% of the cases they reported at least for one sample a value with bias greater than 5% from the reference value. For intra-laboratory variation 7% of the laboratories obtained a relative standard deviation larger than 5%.

Conclusion

Based on the criteria established in the Mexican standard NOM-064-SSA2-1993, 48% of the IVD kits used to measure cholesterol and 49% used to measure glucose by field laboratories participants in the PT are out of specifications for accuracy, and 7% for reproducibility of both cholesterol and glucose.

By using a certified reference value, it was demonstrated that most of the methods and IVD kits employed by field laboratories had bias to higher values and the bias and dispersion could be IVD kit dependent.

The use of certified reference materials is recommended to IVD kit producers to give traceability to their calibrants.

Currently CENAM have available the CRM DMR-263a human serum, which is intended primarily for use in evaluating the accuracy of procedures for the measurement of glucose in human serum, this material is also listed in the JCTLM database of higher-order reference materials: Laboratory medicine and in vitro diagnostics [10].

It is concluded that proficiency testing with reference value is essential for the evaluation of technical competence of clinical laboratories as well as calibrant quality.

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