Model za usporedivost rezultata dobivenih s dva različita biokemijska analizatora u laboratoriju akreditiranom prema normi ISO 15189

A model for results comparison on two different biochemistry analyzers in laboratory accredited according to the ISO 15189

Marijana Miler, Ana-Maria Šimundić, Mario Štefanović, Dragica Ferenec-Ružić, Marina Kvaternik, Elizabeta Topić, Nada Vrkić

Klinički zavod za kemiju, Klinička bolnica Sestre milosrdnice, Zagreb
University Department of Chemistry, Sestre milosrdnice University Hospital, Zagreb, Croatia

Sažetak

Uvod: Laboratoriji akreditirani prema normi ISO 15189 koji imaju dva ili više različitih analizatora ili postupaka ispitivanja za iste analite, moraju definirati mehanizam kojim osiguravaju usporedivost rezultata. Cilj ovog rada je predstaviti model usporedbe rezultata hitnih biokemijskih pretraga s dva različita tipa automatiziranih analizatora za opće biokemijske pretrage.

Materijali i metode: Koncentracije općih biokemijskih hitnih parametara mjerene su u serumu i mokraći na dva automatizirana analizatora: Olympus AU2700 i Olympus AU640 (Olympus, Hamburg, Germany) tijekom 60 dana. Kao referentni analizator služio je Olympus AU2700, a Olympus AU640 bio je pomoćni sustav. Za usporedbu rezultata korišteni su kontrolni uzorci na dvije koncentracijske razine.

Rezultati: U razdoblju od 60 dana prosječno odstupanje za sve pretrage bilo je unutar dopuštenih granica. U manje od 2% slučajeva kontrolni uzorci s niskim vrijednostima odstupali su više od dopuštenih granica, dok uzorci viših koncentracija nisu niti jednom odstupali od dopuštenih kriterija.

Zaključak: Ovaj model usporedbe rezultata osigurava neprekidnu kvalitetu analitičke faze izdavanja laboratorijskih nalaza te poboljšava ukupnu učinkovitost laboratorija.

Ključne riječi: akreditacija; usporedba analizatora; unutarnja kontrola kvalitete; laboratorijska pogreška

Abstract

Introduction: Laboratories accredited according to ISO 15189 standard which have two or more different analyzers or procedures for examinations, should define mechanism for comparison of results. The objective of this study was to present the model for comparison of emergency tests on two different types of automated general biochemistry analyzers.

Materials and methods: General biochemistry emergency tests were measured in serum and urine on two automated analyzers Olympus AU2700 and Olympus AU640 (Olympus, Hamburg, Germany) during 60 day period. Olympus AU2700 was used as the reference analyzer and Olympus AU640 as a backup system. Control samples on two levels were used for result comparison.

Results: Average 60-day period bias was within acceptance criteria for all analyzes included in this model of comparability assessment. Only low control concentrations for some tests were exceeding allowable biases in less than 2% cases and high level controls were never exceeding allowable biases.

Conclusions: This model of results comparison ensures continuous analytical quality of laboratory reports and improves overall efficiency of laboratory services.

Key words: accreditation; analyzer comparison; internal quality control; laboratory error

Pristiglo: 13. kolovoza 2009. *Received: August 13, 2009*

Prihvaćeno: 4. rujna 2009. *Accepted: September 4, 2009*

Uvod

Norma ISO 15189 za medicinske laboratorije temelj je za osiguravanje zahtjeva za sposobnošću i kvalitetom u biokemijskom laboratoriju.

U svakom je laboratoriju od neizmjerne važnosti osigurati unutarnju kontrolu kvalitete (engl. *internal quality control*, IQC). Laboratorij mora biti uključen i u vanjsku procjenu kvalitete (engl. *external quality assurance schemes*, EQAS).

Introduction

The ISO 15189 standard for medical laboratories serves as an inevitable tool for providing requirements for competence and quality in biochemistry laboratory.

In every laboratory it is of outstanding importance to ensure internal quality control (IQC) as well as to be included in external quality assurance schemes (EQAS). If laboratories accredited according to ISO 15189 standard

Ukoliko akreditirani laboratoriji imaju dva ili više analizatora ili postupka za određenu pretragu, moraju definirati mehanizam kojim osiguravaju usporedivost rezultata (1). Usporedivost različitih analitičkih sustava smanjuje analitičko odstupanje i omogućava uspoređivanje pojedinih rezultata pretrage s vrijednostima u populaciji u odnosu na referentni intervale ili granične vrijednosti (2). Usporedivost ujedno omogućava brzo i pouzdano izdavanje nalaza, posebice u hitnom laboratoriju, a neovisno o analitičkom sustavu koji se upotrebljava ili je funkcionalan. Na taj način omogućava se najbolja skrb za bolesnike, što je ključno za proces neprekidnog poboljšavanja u laboratorijima akreditiranim prema ISO 15189.
Cilj ovog rada bio je opisati model za usporedbu rezultata hitnih pretraga dobivenih s dva različita automatizirana analizatora na kojima se svakodnevno radi u laboratoriju.

Materijali i metode

Ustanova

Klinički zavod za kemiju akreditiran je prema normi ISO 15189 od 2007. godine. Zavod je dio Kliničke bolnice „Sestre milosrdnice" u Zagrebu, koja je ustanova tercijarne zdravstvene zaštite, srednje veličine. U laboratorij se tijekom mjesec dana zaprimi oko 30,000 uzoraka od čega je otprilike 11,000 hitnih uzoraka s općim biokemijskim pretragama. Dnevno se u hitni laboratorij zaprimi oko 350 biokemijskih uzoraka.
Laboratorij posjeduje 2 tipa analizatora za određivanje općih biokemijskih pretraga: Olympus AU2700 i Olympus AU640 (Olympus, Hamburg, Germany). Kao referentni analizator služi Olympus AU2700, dok je drugi, Olympus AU640, pričuvni sustav.

Uzorci

Usporedivost je osigurana svakodnevno za sljedeće pretrage u serumu: ukupni i konjugirani bilirubin, glukoza, kreatinin, ureja, ukupni proteini, enzimi (AST, ALT, LDH, CK, CK-MB i α-amilaza), kalij, natrij, kloridi, kalcij, C-reaktivni protein (CRP). Uz navedene pretrage u serumu, uspoređuje se i koncentracija glukoze te aktivnost amilaze u mokraći.
Tijekom razdoblja od 60 dana neprekidno se provodila unutarnja kontrola kvalitete na dvije razine i na dva različita analizatora. Koncentracija CRP određena je iz komercijalno dostupnih kontrolnih uzoraka ITA Control serum level 1 i 2 (Olympus, Hamburg, Njemačka), aktivnost amilaze i koncentracija glukoze u mokraći određena je iz komercijalno dostupnih kontrolnih uzoraka Urine chemistry control 1 i 2 (Bio-Rad Laboratories, Irving, CA, USA), a aktivnost CK-MB iz CK-MB Kontrola (Herbos Dijagnostika, Sisak, Hrvatska). Sve druge pretrage mjerene su iz Control serum 1 i 2 (Olympus, Hamburg, Njemačka). Ciljne vrijednosti kontrolnih uzoraka navedene su u tablici 1.

have two or more different analyzers or procedures for examinations, they should define mechanism for comparison of those results (1). The comparability of different analytical systems minimizes analytical bias and enables comparison of individual test results with the population values based reference interval or with cut-off value (2). It also provides fast and reliable results reporting in laboratory, especially in emergency department, regardless to the analytical system which is used and functional. This ensures the best patient care and is key point for continuous improvement of laboratory accredited according to ISO 15189 standard.
The objective of this study was to describe the model for comparison of emergency tests on two different types of automated analyzers used in laboratory on daily basis.

Materials and methods

Setting

University Department of Chemistry is the laboratory accredited according to ISO 15189 standard since 2007. It is the department of Sestre milosrdnice University Hospital in Zagreb, Croatia, which is tertiary care medium-sized hospital. In laboratory, approximately 30.000 samples per month is admitted, out of which 11.000 emergency samples with general biochemistry tests. On daily basis there are about 350 emergency samples with biochemistry tests.
Laboratory has two types of clinical chemistry analyzers for performing general biochemistry tests: Olympus AU2700 and Olympus AU640 (Olympus, Hamburg, Germany). Olympus AU2700 was used as the reference analyzer while the other, Olympus AU640, was used as a continuous backup system for the reference analyzer.

Samples

Comparability is assured on daily basis for the following serum analyzes: total and conjugated bilirubin, glucose, creatinine, urea, total protein, enzymes (AST, ALT, LDH, CK, CK-MB and α-amylase), potassium, sodium, chloride, calcium, C-reactive protein (CRP). Comparability is also assured for amylase and glucose in urine.
During the period of 60 days internal quality control procedures were continuously performed on two levels with two different analyzers. For determination of CRP concentration commercially available controls ITA Control serum level 1 and 2 (Olympus, Hamburg, Germany) were used, for urine amylase and glucose commercially available Urine chemistry control 1 and 2 (Bio-Rad Laboratories, Irving, CA, USA) and for CK-MB commercially available CK-MB Kontrola (Herbos Dijagnostika, Sisak, Croatia). For all other tests Control serum 1 and 2 (Olympus, Hamburg, Germany) were used. Target control values for all control samples are listed in Table 1.

Tablica 1. Ciljne vrijednosti kontrolnih uzoraka i dopušteni raspon.

Table 1. Control sample target values with acceptable range.

Test (Units)	Target value (± 2SD range)	
	L	H
Total bilirubin (μmol/L)	25.6 (18.9–32.3)	115 (85.0–145)
Conjugated bilirubin (μmol/L)	19.4 (14.4–24.4)	68.0 (50.3–85.7)
Glucose (mmol/L)	5.26 (4.42–6.10)	12.5 (10.5–14.5)
Creatinine (μmol/L)	116 (90.5–142)	452 (353–551)
Urea (mmol/L)	6.34 (4.95–7.73)	27.0 (21.0–32.9)
Total protein (g/L)	39.9 (35.5–44.3)	74.3 (66.1–82.5)
AST (U/L 37°C)	44.2 (34.0–54.4)	128 (98.6–157)
ALT (U/L 37°C)	41.7 (32.1–51.3)	123 (94.5–151)
LDH (U/L 37°C)	151 (123–178)	537 (440–633)
CK (U/L 37°C)	150 (120–180)	387 (309–464)
CK–MB (U/L 37°C)	35 (27–45)	
α–amylase (U/L 37°C)	84.5 (67.6–101)	241 (193–289)
Potassium (mmol/L)	3.75 (3.41–4.09)	6.44 (5.86–7.02)
Sodium (mmol/L)	118 (111–125)	149 (140–159)
Chloride (mmol/L)	90.2 (82.1–98.3)	112 (102–122)
Calcium (mmol/L)	2.26 (2.01–2.51)	3.30 (2.94–3.66)
CRP (mg/L)	18.3 (14.7–22.0)	32.0 (25.6–38.5)
Urine amylase (U/L 37°C)	61.5 (49.2–73.8)	172 (138–206)
Urine glucose (mmol/L)	1.94 (1.55–2.33)	16.3 (13.0–19.6)

* H – control with concentration above reference interval; L – control with concentration within or below reference interval.

Procjena usporedivosti

Usporedivost je procijenjena izračunom odstupanja izmjerenih koncentracija prema sljedećoj jednadžbi:

$$\text{Bias} = \left| \frac{\text{conc. AU2700} - \text{conc. AU640}}{\text{conc. AU2700}} \right| \times 100$$

u kojoj *bias* predstavlja mjeru slaganja između referentnog i pričuvnog analizatora, *conc*. označava izmjerenu koncentraciju određene pretrage, a AU2700 ili AU640 je tip analizatora (Olympus AU2700 ili Olympus AU640). Rezultati su pomnoženi sa 100 kako bi se dobila vrijednost u postotku.

Najveća dopuštena odstupanja za sve pretrage određena su prema vrijednostima koeficijenata varijacije koje je odredilo Hrvatsko društvo medicinskih biokemičara u kriterijima vanjske procjene kvalitete.

Postupnik za usporedbu rezultata

Kontrolni uzorci mjereni su svakodnevno na oba analizatora (Olympus AU2700 i AU640). Svaki dobiveni rezul-

Comparability assessment

Comparability was assessed by calculation of the test concentration bias according to the following equation:

$$\text{Bias} = \left| \frac{\text{conc. AU2700} - \text{conc. AU640}}{\text{conc. AU2700}} \right| \times 100$$

where bias represents a measure of agreement between reference and backup analyzer, conc. means concentration of the particular test, AU2700 or AU640 indicates type of analyzers: Olympus AU2700 or Olympus AU640. Result was multiplied with 100 to obtain the percentage value.

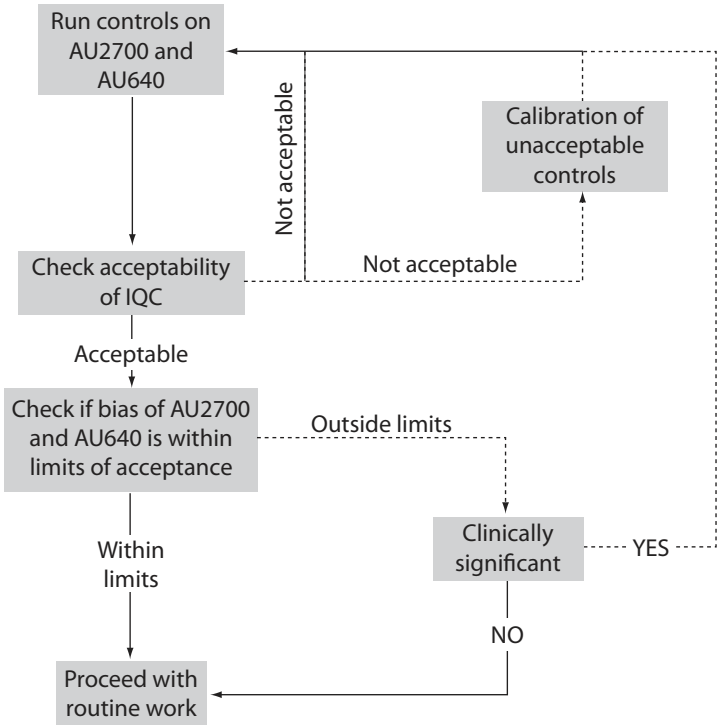
Maximum allowable biases for all tests were defined according to the values of the coefficient of variation (CV) for particular parameter given by the Croatian Society of Medical Biochemists external quality assessment criteria.

Workflow for the results comparison

All control samples were measured on both analyzers (Olympus AU2700 and AU640) on daily basis. Every control

tat upisan je na Levey-Jenningsov graf i provjerena mu je prihvatljivost prema Westgardovim pravilima (ciljna vrijednost ± 2 standardne devijacije (SD)) (3,4). Ukoliko su rezultati za oba kontrolna uzorka bili prihvatljivi na obje koncentracijske razine, uneseni su u model za usporedbu analizatora. Ukoliko rezultati nisu bili unutar prihvatljivog raspona, unutarnju kontrolu kvalitete trebalo je provesti sa svježim kontrolnim uzorcima. Pretrage s rezultatima izvan dopuštenih raspona, potrebno je kalibrirati te ponovno provesti IQC. Ukoliko su rezultati kontrolnih uzoraka na oba analizatora unutar zadanih odstupanja, rutinski rad s uzorcima bolesnika može se nastaviti. Ukoliko vrijednosti na dva analizatora nisu usporedive, medicinski biokemičar treba provjeriti je li razlika među koncentracijama klinički značajna u usporedbi s inter-individualnim biološkim varijacijama prema Westgardu (5). Ukoliko razlika nije klinički značajna, rutinski rad može se nastaviti. Za pretrage koje se razlikuju više od vrijednosti inter-individualnih koeficijenata varijacije (CV), kontrolni uzorci moraju se pustiti ponovno ili je testove potrebno kalibrirati (slika 1).

sample result was plotted on the Levey-Jennings chart and checked for acceptability according to Westgard rules (target value ± 2 standard deviations (SD)) (3,4). If control sample test results were acceptable on both levels, they were entered in the model for analyzer comparison. If results were not within acceptable range, IQC procedure should be re-run with fresh control samples. Analyzes with results outside acceptable range should be calibrated and IQC procedure performed again. When control values on both analyzers fulfilled required IQC criteria and are within acceptable bias, routine work could be proceeded. If control values are not comparable, medical biochemists should check if their difference is clinically significant in comparison to inter-individual biological variations according to Westgard (5). If the difference is not clinically significant, routine work may be continued. For tests with difference above inter-individual coefficient of variation (CV), control samples should be re-run or test calibrated (Figure 1).



Slika 1. Postupnik za provođenje unutarnje kontrole kvalitete i za usporedbu rezultata dobivenih s dva različita analizatora. AU2700 – Olympus AU2700; AU640 - Olympus AU640; IQC – internal quality control

Figure 1. Workflow for internal quality control and results comparability on two different analyzers. AU2700 – Olympus AU2700; AU640 - Olympus AU640; IQC – internal quality control

Rezultati

Srednje odstupanje tijekom razdoblja od 60 dana bilo je unutar dopuštenih granica za sve pretrage koje su uključene u ovaj model procjene usporedivosti (tablica 2). Samo su kontrole niskih koncentracija za bilirubin, kloride, glukozu, kalij, natrij, kreatinin i ureju u manje od 2% slučajeva odstupali više od dopuštenih granica. Vrijednosti koje su prelazile dopušteno odstupanje nisu bile klinički značajna odstupanja te su, kao takve, zanemarene. Kontrolni uzorci s visokim koncentracijama niti jednom nisu bile izvan dopuštenog odstupanja. Koncentracija konjugiranog bilirubina u kontrolnom uzorku s niskim vrijednostima imala je najveće srednje odstupanje (4,17%) kao i najveće apsolutno odstupanje (16,48%). Najmanje srednje odstupanje izračunato je za natrij (1,16%).

Results

Average 60-day period bias was within acceptance criteria for all analyzes included in this model of comparability assessment (Table 2). Only low control concentrations for bilirubin, chloride, glucose, potassium, sodium, creatinine and urea were exceeding allowable biases in less than 2% cases, though those exceeding values were not clinically significant and as such were disregarded. Control samples with high concentration were never exceeding allowable biases. Conjugated bilirubin concentration in the low control level had the largest 60-day period average (4.17%) and maximum bias (16.48%). The minimum average bias was observed for sodium (1.16%).

Tablica 2. Prosječna izmjerena odstupanja za kontrolne uzorke s visokim i niskim koncentracijama analita s dopuštenim odstupanjima.

Table 2. Average measured biases for low and high concentration control samples with allowable bias values.

Test	Average measured bias (%)		Allowable bias** (%)
	L*	H*	
Total bilirubin	1.42 ± 1.37	1.44 ± 1.28	12
Conjugated bilirubin	4.17 ± 3.48	3.90 ± 2.95	12
Glucose	2.25 ± 1.32	1.36 ± 1.25	5
Creatinine	2.60 ± 2.06	2.55 ± 2.10	8
Urea	3.67 ± 2.90	2.79 ± 2.30	10
Total protein	1.56 ± 1.70	1.41 ± 1.13	5
AST	2.22 ± 3.00	1.84 ± 1.57	15
ALT	3.63 ± 3.00	2.93 ± 2.10	15
LDH	2.58 ± 2.40	2.10 ± 1.66	12
CK	1.83 ± 1.73	2.56 ± 2.02	12
CK-MB	3.62 ± 2.90	4.59 ± 2.60	12
α-amylase	2.11 ± 1.71	2.02 ± 1.49	15
Potassium	1.50 ± 1.29	1.86 ± 1.30	5
Sodium	1.16 ± 0.95	1.14 ± 0.81	3
Chloride	1.37 ± 1.34	1.03 ± 0.96	4
Calcium	1.42 ± 1.18	1.32 ± 0.91	5
CRP	1.44 ± 1.18	2.04 ± 1.78	24
Urine amylase	3.41 ± 2.64	2.77 ± 2.21	15
Urine glucose	3.28 ± 3.40	3.03 ± 2.17	22

* H, control with concentration above reference interval; L, control with concentration within or below reference interval.
** According to Croatian Society of Medical Biochemists external quality assessment criteria.

Rasprava

Laboratoriji akreditirani prema normi ISO 15189 moraju osigurati kvalitetne rezultate za sve pretrage. Isto tako moraju osigurati izdavanje nalaza u preporučenom vremenu (engl. *turn-around time,* TAT). TAT se može postići pomoću dva analizatora koji su istovremeno dostupni i funkcionalni, a rezultati su im međusobno usporedivi.

Cilj ovog rada bio je opisati model koji se provodi u laboratoriju, a služi kao mehanizam za neprekidnu provjeru usporedivosti rezultata na dva različita automatizirana analizatora. Provjera usporedivosti provodi se svakodnevno, što je određeno značajkama hitnih pretraga.

Prema našim saznanjima, ovo je prvi objavljeni primjer modela za osiguravanje usporedivosti dva automatizirana analitička sustava.

Kao dopuštena odstupanja pričuvnog od referentnog analizatora preuzete su vrijednosti CV iz kriterija za vanjsku procjenu kvalitete Hrvatskog društva medicinskih biokemičara. Kriteriji uključuju biološku varijaciju, a predstavljaju i ukupno dopuštena odstupanja od srednje vrijednosti (5).

Ovim se radom pokušalo dokazati da se na jednostavan način uvođenjem postupnika može osigurati usporedivost i pouzdanost rezultata hitnih pretraga te stalna pripravnost dva analizatora. Model osigurava brzi prelazak s jednog na drugi analitički sustav ukoliko na referentnom sustavu dođe fatalne greške.

Jedan od glavnih indikatora kvalitete u akreditiranom laboratoriju je osiguravanje pouzdanih i točnih rezultata s prikladnim tumačenjem. Ovim modelom može se mjeriti učinkovitost laboratorija te istovremeno osigurati najtočnije moguće rezultate (6), neovisno o tome na kojem su automatiziranom sustavu određivane koncentracije. Na ovaj način, laboratorij može uvelike doprinijeti postavljanju dijagnoze bolesnika kao i osigurati važan udio najbolje zdravstvene zaštite svakog pojedinog bolesnika. Kada laboratorijski rezultati dobiveni s dva različita analitička sustava ne bi bili usporedivi, povećavala bi se mogućnost za postavljanje pogrešne dijagnoze, a ujedno bi se smanjila kvaliteta brige za bolesnika (7,8). Model osigurava i pouzdanu podlogu za osiguravanje longitudinalnog praćenja pojedinih bolesnika. Prema tome, model može poslužiti i kao jedan od načina standardizacije laboratorijskih postupaka i izdavanja nalaza hitnih pretraga (9).

Iako je većina laboratorijskih grešaka iz prijeanalitičke ili poslijeanalitičke faze (10), greške u analitičkoj fazi uzrokovane kvarom sustava mogu se izbjeći pomoću dva jednako spremna i funkcionalna analizatora. Opisani model usporedivosti može smanjiti analitičke greške nastale zbog kvara referentnog analizatora.

Ovaj model usporedbe rezultata osigurava kvalitetu laboratorijskih nalaza te poboljšava ukupnu učinkovitost laboratorija. Pouzdani i usporedivi rezultati svakodnevno

Discussion

Laboratories accredited according to ISO 15189 standard have to provide quality test results and also test reports in assigned turn-around time (TAT) which is 1 hour for emergency tests. This TAT could be accomplished by the two analyzers both available and functional with comparable results between themselves.

The aim of this study was to describe the model implemented in laboratory which is a mechanism for continuous verification of results comparability on two different automated analyzers. This verification was performed on daily basis, defined due to characteristics of the emergency test procedure.

To the best of our knowledge this is the first published example of the model for ensuring the comparability of two automated analytical systems.

For allowable biases of backup toward reference analyzer, CVs defined by the Croatian Society of Medical Biochemists external quality assessment criteria were used. Those criteria include biological variation and represent the total allowed bias from the mean value (5).

The key finding of this study is that a simple algorithm could ensure continuous comparability and reliability of emergency test results and constant preparedness of two analyzers. The presented model provides fast switch from one to another analytical system due to possible turndown episode of reference analyzer.

One of the principal quality indicator in accredited laboratory is ensuring reliable and accurate results from the samples with appropriate interpretation. This model could measure laboratory performance and also provide the most accurate results (6), regardless on which automated system samples are determined. In this way, laboratory can greatly contribute to patient diagnosis and provide the important part of the patients' best health care. If laboratory results are not comparable from different analytical systems, possibility for incorrect diagnosis and poor quality of patient care is increased (7,8).

This model also provides a trustful basis for ensuring longitudinal patients follow up. Thereby, model is one of the way for laboratory process and emergency test reports standardization (9).

Although the most laboratory errors are preanalytical or postanalytical phase (10), analytical errors due to system failure could be avoided with two equally ready and functional analyzers. The described model for comparability could reduce analytical phase errors occurred due to some failure of the reference analyzer.

This model of results comparison ensures continuous analytical quality of laboratory reports and improves overall efficiency of laboratory services. Reliable and comparable results on daily basis provide high quality of examination procedures and reporting of results in recommen-

osiguravaju visoku kvalitetu postupaka ispitivanja i izdavanje nalaza u preporučenom i prikladnom vremenu, a sve za što bolju skrb bolesnika.

ded and appropriate time to the best of the patient care.

Adresa za dopisivanje:

Marijana Miler
Klinički zavod za kemiju
KB "Sestre milosrdnice"
Vinogradska 29
10 000 Zagreb
e-pošta: marijana.miler@gmail.com

Corresponding author:

Marijana Miler
University Department of Chemistry
Sestre milosrdnice University Hospital
Vinogradska 29
10 000 Zagreb, Croatia
e-mail: marijana.miler@gmail.com

Literatura/References

1. *Medical laboratories – Particular requirements for quality and competence (ISO 15189:2003).*
2. *Ricós C, Perich C, Minchinela J, Álvarez V, Simón M, Biosca C, et al. Application of biological variation. A review. Biochem Med 2009;19:250-9.*
3. *Barry PL. QC - The Levey-Jennings Control Chart. Available at: http://www.westgard.com/lesson12.htm. Accessed August 1st, 2009.*
4. *Kazmierczak SC. Laboratory quality control: Using patient data to assess analytical performance. Clin Chem Lab Med 2003;41:617-27.*
5. *Ricós C, García-Lario JV, Alvarez V, Cava F, Domenech M, Hernández A, et al. Biological variation database, and quality specifications for imprecision, bias and total error. The 2008 update. Available at: http://www.westgard.com/guest36.htm. Accessed August 7th, 2009.*
6. *Simundic AM, Topic E. Quality indicators. Biochem Med 2008;18: 311-9.*
7. *Panteghini M, Forest JC. Standardization in laboratory medicine: New challenges. Clin Chim Acta 2005;355:1-12.*
8. *Guzel O, Guner EI. ISO 15189 Accreditation: Requirements for quality and competence of medical laboratories, experience of a laboratory I. Clin Biochem 2009;42:274-8.*
9. *Myers GL. Introduction to standardization of laboratory results. Steroids 208;73:1293-6.*
10. *Plebani M. Laboratory errors: How to improve pre- and post-analytical phases? Biochem Med 2007;17:5-9.*