Clinical Biochemistry xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Clinical Biochemistry

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

# Practical application of biological variation and Sigma metrics quality models to evaluate 20 chemistry analytes on the Beckman Coulter AU680

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ARTICLE INFO

*Article history:*
Received 14 July 2016
Received in revised form 8 August 2016
Accepted 10 August 2016
Available online xxxx

*Keywords:*
Analytical method evaluation
Imprecision
Bias
Biological variation
Fitness for purpose
Sigma metrics

ABSTRACT

**Objectives:** This study aimed to evaluate the imprecision and bias data generated for 20 routine chemistry analytes against both the biological variation fitness for purpose (FFP) and Sigma metrics (SM) criteria.

**Design and method:** Twenty serum/plasma analytes were evaluated on the Beckman Coulter AU680. Third party commercial lyophilized internal quality control samples of human origin were used for day-to-day imprecision calculations. Commercial external quality assurance (EQA) samples were used to determine the systematic error between the test method result and the instrument group mean result from the EQA program for each analyte. Biological variation data was used to calculate the *minimum*, *desirable* and *optimal* imprecision and bias for determination of FFP. The *desirable* total allowable error was determined from biological variation data and applied to the SM calculation. The outcomes of both quality approaches were then compared.

**Results:** The day-to-day imprecision of most tested analytes (except sodium and chloride) were smaller than the allowable imprecision (ranging from *minimum* to *optimum*). Most analytes achieved at least *minimum* bias. The SM varied with analyte concentration with six analytes producing low Sigma values. Comparing the quality processes eleven analytes produced a green light for both FFP and SM. There was some difference seen in interpretation for the other nine analytes.

**Conclusions:** The individual interpretation of bias and imprecision using FFP criteria allowed for the clear determination of the major source of error. Whereas, SM provided a summative evaluation of method performance. But the selection of total allowable error (TEa) is fundamental to this interpretation and harmonisation of the TEa calculation is needed.



## 1. Introduction

Quality is the way forward. The concept of quality promoted by Deming in his post-World War II seminars to industry, parallels the quality requirements we now describe for the clinical diagnostic laboratory [1]. Quality initiatives in clinical biochemistry testing actually stem back to this era with the key concepts of internal quality control (IQC) established by Levey and Jennings [2,3] followed by the essential interpretative rules published by Westgard and colleagues [4,5]. To complement IQC, external quality assurance (EQA) programs started to be established from the 1980s to provide an ongoing mechanism of peer comparison [6]. The formalization of these IQC and EQA processes were led through laboratory accreditation standards in the late 1980s and 1990s; firstly with ISO17025 and then in 2003 with the first version of ISO15189 [7]. As a result of these quality initiatives, we now consider the minimization of imprecision (random error), primarily determined through IQC and bias (systematic error), primarily determined through EQA fundamental tools for quality management in laboratory medicine [8].

With the basic processes in place, calculations related to quality decision specifications have been recommended over the last 20 plus years as a mechanism to further progress quality in the clinical laboratory [9]. As an outcome of the 1999 Consensus Conference in Stockholm laboratories have refocused their attention towards evidence based decisions in their quest for quality [10]; leading to the five levels of the Stockholm Hierarchy, developed to promote preferred decision approaches. This Hierarchy more recently has been updated to the three Models as an outcome of the 2014 Milan Consensus Statement [11]. The Milan Models are effectively a simplification of the Stockholm Hierarchy, with one significant difference, in that Milan's Models 1 and 2 are equal and hence there is no preference (i.e. no hierarchy)

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http://dx.doi.org/10.1016/j.clinbiochem.2016.08.008
0009-9120/

**Table 1**
Methods and reagents used in the evaluation of Beckman Coulter AU680.

| Analyte | Method | Traceability of calibrator | Linearity | Unit |
|---|---|---|---|---|
| Albumin | BCG | IFCC standard CRM 470 | 15–60 | g/L |
| ALP | IFCC, p-NPP-AMP 37 °C | Olympus Master Calibrator | 5–1500 | U/L |
| ALT | UV 37 °C without PP | Olympus Master Calibrator | 3–500 | U/L |
| Amylase | IFCC-ethylidene G7-PNP 37 °C | IFCC reference method and IRMM/IFCC-456 | 10–1500 | U/L |
| AST | UV 37 °C without PP | Olympus Master Calibrator | 3–1000 | U/L |
| Calcium | O-cresolphthalein | NISTSRM 909b Level 1 | 0–4.5 | mmol/L |
| Chloride | Indirect ISE | NISTSRM 956a | 50–200 | mmol/L |
| CK | IFCC-CKNAC 37 °C | IFCC reference method | 10–2000 | U/L |
| Creatinine | Jaffe kinetic | NISTSRM 909b Level 2 | 18–2200 | μmol/L |
| CRP | Immunoturbidimetry | IFCC standard CRM 470 | 0–480 | mg/L |
| GGT | IFCC, kinetic colour test | IFCC reference method and IRMM/IFCC-452 | 5–1200 | U/L |
| Glucose | Hexokinase | NISTSRM 965 | 0–45 | mmol/L |
| Iron | TPTZ | Olympus Master Calibrator | 0–179 | μmol/L |
| LDH | IFCC 37 °C, lactate to pyruvate | IFCC reference method and IRMM/IFCC-453 | 25–1500 | U/L |
| Potassium | Indirect ISE | NISTSRM 956a | 1–10 | mmol/L |
| Sodium | Indirect ISE | NISTSRM 956a | 50–200 | mmol/L |
| Total bilirubin | DPD method | NISTSRM 916a | 0–513 | μmol/L |
| Total protein | Photometric colour test | NISTSRM 927c | 30–120 | g/L |
| Urate | Uricase PAP | NISTSRM 909b level 1 | 89–1785 | μmol/L |
| Urea | UV kinetic | NISTSRM 909b level 1 | 0.8–50 | mmol/L |

for either [12]. For most of the common analytes measured in clinical biochemistry diagnostic laboratories, biological variation (BV) data is available and Level 2 (Stockholm) or Model 2 (Milan) quality specifications can be applied to estimate fitness for the intended clinical purpose [13].

The terms *minimal*, *desirable* and *optimal* performance in relation to both analytical imprecision and bias compared to biological variation are now routinely applied. This provides us with an evidence based objective assessment of method performance. Supporting this work practically is the biological variation database maintained by Dr Ricos and colleagues [14]. This data has been applied broadly by laboratories and EQA organizers [15] in setting quality specifications and has been used also in the calculation of allowable total error (TEa) [13]. This concept of TEa is fundamental to the application and interpretation of Sigma metrics (SM) models [16].

Along with a predetermined TEa, SM utilises the information on imprecision and bias that laboratories acquire initially during method evaluation studies and the data available on a continuing basis from IQC and EQA data [17]. The goal is to strive for 6-Sigma quality, with the common minimum level of acceptable quality broadly considered to be 3-Sigma [17]. In addition, a purported advantage of the use of SM, is its role in determining IQC frequency; thus avoiding repeated testing of IQC in a period when the system is performing stably, consequently minimizing unnecessary cost expenditure and man-hour wastage [18].

Quite recently there has been extensive debate in the peer reviewed literature with point and counterpoint applied to the various approaches to assess quality [19–27]. Essentially there appears to be two approaches: 1) to assess against performance standards based on the individual components for imprecision and bias with *optimal*, *desirable* or *minimum* fitness for purpose (FFP) criteria; and 2) to incorporate TEa and set or select quality limits and design a system that supports and encourages 6-Sigma capability. Whilst experts discuss the best approach, the clinical laboratory is left with developing and implementing quality protocols on a day-to-day basis. How do laboratories move beyond this peer reviewed literature debate to direct application in the daily operation of the laboratory requires clarification. What is practical and whether there is a clear difference in outcome with the various quality approaches is not often considered in a real-world context.

Ultimately the aim for both quality approaches is to ensure a level of quality to enable informed clinical decisions to be made. The objective of this study is to evaluate the imprecision and bias data generated for 20 routine chemistry analytes against both the biological variation FFP and SM criteria to determine if the outcomes are consistent between the two quality approaches.

**Table 2**
Biological variation data and desirable specifications for the 20 analytes. Adapted from the Ricos biological variation database [14].

| Matrix | Analyte | CVi % | CVg % | TEa % |
|---|---|---|---|---|
| Serum | Albumin | 3.2 | 4.75 | 4.07 |
| Serum | ALP | 6.45 | 26.1 | 12.04 |
| Serum | ALT | 19.4 | 41.6 | 27.48 |
| Serum | Amylase | 8.7 | 28.3 | 14.6 |
| Serum | AST | 12.3 | 23.1 | 16.69 |
| Serum | Calcium | 2.1 | 2.5 | 2.55 |
| Serum | Chloride | 1.2 | 1.5 | 1.5 |
| Serum | CK | 22.8 | 40 | 30.3 |
| Serum | Creatinine | 5.95 | 14.7 | 8.87 |
| Serum | CRP | 42.2 | 76.3 | 56.6 |
| Serum | GGT | 13.4 | 42.15 | 22.11 |
| Plasma | Glucose | 4.5 | 5.8 | 5.5 |
| Serum | Iron | 26.5 | 23.2 | 30.7 |
| Serum | LDH | 8.6 | 14.7 | 11.4 |
| Serum | Potassium | 4.6 | 5.6 | 5.61 |
| Serum | Sodium | 0.6 | 0.7 | 0.73 |
| Serum | Bilirubin total | 21.8 | 28.4 | 26.94 |
| Serum | Protein total | 2.75 | 4.7 | 3.63 |
| Serum | Urate | 8.6 | 17.5 | 11.97 |
| Serum | Urea | 12.1 | 18.7 | 15.55 |

## 2. Material and method

### 2.1. Location

This study was performed in the Clinical Biochemistry Laboratory at the National Hospital of Pediatrics (NHP), Hanoi, Vietnam. The laboratory is accredited to the International Organization for Standardization (ISO) 15189 2012 by the Bureau of Accreditation in Vietnam.

### 2.2. Instrument

The Beckman Coulter AU680, designed for clinical chemistry laboratories, is an automated, multi-channel, selective analyser where the measurements are carried out using the spectrophotometry, turbidimetry and indirect ion selective electrode (ISE) method principles applicable to serum/plasma, urine, cerebrospinal fluid and other body fluids. The analytical evaluation of this analyser was conducted

Please cite this article as: M.T.C. Tran, et al., Practical application of biological variation and Sigma metrics quality models to evaluate 20 chemistry analytes on the Beckman Co..., Clin Biochem (2016), http://dx.doi.org/10.1016/j.clinbiochem.2016.08.008