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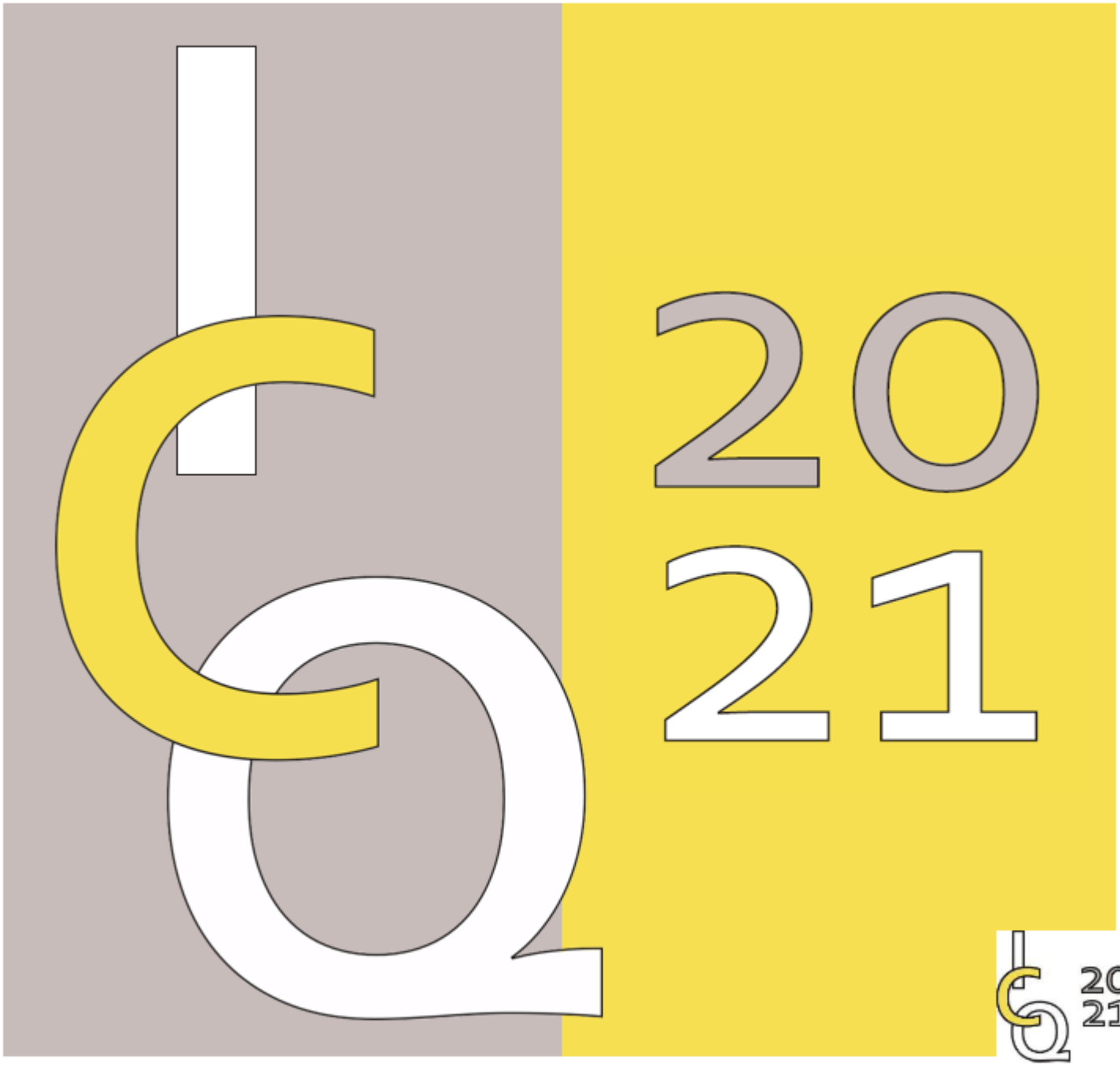

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BIAS IN MEDICAL BIOCHEMISTRY- WHAT LABORATORY PROFESSIONALS NEED TO KNOW?

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Abstract: In medical laboratories, bias presents quantitative expression of trueness, as analytical performance characteristic that describes systematic errors. Despite bias evaluation is an integral part of basic lessons of laboratory quality management, it is still difficult to achieve adequate bias estimation in routine laboratory practice. There are several principles that could be used to estimate bias, but fundamental for evaluating bias in routine medical laboratories is the availability of a suitable reference materials. Besides, it is important that the measuring method and measuring analytical system are in a stable state, and that they have completed an appropriate validation or verification process. This could be checked routinely by the results of internal and/or external quality control. In addition, information about the uncertainty of the certified reference material is a prerequisite for testing the bias. Significant efforts were made to minimized bias in routine laboratory practice, using reference measurement methods and commutable reference materials. Still, there are some challenges that remain for the laboratory professionals as the end users, due to remaining bias between measurement methods and systems from different and/or the same manufacturers.

Key Words*: bias, medical biochemistry, quality control*

1. INTRODUCTION

The core duty of the medical laboratory is to provide accurate and precise test result at the request of the clinician or patient itself. This is not an easy task considering different phases in total laboratory testing process that contribute to the final product, i.e. laboratory test result. It is believed that 80% of errors originate from preanalytical and postanalytical phases, whereas only 20% of the errors arrive from the analytical phase [1]. That is why less importance is given to analytical quality, which is assumed to be the least problematic domain. Although, the analytical phase in total laboratory testing chain could be strictly controlled using precisely defined quality control (QC) steps, laboratory professionals need to consider this as continuous process.

Quality control in the medical laboratory is a statistical process used to monitor and evaluate the analytical process. It implies regular testing of quality control material along with patient samples and comparison of quality control results to specific statistical limits. It includes two basic types of schemes: internal QC (IQC) and external QC (EQC) [2]. IQC implies continuous everyday monitoring of the analytical system, while EQC serves to analyse and report results of control samples given to the laboratory by an external agency once a month. Basically, using IQC and EQC medical laboratory could estimate analytical imprecision and analytical bias, i.e. random and systematic errors, respectively. Random error represents the component of measurement error that can vary in an unpredictable manner, whilst systematic error does not vary, but remains constant, or can change in a predictable manner [3]. In addition, combination of imprecision and bias into a single parameter could help to simplify daily quality assurance [4]. However, there is no practical benefit of such a combination in daily laboratory quality assurance. Medical laboratories usually evaluate these two measurement errors separately. In fact, medical laboratories routinely calculate imprecision using IQC data, but not bias.

While in the case of imprecision, estimation is sufficiently clear and elaborate,

estimation of bias is still a far less understandable item and represents a more challenging concept. Scientific literature data confirmed that even if bias definition is clear and understandable, its estimation includes the use of a reference quantity value [5, 6]. Reference quantities may be obtained either by certified reference materials (CRM) or by reference measurement procedures (RMP), both guarantying metrological traceability of data [5, 6]. The fact that CRM and RMP are available for the limited number of measurands, restricts the applicability of the calculation of bias through reference quantities. However, there is alternative mode for bias estimation in routine laboratory practice, using assigned values, derived by a consensus agreement, either by external quality assessment schemes (EQAs) or proficiency testing (PT). Still, there are a number of medical laboratories that do not participate in EQAs and PT, and in addition, these quality control programs do not provide data for all parameters that are routinely measured in medical laboratory. IQC and EQC can be observed as different parts that contribute equally to laboratory total quality management [7]. But, regarding the time, cost and applicability, IQC is mandatory, while EQC is recommended.

2. CAUSES OF BIAS IN MEDICAL LABORATORY

There are numerous reasons for bias in medical laboratory, taking into account stratified overall laboratory testing process [8].

It may refer to the preanalytical phase, and steps involved in sampling of biological material, transport and storage of samples and uncorrected loss of measurand during preparation or extraction sample for the measurement procedure. Bias can be caused by the presence of molecules which specifically interfere with the reagents used in the measurement process, e.g. heterophilic antibodies, or presence of different interferences in the sample, e.g. the colour of hemoglobin and bilirubin in hemolytic and icteric samples or the presence of high concentrations of proteins or lipids in the lipemic sample. Additionally, bias can exist due to the errors related to the calibrator preparation, including errors in measuring the volume or in weighing of calibrators [8].

In the analytical phase of laboratory testing process, bias can be a consequence of the specificity of the reagents/test, especially when using immunochemical measurement methods, and detection antibody specific for different epitopes in macromolecules of the measurand. Matrix of the stable materials for internal quality control or proficiency testing programs, used to check accuracy and imprecision of the measuring system, usually differs from the matrix in the patient samples. That is why important to be aware of the commutability of a CRM, which is the measure of the ability of a CRM to have interassay properties comparable to the properties similar to those of authentic fresh natural samples when measured by more than one analytical method [9]. Fresh natural patient samples represent the ultimately commutable materials for comparing measurement methods in clinical chemistry [8]. On the other side, bias exists because of different regents or CRM lots that laboratory sometimes forced to use. This bias is one of the easiest to correct if laboratory professionals follow principles of good laboratory practice and recalibrate after each switch, comply with the crossover period between the old and new control lots of several weeks to several days, depending on the stability of the control lots [10].

Bias can exist between identical methods or analysers in the same laboratory. This is not unexpected, but it should be controlled and checked by the method verification process. In the similarly way, one could analysed bias from a comparative method as part of the method validation process. Laboratory professionals need to decide, according to the manufacturers recommended performance specification, if that bias has significant influence on clinical decision.

3. BIAS ESTIMATION

Bias is the difference between the mean of the test results and the reference value, and is calculated using the following formula (1):

$$Bias = \bar{X} - Y \quad (1)$$

where $\bar{X}$ is the mean of the obtained values, and Y is the target/reference value [8, 11]. Bias is frequently expressed as relative bias or the fraction of the reference concentration, using following formula (2):

$$Bias\ (relative) = \frac{\bar{X}-Y}{Y} \quad (2)$$

or as percentage, as shown in formula (3):

$$Bias\ (\%) = \frac{\bar{X}-Y}{Y}\ x\ 100 \quad (3)$$

where $\bar{X}$ is arithmetic mean and Y is known concentration of the analyte. There are two types of bias: constant and proportional to the quantity value. Constant bias is expressed in an absolute values, while proportional bias is expressed in a relative values [8].

Crucial for the estimation of bias is the availability of a suitable reference materials. It is required that the material has the following properties: known concentration of the measurand with sufficiently low uncertainty; it covers the clinically relevant range of concentrations and it has an appropriate matrix for the method to be tested [8]. The most common options are: CRM, natural patient samples, for example, plasma, serum or urine, measured using a reference method; or natural samples with a known concentration of the analyte. Reference material used to assess bias must be completely independent from the material used for calibration of the instrument/method [12].

Taking into account fact that nowadays working laboratory methods are calibrated against primary reference measurement method, one could say that any possible bias in the measurement process is minimized. It is considered that automation has reduced repeatability and day-to-day variation considerably, and that bias has been reduced to a lesser extent by reference measurement systems [8]. However, laboratory professionals should be aware that, not so rarely uncorrected bias can occurs in routine testing process, that may has impact on overall uncertainty statement [13, 14].

In 1974. Westgard et al. [15] introduced concept that is expressed by total error (TE), which implies a total analytical error of measurement laboratory process and refers to analytical performance specification that represents the expression of the total deviation of test results from its “true value”. This expression refers to trueness, which present the closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value, and is quantitatively expressed as bias [15]. Primarily, this concept was effort to provide a quantitative measure for the acceptability of measurement method performance, especially for proficiency testing, because in laboratory testing exact value of the analyte is known only for quality control material [3].

TE has been originally formulated using following formula (4):

$$TE = bias + z \times CVa \quad (4)$$

where z is the coverage factor refers to proper confidence interval (CI), and CVa is analytical coefficient of variation. The most commonly used coverage factor for two sided 95% limit in a Gaussian probability density function is z = 1.96 [16]. Analytical coefficient of variation represents the percentage of the standard deviation of the mean value of the result, as shown by the formula (5):

$$CVa = \frac{SD}{\bar{X}}\ \mathrm{x}\ 100 \quad (5)$$

where SD is standard deviation of the mean, and $\bar{X}$ is arithmetic mean [17]. The estimation of the TE takes into account both random and systemic errors: it means knowledge of the bias and the analytical coefficient of variation.

Reference laboratories estimate imprecision and bias separately by replicate measurements. In routine medical laboratories, however, patient and quality assurance samples are routinely assayed only once. TE in these circumstances depends on the combined effect of the random and systematic errors of the method, which is compared with a defined allowable or permissible total error [18].

4. PURPOSES OF THE BIAS ESTIMATION

Knowing bias, beside the imprecision of the measurement in analytical phase of laboratory testing process, help to

discover/detect unpredictable systematic errors that lead to wrong result and erroneous laboratory information send to end user (physician or patient). However, it is difficult to know “real” bias in routine patient sample, because it is impossible to know the true value of the measurand in the patient sample. Nevertheless, there are some other situations in which estimation and knowledge of the bias is significant, which are listed in the order that they refer to the steps, in which the bias needs to be known, in order to make it the smallest at the end, toward issuing accurate laboratory results as an end product of total laboratory process.

4.1. Evaluation of performance specifications

From Stockholm consensus statement on quality specifications in medical laboratories, that was held in 1999, to Milan conference in 2014, and later efforts of an EFLM Task and Finish Group on Total Error, there were some developments that are mostly related to the requirements of ISO 17025 and 15189 standards and what laboratories should routinely provide [19-21]. Still, the performance specifications are evaluated based on the biological variation.

Performance specifications are basically, closely related to the Westgard concept of total analytical error. Using the result of the total analytical error it is possible to provide a quantitative measure to check wheatear the analytical performance of the routine laboratory method is acceptable comparing with a defined allowable or permissible total error. In addition, the fact that both systematic and random error could influence the measured result and that analytical performance specification depends on both imprecision and bias, it is recommended to combine both bias and imprecision in the one equation to calculate analytical performance specification [22].

Originally suggested calculation for analytical performance specification taking into account only SD, has expanded to combination of SD and bias [22, 24]. This first model is based on reference values and total biological variation, and was applied for diagnosis, but not for monitoring [18]. This calculation was later adapted, because some measurands are subject to tight homeostatic control (e.g., electrolytes), leading to unrealistic performance specifications [24]. There are three proposed quality levels that are used for imprecision and bias: optimum (CVa ≤0.25CVI, Bias ≤0.125CVbiol), desirable (CVa ≤0.5CVI, Bias ≤0.25CVbiol) and minimum (CVa ≤0.75CVI, Bias ≤0.375CVbiol), where CVa applies to analytical performance specification, CVI applies to imprecision and CVbiol is biological variability.

However, most tests are used for monitoring, so performance specification should be checked using reference change value that combines analytical and intra-individual variability. In most distributions, between subject coefficient of variation (CVG) and CVI are log-Gaussian, as are most reference ranges [25]. Using this model it has been proposed that performance specifications should be derived from biological data and should ideally be based on log-Gaussian distribution. However, the most routinely used models combine bias and imprecision. That is why, knowing and minimising bias is important task to allow better performance specifications in routine medical laboratories.

4.2. Estimating uncertainty in measurement of the results

Several years after the proposed total error concept, different metrological organizations, standardization bodies and scientific societies started the collaborative efforts, and presented measurement uncertainty concept. Basic principles and estimation were published in the fundamental document on expression of uncertainty in measurement, the ISO/IEC Guide to the Expression of Uncertainty in Measurement (‘GUM’). Unlike the total analytical error concept that includes bias in the calculation, uncertainties of final laboratory results are expressed as standard deviations (standard uncertainty) or by multiples of standard deviations (expanded uncertainty) with a specified numerical factor (coverage factor) [26]. The concept of uncertainty and the basic principles of uncertainty evaluation are mandatory according to the standards for laboratory competence – ISO/IEC 17025 and ISO

15189. It is widely accepted in all fields of quantitative measurement application, but unlike the measurement in analytical chemistry, it is difficult to be applied in medical biochemistry and in routine laboratory testing process. There are some propositions that routine laboratory could apply, but strategy that is explained in detail is validation and quality control approach where the reproducibility within-laboratory is combined with estimates of the method and laboratory bias according to Nordtest handbook TR 537 [27]. This include a clear definition of the measurand, comprehensive specification of the measurement procedure and the test items and comprehensive analysis of all effects (random and systematic) on the measurement results, using data for within-laboratory reproducibility and data for bias evaluated from the laboratory participating in EQAS/PT [26]. Although in the uncertainty concept random and systematic effects are combined into one uncertainty value expressed as a probability distribution, there is an explanation that treatment of bias as variance leads to an erroneous prediction of the influence of test performance in clinical practice, and that bias should not be included as a variance component in estimation of measurement uncertainty but should be reported separately [28].

4.3. Standardisation and harmonisation

In order to enable issuing the accurate result and optimal use of clinical guidelines for diagnosing the disease and for adequate management of the patient, it is very important to have standardized and harmonized medical laboratory measurement procedures or performance specifications. Process of standardization ensures traceability of these procedures to the International System of Units, while harmonization ensures traceability to a reference system agreed on by convention [29]. In relation to this, to evaluate performance specifications, it is important for laboratory to meet specific metrological criteria and to participate in EQAS [30, 31].

Basic component of an EQAS is an analytical performance specification for each measurand that a laboratory can use to assess the extent of deviation of the obtained results from the target value [31]. There are several variations in models used to assign analytical performance specifications to EQAS [31]. Most of these programs used biological variation data, as crucial component to provide appropriate performance specification, but in combination with statistical data by which analytical characteristics are usually evaluated (total error, bias and imprecision) [31]. Bias and imprecision can only be determined by calculation based on a number of measurements. In routine laboratory conditions assessment of the performance is based on a single result, so it is logical to use total error concept which involves a combination of bias and imprecision. But, what the most important is to document every procedure of calculation.

Ultimately, assessment of the state of the art analytical quality specifications is primary task for manufacturers of the measurement procedures. Participation for routine medical laboratory in EQAS is useful to ensure if analytical specification of the measurement procedure is applicable and acceptable in routine laboratory working conditions. Although, there are specific recommendations for meeting analytical performance specification and clear invitation from EQAS providers, participation in EQAS is still a bit expensive.

There are some additional terms beside bias that needs to be understood, and some facts that do not depend on routine laboratories for finalisation of standardisation and harmonisation process of routine measurement procedures. Until the end of this process, routine laboratory should operate in accordance with good laboratory practice.

4.4. Impact on the significance of clinical decision

Whatever the cause of bias, and whatever is the way to evaluate it, the most important is to be aware that estimated bias could be clinically important. This depends on the purpose of the measured result. Results are mostly compare with the reference values, and used for diagnosing a disease or monitoring the effects of treatment.

When measured result is used for diagnosing a disease, the decision of the clinicians is based on the diagnostic characteristics of the measurand. This means that clinicians most likely make conclusion on whether a concentration of a measurand in a patient sample belongs to the population of the healthy or to the population of the diseased. However, this is ultimately influenced by the uncertainty of the measurement result, which consist of measurement uncertainty (bias and imprecision), of uncertainty in the sampling and sample handling and of the spontaneous biological variation of the measurand in the healthy subjects and patients [8]. If estimated bias influences the clinical decision between health and disease when studied in the context of all the other uncertainty components involved, including biological variation, it is called a clinically important bias (with a predefined probability – commonly $p > 0.05$) [8]. Theodorsson et al. [8] present a very simple explanation by example of glycohemoglobin (HbA1c) and Alanine aminotransferase (ALT).

Within-individual and between-individuals biological variation of HbA1c is 1.9% and 5.7%, respectively. Within-individual and between-individuals biological variation of ALT is 19.4% and 41.6%, respectively. Since these two biological variations of HbA1c is much smaller than for ALT, a possible bias in the measurement of the concentrations of HbA1c is much more likely to influence clinical decisions in diagnosing diabetes mellitus than a possible bias in the measurement of ALT when diagnosing liver conditions, due to the fact that the large biological variation of ALT is likely to be the major uncertainty component when the concentrations/activity of ALT is used for diagnosis [8]. So it could be concluded, that even a bias of 5%, for example, when measuring the concentrations/activity of ALT is usually clinically unimportant, unlike HbA1c concentrations/fraction.

If parameter is used for monitoring treatment within a single patient, the within-individual biological variation determines the uncertainty caused by biological variation, under conditions that sampling and sample handling variation are considered constant [8]. When several measurement systems are used for monitoring the patient (for example, self-monitoring instrument, laboratory instrument, hospital instrument, university hospital instruments) bias between the measurement systems becomes crucial [8]. If we observe bias of 5% for HbA1c, it is higher than within-individual biological variation (1.9%) and is, therefore, important in the overall uncertainty of the clinical decision, and an increase of 5% in the concentration/fraction of HbA1c is known to presents an increased risk for the patient, unlike the ALT within-individual variation.

These examples indicate that change in concentrations have significant influence on the medical risk, and that knowledge about that is very important, whether the measurement is used for diagnosis or for monitoring of the treatment effects. However, in addition to knowledge of bias and bias assessment, the greatest influence comes ultimately from biological variation of the measurand.

5. CONCLUSION

Bias presents expression of an important concept of trueness, and still it is a challenge for routine laboratory professionals. It should be consider as inevitable and integral part of routine quality control in medical laboratories. Estimating bias is not enough to improve analytical performance, as well as to minimise total measurement uncertainty in laboratory working process. Important is awareness that bias should be monitored and can be eliminated through permanent application of good laboratory practice postulates. However, authoritative international or national organizations should perform future efforts to make available and applicable practical guidance for continuously managing bias in routine laboratory practice.

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