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A Six Sigma approach towards analytical quality control

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Introduction

The laboratory test menu shows a very great variation in analytical quality. However, there is also a wide range in the tolerance limits for the precision of different assays, as there is also a very wide range in the biological variability within the laboratory's test menu (1, 2). Tolerance limits may be based on biological variation (1) or on legislation, like CLIA (3) and Rilibäk proficiency testing acceptability criteria (4). Although analytical quality has been improved over the decades, analytical quality control is still highly needed to check whether the analysis is within the tolerance limits set. Simplified Westgard rules (2SD and 3SD) are being used in most clinical chemistry laboratories, although it has been known for many years, that these rules lack sufficient power for adequate error detection and generate many false alarms. In the past decades tools have become available to select control procedures to assure the quality needed for each assay. The availability of modern laboratory information systems and sufficient computer power, has it made possible to implement more subtle rules. In addition, Six Sigma® quality basics offer a framework to further rationalize analytical quality control (5). Six Sigma quality management postulates that a decrease in process quality of 1.5 standard deviations (SD) should be tolerable without significant increase in defect rate. For analytical quality this means that a 1.5 SD bias should be readily detected by quality control rules. Moreover, precision should desirably be smaller than 1/6th of the tolerance specification. We evaluated the applicability of Six Sigma basics and selection tools for QC-procedures in our laboratory.

Methods

The process capability (C_{pk}) (6) for precision and accuracy was calculated for all chemistry, hemocytometry, blood gas and immunochemistry assays. Process capability for precision and accuracy was defined as (tolerance limit – bias) /3 * $SD_{analytical}$, where for the tolerance limit the total allowable error (TE_a) was taken as defined by CLIA and for $SD_{analytical}$ the analytical imprecision (expressed as standard deviation) was taken (5). C_{pk} <1 indicates a poor process, while C_{pk}> 2 indicates an excellent process. Based on the process capability an initial selection was made of tests for which once-a-day QC-rules could be implemented. New QC-rules were defined for chemistry tests (creatinine, potassium, calcium, phosphate, ASAT, ALAT, LD, GGT, total bilirubin, direct bilirubin, ALP, TP, ALB, CK, uric acid, amlyase, cholesterol, triglycerides, HDL-cholesterol, glucose, iron, magnesium), hemocytometry (rbc, wbc, plt, hb) and blood gas analysis (pH, pCO_2). These new rules were selected using commercial software (QCValidator and EZ-rules, www.westgard.com) (7, 8) with the analytical variation at a clinical decision level (which is in practice dictated by the assigned value of the control material) and an assumed bias of 0%, and CLIA-based tolerance limits as inputs. The probability of false rejection (P_{fr}) was kept as low as possible (<0.05), while the probability of error detection (P_{ed}) was maximized. QC-materials are barcoded and processed automatically within the laboratory information system (LIS). The measuring channel is automatically set unreliable, whenever the QC-result is beyond the targets. In this case action (calibration, instrument servicing) is required.

Results

Process capability for the selected tests ranged from 3 to 15, which means that all selected analytes were within good analytical control. For 10 assays (hemoglobin, glucose (both potentiometric and enzymatic), cholesterol, total protein, albumin, ALAT, direct bilirubin, rbc, total bilirubin), the QC rules had to be thightened from 3SD rule to 2.5 SD rule. For two assays (iron and platelet count), the 3SD rule was remained. For 16 assays (uric acid, phosphate, ASAT, GGT, alkaline phosphatase, potassium, calcium, creatinine, LD, triglycerides, WBC, HDL-cholesterol, magnesium, amylase and CK) a wider tolerance limit (3.5 SD) could be set for QC-results.

Conclusions

Our first experience with Six Sigma based quantitatieve tools towards analytical quality control is very promising. Most important is that the analytical qualitiy control has been rationalized. For every assay the (analytical) process capability is known, which is very helpfull in the priority setting of analytical problems. In addition, the number of analytical reruns, and therewith the consumption of quality material decreased with approximately 40%. Since technicians have to take action on different QC rules, all QC values requiring corrective action are flagged by a "severity code" in the LIS. Since most QC samples are processed automatically, this is a very efficient process. Although the tools for selecting QC proce-

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dures are used by specialized staff only, much attention has to be given to the education of laboratory staff for a proper understanding. Up till now, rules were selected for two samples at two decision levels (low and high). In the near future more complex rules will be introduced. A next step will be the real time monitoring of process capability with automatic adjustment of QC procedures.

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Vergelijking M-proteïneonderzoek middels apparatuur van Helena en Sebia

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Inleiding

In het kader van vervanging van de huidige apparatuur voor M-proteïneonderzoek (Beckman; Paragon) en aanpassing aan de CBO-richtlijn Monoklonale gammopathie zijn geautomatiseerde technieken voor eiwitelektroforese en immuunfixatie van Sebia en Helena uitgetest. Er is gekeken naar capaciteit, gevoeligheid, gebruikersvriendelijkheid en variatie in eindresultaat van beide systemen.

Materiaal en Methoden

Serummonsters: Van 19 bekende monsters met aangetoond M-proteïne in serum zijn zowel een eiwitelektroforese, immunofixatie als kwantificering van M-proteïne piek uitgevoerd. Selectie: Monsters zijn geselecteerd op type en concentratie van M-proteïne (middels Beckman methode (Paragon)). Apparatuur: Helena (VWR): SAS-1 plus (auto-applicator)/ SAS-2 (auto-stainer)/Platinum (gel analysis software). Sebia: Hydrasys (incl. Dynamic Mask)/Hyrys 2 (densitometer incl. software). Variatie (intra/inter): Intravariatie: serum van enkele patiënten is in meervoud geanalyseerd tijdens 1 run elektroforese/immuunfixatie, waarna M-proteïne-piekanalyse heeft plaatsgevonden. Intervariatie: serum van enkele patiënten is in meerdere runs meegenomen voor elektroforese-/immuunfixatieonderzoek, waarna M-proteïne-piekanalyse heeft plaatsgevonden. Om de intervariatie tussen analisten tegen te gaan is het onderzoek door 1 analist uitgevoerd.

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Resultaten

Eiwitspectra: Eiwitelektroforese uitgevoerd met zowel de SAS-1/SAS-2 als Hydrasys geeft geen verschil in eindresultaat te zien. Enige verschil is dat de monstercapaciteit van Helena kleiner is dan die van Sebia (24 versus 30).

Tabel 1. Immuunfixatie uitgevoerd met SS-1 plus/SAS-2 (Helena) en Hydrasys (Sebia) vergeleken met Beckman (Paragon); dzb = dubieus zwak bandje; gb = geen bijzonderheden

nr.	Beckman	Helena	Sebia
1	IgMk	IgMk	IgMk
2	dzb IgG k	IgG k	IgG k
3	dzb IgMk	IgMk	IgMk
4	IgMk	IgMk	IgMk
5	IgG l	IgG l	IgG l
6	IgG k	IgG k	IgG k
7	IgG k	IgG k	IgG k
8	IgG k	IgG k	IgG k
9	gb	gb	gb
10	gb	gb	gb
11	IgG l	IgG l	IgG l
12	IgA k	IgA k	IgA k
13	gb	gb	gb
14	IgG l	IgG l	IgG l
15	dzb IgG k	IgG k	IgG k
16	dzb IgG k	IgG k	IgG k
17	dzb IgG k	IgG k	IgG k
18	gb	gb	gb
19	gb	gb	gb