J Bras Patol Med Lab. 2018 Jun; 54(3): 158-163.

10.5935/1676-2444.20180028

Harmonization study of results between biochemical analyzers Labmax 240® and Labmax 240 Premium®

Estudo de harmonização de resultados entre analisadores bioquímicos Labmax 240® e Labmax 240 Premium®

Luisa D. Scapin[1]; Vanessa P. Ramos[1]; Marion de Marco[2]; Rodrigo P. Siqueira[2]; Rejane G. Tavares[1]

1. Universidade Federal de Pelotas (UFPel), Rio Grande do Sul, Brazil. 2. Laboratório Antonello, Rio Grande do Sul, Brazil.

ABSTRACT

Introduction: The harmonization of equipment is recommended in clinical laboratory practice aiming for the homogeneity of results when similar or equivalent analyzers are used to perform routine testing. **Objectives:** To conduct a study of equivalence between the biochemical analyzers Labmax 240® (E1) and Labmax 240 Premium® (E2) through the matching results and the statistical value analysis of dosages. **Materials and methods:** We evaluated tests with glucose, total cholesterol, triglycerides, uric acid, aspartate transaminase (AST), alanine transaminase (ALT) and lactate dehydrogenase (LDH), all with 40 repeated measurements, performed in both equipments. The Clinical and Laboratory Standards Institute (CLSI) EP09-3A protocol was used to conduct the comparison test between E1 and E2 equipment, with subsequent evaluation of the results for statistical analysis determining the Pearson correlation coefficient (r) and indexes comparison error with EP Evaluator® software. **Results:** Regarding the values of the Pearson correlation coefficient, all tests showed a strong correlation between equipment with $r > 0.989$, except for the dosage of LDH ($r = 0.982$). This dosage failed not because the value of r, but due to the values obtained in the error index being larger than the total errors index allowed. **Discussion:** Compared to clinical criteria, the results of the analyzers are approximately equal, but this control process must be done continuously in order to prevent and track random errors within the laboratory routine. **Conclusion:** The process of harmonization of multiple devices that perform the same laboratory parameters is essential for ensuring quality and reliability of laboratory results and should be standardized and included in routine clinical analysis laboratories.

Key words: quality control; quality assurance health care; laboratory equipment; automation laboratory.

INTRODUCTION

The clinical biochemistry sector, inside a clinical laboratory, is generally that with the largest volume of samples and different tests to be carried out. Therefore, this sector proves extremely important, regarding both financial matters, and quality and safety of the presented diagnosis, seen that the reported results are essential to indicate a patient's state, helping medical decision-making and therapeutic conduct[1]. Considering the relevance of the obtained results, it is increasingly necessary to have timely and good-quality analyses performed and released in the laboratory reports.

Continuously improve processes must be the main focus of any organization, as those initiatives aim at, lastly, offering better products or services to their clients, fully meeting their needs and thus preserving and, if possible, improving the level of competitiveness of the enterprise in the market. In the field of medicine, more than trying to satisfy clients' desires, one tries unceasingly to optimize processes, aiming at minimizing risks to patients' lives. This attitude is materialized in the provision of consistent and reliable diagnostic information in the exact moments they are more necessary[2].

Technological advances in the area of laboratory biochemistry allowed the evolution of several types of analysis equipment that conduct tests with diverse methods, being able to analyze a great deal of samples in a short period of time. Laboratories that have high test volume in their routines, generally end up having more than one biochemical analyzer for sample processing, so as to optimize time in which one has the result delivered[3].

First submission on 12/08/17; last submission on 03/24/18; accepted for publication on 05/22/18; published on 06/20/18

However, to ensure laboratory quality, it is essential that result equivalence be obtained in all used biochemical analyzers for test conduction. Two or more instruments of the same capacity, potency, trademark, model and manufacturer, for example, do not necessarily have similar work and performance. According to Berlitz (2010)[2], documentary evidence is necessary, with adequate statistical analyses that prove equivalence among all the tested instruments, based on the obtained results. Among the statistical tests used, we can cite Deming regression and Passing Bablok, as well as Bland-Altman agreement analysis between methods, which aim at identifying possible discrepancies between the analysis values, so that all can be used in a same process, safely[4]. This question directly relates to continuous internal quality control, calibration performance and equipment maintenance. Equipment harmonization is obligatory to ensure that different instruments can release equivalent laboratory results, thus establishing the laboratory excellence standards.

OBJECTIVES

Conduct an equivalence study between biochemical analyzers, Labmax 240® e Labmax 240 Premium®, by result comparison, using statistical tools.

MATERIALS AND METHODS

This study was carried out by comparison of results obtained in two automated systems for biochemical analysis, based on protocol EP09-3A[5] of result harmonization, aimed at minimizing the interference of analytical process in the results obtained in different analytical systems, referenced by agreement methods linked to analysis of allowed errors. Systems Labmax 240® and Labmax 240 Premium® were used, designated E1 and E2, respectively, for the following tests: alanine transaminase (ALT), aspartate transaminase (AST), uric acid (UA), total cholesterol (TC), glucose (GLU), lactate dehydrogenase (LDH), and triglycerides (TG), with four of them being of enzyme colorimetric method (Uric Acid Liquiform, Triglycerides Liquiform, Glucose Liquiform, and Cholesterol Liquiform), and the other three of kinetic method (AST/GOT Liquiform, ALT/GPT Liquiform, and LDH Liquiform).

Forty samples of whole blood were selected, obtained from random patients, regardless of sex or age, according to the minimum number indicated by the EP09-3A[5] protocol. All sample selection criteria indicated by the protocol were observed, in relation to the good practices of sample collection and handling, besides assessment of minimum sample volume and occurrence of lipemia, turbidity, hemolysis or icterus. All measurements were done in duplicate to decrease measurement uncertainty, as indicated by the protocol.

The assessed samples were obtained from the laboratory routine on May 13, 2016, and were stored in gel separator tubes, centrifuged at 3,250 rpm for 10 minutes (Centurion centrifuge of Laborline®) for obtaining serum. All samples were processed in both analyzers, sequentially. Prior to measurements, procedures of analytical quality control were conducted, with calibration and calibration verification with control samples in two levels, using controls Qualitrol 1H and Qualitrol 2H of Labtest®, in both instruments.

The obtained results were evaluated in EP Evaluator® software, by means of Deming regression, followed by comparison with Bland-Altman graphs and Pearson's correlation. As assessment criterion, the desirable specification for allowable total error (TEa) was used, as described in the table of biological variation[6]. When the obtained values were within the defined ranges, correlation is classified as adequate.

RESULTS

For data analysis, 280 biochemical measurements were conducted in each instrument, 40 of each selected test. For comparative statistical analysis, the TEa values allowed were those obtained from the biological variation table[6]. The values of systematic error, Pearson's correlation coefficient (r), and values resulting from the linear equation are described in the **Table**.

When assessing agreement between the tested instruments for better analysis, data were divided according to their measurement method. As representative of the kinetic method, analytes AST, ALT, and LDH were selected. In both transaminases, there was strong correlation between measures, demonstrated by the value of Pearson's correlation: (ALT, $r = 0.992$) (**Figure 1A**) and (AST, $r = 0.989$) (**Figure 2A**). In **Figures 1B** and **2B**, we can evaluate data distribution by means of the error ratio chart (ALT Figure 1B and AST Figure 2B).

For evaluation of analyte LDH, although Pearson's correlation coefficient indicates the existence of correlation between both instruments ($r = 0.982$), one can observe the existence of several bordering values and outside the TEa value (**Figure 3A**), what does not allow to assure equivalence between the obtained results in both instruments. These non-harmonic data can also be observed in relation to distribution of error ratio between the instruments (**Figure 3B**).

TABLE – Results of the comparative statistical analysis of data obtained by instruments Labmax 240® (E1) and Labmax 240 Premium® (E2); $n = 40$, linear regression analysis[1] obtained by EP Evaluator® software

	Pearson's correlation coefficient (r)	Slope	Y Intercept	Concentration range of the analyzed samples	Systematic error	TEa	Result
ALT	0.992	0.98	- 0.3	7-528 U/l	1.2%	27.5%	Acceptable
AST	0.989	1.045	- 0.6	15-276 U/l	1.6%	16.7%	Acceptable
UA	0.998	0.979	0.03	1.8-9.4 mg/dl	0.13%	12%	Acceptable
TC	0.998	0.981	1.7	108-363 mg/dl	5.2%	9%	Acceptable
GLU	0.998	0.933	2.5	68-302 mg/dl	1.6%	7%	Acceptable
LDH	0.982	0.902	4.6	225-1,381 U/l	18.9%	11.4%	Unacceptable
TG	0.997	0.992	1.8	64-764 mg/dl	8.7%	26%	Acceptable

*[1]Equation for the correlation: Y = slope*X + intercept; ALT: alanine transaminase; AST: aspartate transaminase; UA: uric acid; TC: total cholesterol; GLU: glucose; LDH: lactate dehydrogenase; TG: triglycerides; TEa: allowable total error.*

Concerning colorimetric methods, analytes UA, TC, GLU, and TG were selected. In all analyses, it was possible to observe the existence of strong correlation between measures, demonstrated by the value of Pearson's correlation coefficient, for the tests (UA, $r = 0.998$ – **Figure 4A**; TC, $r = 0.998$ – **Figure 5A**; GLU, $r = 0.998$ – **Figure 6A**; TG, $r = 0.997$ – **Figure 7A**). Dispersion graphs of data related to error variation for UA, TC, GLU, and TG can be visualized in **Figures 4B**, **5B**, **6B**, and **7B**, respectively.

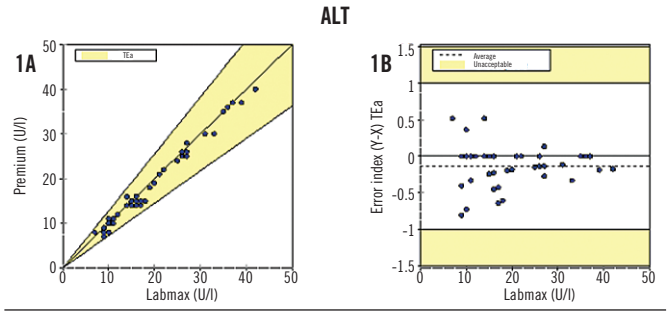

FIGURE 1 – *Comparisons between ALT measurement for 2 automated chemistry platforms*

A) linear regression for ALT measurements between instruments Labmax 240® (E1) and Labmax 240 Premium® (E2): n = *40,* r = *0.992,* p < *0.05; equation for the correlation: E2 = 0.98*E1 - 0.3; TEa = 27.5%; B) graph comparing the systems Labmax 240® (E1) and Labmax 240 Premium® (E2) for ALT measurement: error index = [(result - mean)/TEa] (table of biological variation); results > +1 and < -1 are considered inadequate* (n = *40).*

ALT: alanine transaminase; TEa: allowable total error.

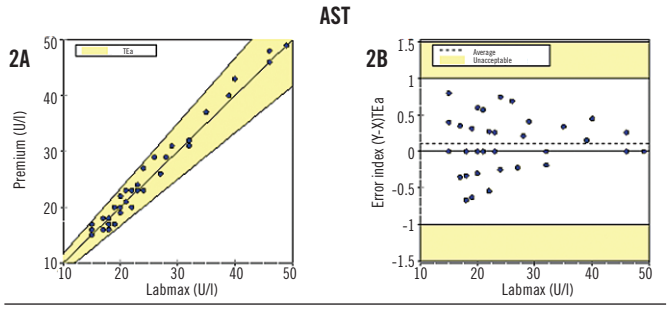

FIGURE 2 – *Comparisons between AST measurement for 2 automated chemistry platforms*

A) linear regression for AST measurements between instruments Labmax 240® (E1) and Labmax 240 Premium® (E2): n = *40,* r = *0.989;* p < *0.05; equation for the correlation: E2 = 1.045*E1 - 0.6; TEa = 16.7%; B) graph comparing the systems Labmax 240® (E1) and Labmax 240 Premium® (E2) for AST measurement: error index = [(result - mean)/TEa] (table of biological variation); results > +1 and < -1 are considered inadequate* (n = *40).*

AST: aspartate transaminase; TEa: allowable total error.

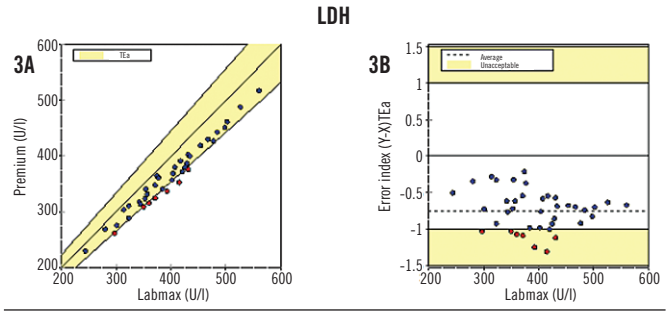

FIGURE 3 – *Comparisons between LDH measurement for automated chemistry platforms*

A) linear regression for LDH measurements between instruments Labmax 240® (E1) and Labmax 240 Premium® (E2): n = *40,* r = *0.983,* p < *0.05; equation for the correlation: E2 = 0.902*E1 + 4.6; TEa = 11.4%; B) graph comparing the systems Labmax 240® (E1) and Labmax 240 Premium® (E2) for LDH measurement: error index = [(result - mean)/TEa] (table of biological variation); results > +1 and < -1 are considered inadequate* (n = *40).*

LDH: lactate dehydrogenase; TEa: allowable total error.

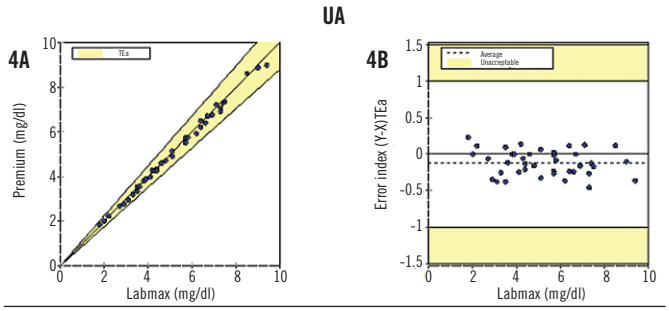

FIGURE 4 – *Comparisons between UA measurement for 2 automated chemistry platforms*

A) linear regression for UA measurements between instruments Labmax 240® (E1) and Labmax 240 Premium® (E2): n = *40,* r = *0.998,* p < *0.05; equation for the correlation: E2 = 0.979*E1 + 0.03; TEa = 12%; B) graph comparing the systems Labmax 240® (E1) and Labmax 240 Premium® (E2) for UA measurement: error index = [(result - mean)/TEa] (table of biological variation); results > +1 and < -1 are considered inadequate* (n = *40).*

A: uric acid; TEa: allowable total error.

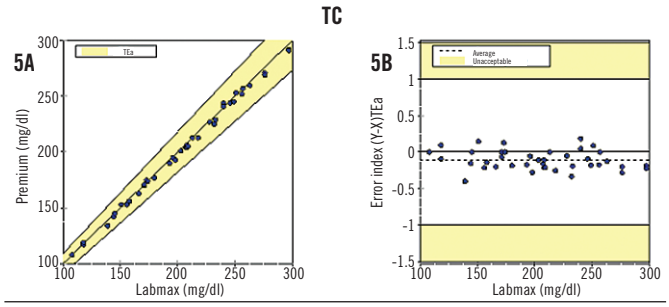

FIGURE 5 – *Comparisons between TC measurement for 2 automated chemistry platforms*

A) linear regression for TC measurements between instruments Labmax 240® (E1) and Labmax 240 Premium® (E2): n = *40,* r = *0.998,* p < *0.05; equation for the correlation: E2 = 0.981*E1 + 1.7; TEa = 9%; B) graph comparing the systems Labmax 240® (E1) and Labmax 240 Premium® (E2) for TC measurement: error index = [(result - mean)/TEa] (table of biological variation); results > +1 and < -1 are considered inadequate* (n = *40).*

TC: total cholesterol; TEa: allowable total error.

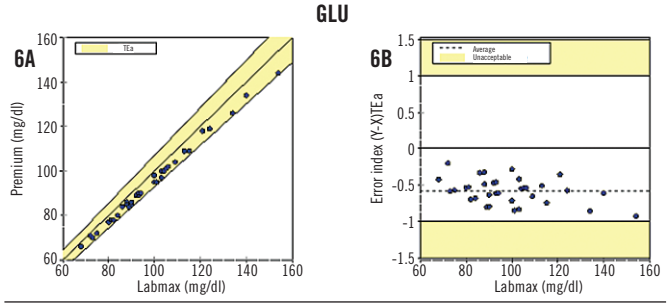

FIGURE 6 – *Comparisons between GLU measurement for 2 automated chemistry platforms*

A) linear regression for GLU measurements between instruments Labmax 240® (E1) and Labmax 240 Premium® (E2): n = *40,* r = *0.998,* p < *0.05; equation for the correlation: E2 = 0.933*E1 + 2.5; TEa = 7%; B) graph comparing the systems Labmax 240® (E1) and Labmax 240 Premium® (E2) for GLU measurement: error index = [(result - mean)/TEa] (table of biological variation); results > +1 and < -1 are considered inadequate* (n = *40).*

GLU: glucose; TEa: allowable total error.

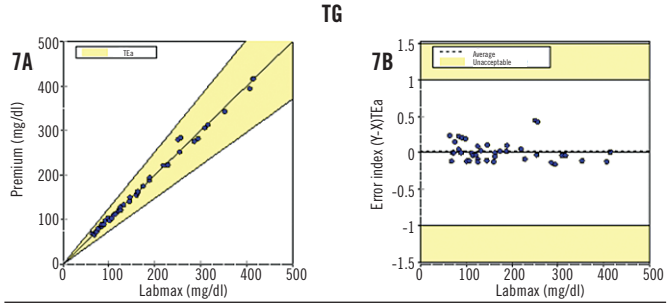

FIGURE 7 – *Comparisons between TG measurement for 2 automated chemistry platforms*

A) linear regression for TG measurements between Labmax 240® (E1) and Labmax 240 Premium® (E2): n = *40,* r = *0.997,* p > *0.05; equation for the correlation: E2 = 0.992*E1 + 1.8; TEa = 26%; B) graph comparing the systems Labmax 240® (E1) and Labmax 240 Premium® (E2) for TG measurement: error index = [(result - mean)/TEa] (table of biological variation); results > +1 and < -1 are considered inadequate* (n = *40).*

TG: triglycerides; TEa: allowable total error.

DISCUSSION

Between the 1980 and 1990 decades, automated instruments for laboratory tests started being commercialized in Brazil. During a long time, just large laboratories from big cities had these instruments introduced in their routine, due to massive investment and laboratories' need to have a large number of patients, so that these instruments would meet a great demand of tests, thus compensating for the investment. With the advent of automation, inclusion of these automated methods became a necessity in laboratory routine, as well as in sectors such as biochemistry, in which classically there is the conduction of a larger number of tests in clinical analyses. This inclusion of automated, standardized and precise methods in laboratory routine, along with procedures of quality control and trained and skilled professionals, has, in these latest years, contributed significantly, helping physicians in rapid and correct diagnostic decision[3].

According to Vieira *et al.* (2011)[7], for requirements of accuracy and precision to be respected, besides standardization of procedures in pre-analytical, analytical and post-analytical phases, it is essential that laboratories be recognized through processes of quality assurance. One of the tools for quality assurance is the use of indicators of quality by the clinical laboratory to quantify errors in laboratory processes and implement corrective measures, for instance, in relation to performance of a certain process. If it is satisfying, it is within the limits established by indicators; if not, it is possible to take preventive measures, which are used to eliminate the cause of a potential non-conformity[8].

The use of different instruments in the laboratory routine is a constant, either for economic reasons or for modernization of the technological park. For a better equivalence between instruments, in our study, both were obtained from the same manufacturer, using identical reagents, controls and methods, in order to eliminate the largest number of variables. Additionally, relevant technical differences are not observed between Labmax 240® and Labmax 240 Premium®.

For tests using end-point enzyme/colorimetric method, such as GLU, TC, TG and UA, one can notice by the Pearson's linear correlation (*r*), the existence of strong correlation between all the instruments, for all the tested analytes. This can be described, seen that all correlations present $r > 0.975$. However, only assessment of the number related to *r*, sometimes, is not enough to indicate actual equivalence between the different instruments used in the laboratory. Thus, use of additional statistical tests is necessary. In this study, graphic evaluation of error dispersion index was conducted, which permits a more detailed analysis in relation to the mean obtained data[4].

Even with the use and importance of statistical analysis, during the process of data tabulation it was possible to observe that, although no significant difference was obtained between two different instruments, GLU presented variation of absolute value. This could lead to test repetition in the analytical sector, or an erroneous diagnosis, with need to confirm the measurement in another opportunity, or ordering of additional tests, burdening the health system.

For comparisons of enzyme measurements, a strong correlation was obtained between the analyzed instruments ($r > 0.975$). However, in the graphic analysis of dispersion of LDH levels, a significant systematic error was observed, what implies rejection in the equivalence test. This evaluation plays an important role as just a small part of the tests performed in laboratory routine were compared, what may represent considerable variability in the released results. The implication of this variation in clinical interpretation is especially related to bordering values of the indicated value as "normality", which can generate the need of new confirming tests, or even, order of additional tests. At the same time, it is important to stress that wrong laboratory information, caused by failures in the laboratory process and conveyed to physicians, can directly affect the results of assistance and patient's safety.

It is important to observe that although the process of harmonization between instruments is not required by the Brazilian law concerning clinical laboratories, RDC 302[9], it enables the interchange of instrument usage, either in conditions of increased demand, or in situations of mechanical or operational problems in some instruments. There is no consensus procedure to demonstrate comparability of patients' results for samples measured in different measurement systems. There is a variety of approaches for the frequency of test conduction, number and type of samples to be tested (at random, high/low concentrations or mean value of the work range), the evaluation criteria and acceptance of comparison results[4], as described among the items evaluated by national programs of laboratory accreditation and certification, for example, the Program for Accreditation of Clinical Laboratories (PALC), kept by Sociedade Brasileira de Patologia Clínica e Medicina Laboratorial (SBPC/ML)[10] or the Departamento de Inspeção e Controle de Qualidade (DICQ), kept by Sociedade Brasileira de Análises Clínicas (SBAC)[11], which use the American law for their audits. The document of the CLSI EP09-3A[5], which deals with comparisons between methods and bias estimate with the use of samples, presents a strict protocol which requires efforts in practice. It was established for the comparison of two methods with similar measurement units and requires a comparison with more than 40 samples in duplicate, at an interval of up to two hours between them, for at least two methods per experiment. The document clarifies that the quality of the study of method comparison assumes adequately measured samples, with good result distribution, and values within the analytical interval of measures[4]. Even with the use of the number of samples indicated by the protocol, it is important to observe that the equivalence study performed is applicable only in the range of analyzed values, as numeric data of comparison (linear regression) cannot be extrapolated to concentration values outside the used range.

Besides satisfying legal requirements, equivalence between results obtained by different instruments certainly brings more safety and reliability to the laboratory, and when associated with other analytical control practices, such as use of internal and external control, can decrease the necessity for test repetition, ordering of new collections, or even erroneous results, which could result in legal actions[12]. Additionally, the tests conducted automatically offer a margin of error much smaller in relation to non-automated instruments, needing a smaller volume of samples to be collected, as well as smaller volumes of reagents, what also brings savings[13].

CONCLUSION

Our data permit to infer that the harmonization process between instruments, associated with the adequate use of calibrations and the effective participation in quality control programs (internal and external), is important for reliability of results released by the laboratory, and must be standardized and included in the routine of clinical laboratories.

RESUMO

Introdução: *No laboratório clínico, é recomendável a harmonização de equipamentos que visem à homogeneidade dos resultados, quando analisadores similares ou equivalentes são utilizados para desempenho da rotina de realização dos testes.* ***Objetivos:*** *Realizar um estudo de equivalência entre os analisadores bioquímicos Labmax 240® (E1) e Labmax 240 Premium® (E2).* ***Materiais e métodos:*** *Foram avaliados os testes glicose (GLI), colesterol total (COL), triglicerídeos (TRI), ácido úrico (AU), aspartato aminotransferase (AST), alanina aminotransferase (ALT) e lactato desidrogenase (LDH), todos com 40 dosagens repetidas, realizadas em ambos os equipamentos. O protocolo do Clinical and Laboratory Standards Institute (CLSI) EP09-3A foi utilizado para conduzir o teste de comparação, com posterior avaliação dos resultados pela análise estatística no* software *EP Evaluator®,*

*com determinação do coeficiente de correlação de Pearson (*r*) e comparação de índices de erro.* ***Resultados:*** *Em relação aos valores do coeficiente de correlação de Pearson, todos os testes apresentaram forte correlação entre os equipamentos, com* r *> 0,989, exceto para a dosagem de LDH (*r *= 0,982), que foi reprovada, não em função do valor de* r*, mas devido aos valores obtidos em relação ao índice de erro, o qual é maior do que os índices de erro total permitido.* ***Discussão:*** *Diante dos critérios clínicos, os resultados dos analisadores são aproximadamente iguais, porém esse controle do processo deve ser feito continuamente a fim de impedir e rastrear erros aleatórios dentro da rotina laboratorial.* ***Conclusão:*** *O processo de harmonização de múltiplos equipamentos que realizam os mesmos parâmetros laboratoriais é fundamental para a garantia da qualidade e da confiabilidade dos resultados laboratoriais, devendo ser padronizado e incluído na rotina dos laboratórios de análises clínicas.*

Unitermos: *controle de qualidade; gestão de qualidade; equipamentos para diagnóstico; automação laboratorial.*

REFERENCES

1. Westgard J, Darcy T. The truth about quality: medical usefulness and analytical reliability of laboratory tests. Clin Chim Acta. 2004; 346(1): 3-11.

2. Berlitz FA. Controle da qualidade no laboratório clínico: alinhando melhoria de processos, confiabilidade e segurança do paciente. J Bras Patol Med Lab. 2010; 46(5): 353-63.

3. Vilela S. Equipamentos automatizados – resultados de exames laboratoriais mais precisos. Available at: http://www.plugbr.net/equipamentos-automatizados-resultados-de-exames-laboratoriais-mais-precisos/. Acesso em: 6 Dez, 2017.

4. Oliveira CA, Mendes ME. Equivalência de sistema analítico. In: Oliveira CA, Mendes ME, org. Gestão da fase analítica do laboratório: como assegurar a qualidade na prática. vol. 2, 1 ed. Rio de Janeiro: Controllab; 2011.

5. Clinical and Laboratory Standards Institute. CLSI – EP09-3A. Method comparison and bias estimation using patient samples; approved guideline – second edition. Available at: http://clsi.org/. Access on: 6 Jun, 2017.

6. Ricos C, Alvarez V, Cava F, et al. Current databases on biologic variation: pros, cons and progress. Scand J Clin Lab Invest. 1999; 59(7): 491-500.

7. Vieira KF, Shitara ES, Mendes ME, Sumita NM. A utilidade dos indicadores da qualidade no gerenciamento de laboratórios clínicos. J Bras Patol Med Lab. 2011; 47(3): 201-10.

8. Weber C. Garantia da qualidade no setor de bioquímica do laboratório de análises clínicas de um hospital público de Porto Alegre [monografia]. Instituto de Comunicação e Informação Científica e Tecnológica em Saúde, Fundação Oswaldo Cruz/Grupo Hospitalar Conceição, Rio Grande do Sul; 2012.

9. Agência Nacional de Vigilância Sanitária. ANVISA. RDC 302, de 13 de outubro de 2005. Available at: http://portal.anvisa.gov.br/documents/10181/2718376/RDC_302_2005_COMP.pdf/7038e853-afae-4729-948b-ef6eb3931b19. Access on: 6 Dec, 2017.

10. Sociedade Brasileira de Patologia Clínica e Medicina Laboratorial. Normativas e avaliação PALC. Available at: http://acreditacao.org.br/acreditacao-do-sistema-de-qualidade-do-laboratorio-clinico-pelo-sistema-dicq-sbac. Access on: 6 Dec, 2017.

11. Sociedade Brasileira de Análises Clínicas. Acreditação do sistema de qualidade do laboratório clínico. Available at: http://acreditacao.org.br/acreditacao-do-sistema-de-qualidade-do-laboratorio-clinico-pelo-sistema-dicq-sbac/. Access on: 6 Dec, 2017.

12. Lopes HJJ. Garantia e controle da qualidade no laboratório clínico. Assessoria técnico-científica da Gold Analisa Diagnóstico Ltda. Available at: http://www.goldanalisa.com.br/arquivos/%7B8530AFBA-AE96-4413-90EE-9C929C896B39%7D_Garantia_e_Controle_da_Qualidade_no_Laboratorio_Clinico[1].pdf. Access on: 6 Dec, 2017.

13. Campana GA, Oplustil CP. Conceitos de automação na medicina laboratorial: revisão de literatura. J Bras Patol Med Lab. 2011; 47(3): 119-27.

CORRESPONDING AUTHOR

Rejane Giacomelli Tavares
Rua Coronel Alberto Rosa, 1886, apto 302; CEP: 96010-770; Pelotas-RS, Brasil; Phone: +55 (53) 3275-7355; e-mail: tavares.rejane@gmail.com.