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Analytical Quality in the Medical Laboratory – The ASAP Concept Part 1: Analytical Quality Specifications

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SUMMARY
This is the first article in a series of small, „loose" contributions to this journal. The articles touch, what we think, is important about analytical quality in the medical laboratory The articles will address topics such as metrology (philosophy of the measurand), statistics, internal quality control (IQC), external quality assessment (EQA), critiques to the discipline. All contributions follow the ASAP-concept, meaning **A**s **S**imple **A**s **P**ossible. Here, we explore the „ASAP" concept for analytical quality specifications derived from biological variation. The application of the concept results for the great majority of the mainstream serum-, plasma-, and blood-analytes in CV_a values within boundaries of 0.4 – 15 % and for Delta-SE within boundaries of 0.2 – 10 %. The take-home message is: analytical quality in the medical laboratory must **NOT** be viewed in absolute terms („a CV_a of 2 % is good"), **BUT** in relative terms. A CV_a of 2 % is good for S-cholesterol analysis, but NOT for S-Na analysis!
Keywords: ASAP-concept, analytical quality specifications, biological variation, Na in serum

SOUHRN
Stepman H., Stöckl D.: Analytická kvalita v lékařské laboratoři – Koncept ASAP.
Část 1: Specifikace analytické kvality.
Je předložena první část plánovaného souboru malých prací, určených pro tento časopis. Práce se týká věcí, podle našeho názoru důležitých pro analytickou kvalitu v klinické laboratoři. Celý soubor prací se bude zabývat tématy metrologie (charakteru předmětů měření), statistikou, vnitřní kontrolou kvality, externím hodnocením kvality a kritickými postřehy v uvedených oblastech. Příspěvky jsou napsány s maximální snahou po jednoduchosti podle konceptu ASAP-„as simple as possible". V prvním příspěvku byl aplikován tento přístup pro odvození požadavků na analytickou kvalitu z hodnot biologických variabilit: je diskutována situace při měření koncentrace Na v krevním séru. Analytická kvalita tohoto měření je akceptovatelná, pokud dlouhodobě sledované výsledky vykazují stabilitu v rozmezí 1 %. Této stability je možné dosáhnout.
Klíčová slova: koncept ASAP, specifikace analytické kvality, biologická variabilita Na v séru

Introduction

This is the first article in a series of small, „loose" contributions to this journal. The series is put under the Motto: *„Die Wahrheit ist dem Menschen zumutbar"* (Ingeborg Bachmann). The articles touch, what we think, is important about analytical quality in the medical laboratory (not necessarily in „logical order"). The articles will address topics such as metrology (philosophy of the measurand), statistics, internal quality control (IQC), external quality assessment (EQA), critiques to the discipline (see also: www.stt-consulting.com, „Tin Cans"), or any other topic that might be of interest to the reader of this journal. All contributions follow the ASAP-concept, meaning **A**s **S**imple **A**s **P**ossible.

Some words to the authors; Hedwig Stepman is a PhD student in the laboratory of Prof. Linda Thienpont and follows the education towards Clinical Biochemist. Dietmar Stöckl is an analytical chemist by training. He earned his PhD at Cologne University in the laboratory of Prof. Dr. Herbert Budzikiewicz (Negative Chemical Ionization Mass Spectrometry). He came into laboratory medicine in 1988, only, when the German RILIBÄK required reference measurement procedure values for the German EQA surveys. He was picked by Prof. Dr. Hans Reinauer for building the reference laboratory at INSTAND eV. This developed a wonderful story thanks to the excellent cooperation with Prof. Dr. Linda Thienpont.

Why analytical quality specifications (goals) as first topic? When I (Dietmar) came into the field of laboratory medicine, my first task was to develop reference measurement procedures. The immediate question was: which quality was required? This was an important question because high analytical precision and excellent trueness have their price, and the price for quality is going up exponentially. Analytical quality specifications were at my heart from the very beginning and, indeed, are at the very heart of laboratory medicine.

I wish to express at this place my sincere thanks to „The Westgards" who regularly „give voice" to my ideas and parts of this article have appeared before on their site (www.westgard.com).

Analytical quality specifications (analytical „goals")

Analytical quality specifications should be based on the Stockholm approaches and the Stockholm hierarchy [1]: i) clinical outcome; ii) questionnaires to clinicians,

iii) biological variation; iv) expert opinion; v) state-of-the art. Despite 3rd in the Stockholm hierarchy, specifications based on biological variation are the most straightforward ones and are easily available (http://westgard.com/biodatabase1.htm). However, there are several ones and some concepts are still improving [2].

Here, we explore the „ASAP“ concept for analytical quality specifications derived from biological variation. First, analytical quality specifications for monitoring are typically more demanding than those for diagnosis. Typical mainstream assays are used for both situations, diagnosis as well as monitoring, thus they should fulfill the quality specifications for monitoring. The most simple specification for monitoring is CV_a (a = analytical) ≤ ½ CV_w (w = within-subject biological variation) [3, 4]. Using this as starting point, we come to a specification for systematic error (SE), or more precisely, for a change in SE (Delta-SE) during monitoring Delta-SE ≤ ⅓ CV_w [5]. Note, strictly, these fractions apply ONLY when one of the 2 error components is absent (either no RE or no SE). In principle, RE and SE have to be split according a non-linear relationship [5]. Anyway, the 2 simple formula's are the basis of our ASAP concept [see 6 – 8 for some additional reading]. The application of the concept results for the great majority of the mainstream serum-, plasma-, and blood-analytes in CV_a values within boundaries of 0.4 – 15 % and for Delta-SE within boundaries of 0.2 – 10 %.

We want to stress here that manufacturers need to supply tests with better „stable“ performance, because working with tests that just fulfill the maximum specifications will lead to „out-of-specification“ in 50 % of the time due to unavoidable variation in test performance. Here is where **internal quality control** comes into play.

Application – Serum sodium

The within subject biological variation of serum-sodium (S-Na) is 0.7 %, resulting in CV_a ≤ 0.35 % and in Delta-SE ≤ 0.23 %. You will immediately ask: do we really need such a tight control for S-Na measurements? To answer that question, we will look into the long-term stability of patients' data in a laboratory [9]. The 50th-percentile ranged over a period of several years from 138 mmol/L to 141.5 mmol/L (difference = 2.5 %). This corresponds to a difference of about ± 1.3 % from the long-term average of 140 mmol/L. When we investigate the fraction of results < 135 mmol/L (indicating mild hyponatraemia), we observe a triplication of mild hyponatraemia in negatively biased periods compared to positively biased periods (15 % versus 5 %). This triplication is considered far too much and process variation < 1 % is clearly indicated (note: hyponatraemia is by far the most commonly encountered electrolyte disorder in a hospital). Because of the utmost importance of well-controlled S-Na values, some even propose an „operational definition of normonatremia“ of 138 to 142 mmol/L („every mmol counts!“) [10].

But are such numbers realistic? When we look into the stability data of another laboratory [9], we observe a „mmol/L“ stability of the 50th percentile over 7 years! Indeed, long-term stability of laboratory tests of ~1 % are achieved and, thus, should be required from manufacturers when necessary.

General application (see also Fig. 1)

Analytical quality specifications established from biological variation are, indeed, relevant. Those are most stringent for S-Na, however, taking S-Na as benchmark for what can be achieved in practice, process stability of ~1 % is a reality. Naturally, there are practical limits and it is questionable whether a stability of 0.2 % can be achieved [11]. But a 1 % stability would suit all analytes except S-Na and S-Cl.

Having defined a low-limit for stability in the laboratory (~1 %) we propose a high-limit of ~5 % for the manufacturer. Remember from above that Delta-SE is within boundaries of 0.2 – 10 % for the great majority of the common analytes. However, to achieve this kind of stability in the laboratory, the laboratory itself has to receive a test with better stability from the manufacturer: there must be some room for internal quality control!

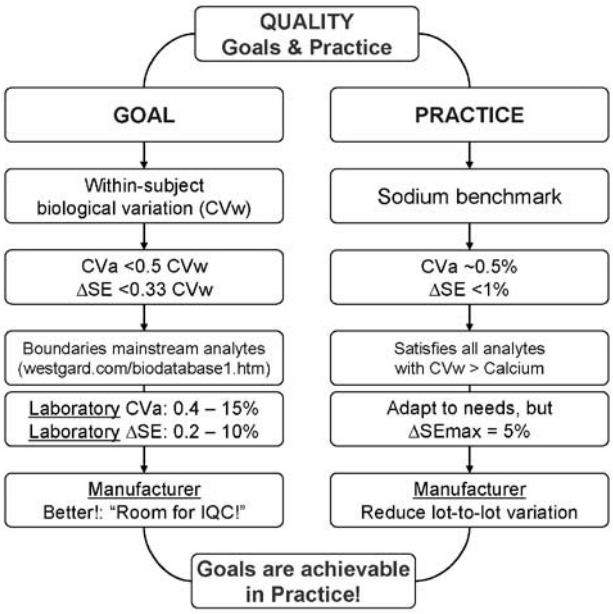

Fig. 1. Analytical quality specifications established from biological variation according to the ASAP concept compared with analytical „benchmark" performance.

Take - home message

Analytical quality in the medical laboratory must **NOT** be viewed in absolute terms („a CV_a of 2 % is good“), **BUT** in relative terms. A CV_a of 2 % is good for S-cholesterol analysis, but NOT for S-Na analysis!

S-Na is one of the most stable assays in absolute terms, but one of the most critical in relative terms!

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