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Steady state errors and risk of a QC strategy☆

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ABSTRACT

Background: To minimise the risk of patient harm from results, laboratories should establish QC strategies and monitor the performance of assays in line with the analytical and clinical risk.
Methods: Steady state errors were calculated from a distribution normalized for an Analytical Performance Specification expressed as Assay Capability (imprecision) minus Assay Stability (drift). Inverting this error rate gave QC run length containing one error. Multiplying by error detection of a critical shift gave a QC functional run length for stable and unstable situations. Suitability of this technique was examined using laboratory EQA imprecision and drift data against various analytical and clinical performance specifications.
Results: Steady state errors and error detection, and hence QC functional run length, were dramatically affected by worsening imprecision, drift or changing performance specifications. For a single analyser type, laboratory steady state errors against RCPAQAP performance specification ranged over five orders of magnitude, with contributions from Assay Capability and Assay Stability varying by laboratory.
Conclusions: Steady state errors accumulate for all assays. Our functional QC run length based on steady state error rate adjusted for error detection of the QC algorithm, amounts to a risk approach using the first two elements of FMEA-like calculation and allows laboratories to examine the suitability of their combinations of QC run length, algorithm, workload and timing of QC challenges. An appropriate common performance specification is critical when assessing and comparing risk.

The latest versions of standards such as ISO 15189 [1] and of models for Internal Quality Control (QC) [2,3] reflect current awareness that a new paradigm, ie moving from compliance to risk, is required as the next step in improving performance quality of health care organisations, including laboratories [4,5].

Quality Control strategies do not usually consider patient risk directly, they are concerned with detection of analytical error, with the traditional approach being to develop QC rules and QC sample frequencies (algorithms) that allow high error detection rates (P_{ed}) combined with a low probability of false rejection (P_{fr}) [6,7]. Parvin [8] introduced the risk-based variable, expected number of patient reports with an unacceptable error condition E(N_{uf}), which is the product of the increased probability of a result having an unacceptable amount of error due to an error state and the average number of results reported during an error state. But there are many different QC rules and frequencies that meet a given E(N_{uf}).

We have been developing risk-based approaches that apply to QC and EQA [9,10], to laboratory inputs, outputs and processes [11] and to incident monitoring [12], and where possible with components that align with the three factor FMEA model of risk: (a) frequency of errors times (b) the ability to detect errors times (c) the harm outcome. This simple but systematic approach allows laboratories to identify high patient risk assays.

Assay Capability (Cp_a) is imprecision compared to Analytical Performance Specification (APS) and reflects the frequency of analytical errors. We produced a FMEA-like risk calculation based on a 3 × 3 grid of Cp_a compared to peer performance to prioritise assays that should be improved [9] and studied the impact of the scatter in the average bias of the method, termed SE_{drift}, which we included as a

Abbreviations: APS, Analytical Performance Specifications (Allowable Performance Limit, Total Allowable Error); APS-Z, the number of SD left inside the APS at a shift of Z (single-sided); Cp_a, Assay Capability = APS/CV_a = APS/SD_a; CPS, Clinical Performance Specification; CV_a, Assay coefficient of variation, Coefficient of Variation (%) for the Analytical Error; CV_i, Individual Biological Variation; E(N_{uf}), the expected number of patient reports with an unacceptable error condition; FMEA, Failure Modes and Effects Analysis; P_{ed}, the probability of detecting a critical shift, a change in SE_{crit}; P_{fr}, the probability of false rejection; SDa, assay standard deviation; SE_{crit}, the critical shift to be detected by the QC strategy to satisfy a specified condition, eg a shift causing 5% single-sided errors; SE_{drift}, Assay Stability is scatter around the average bias, often seen as drift in a QC mean; Z, a shift in the mean of a distribution, measured in standard deviations

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component of an error budget because of the reduction it caused in P_{ed} [10].

The focus of these papers was to find operational performance boundaries of key parameters used in establishing and monitoring assays. Laboratories may use APS from a number of different sources including biological variation, State of the Art, Regulatory (e.g. CLIA) and expert opinion [13] and laboratories can remove constant bias by means other than analytical performance, e.g. factoring results [14], but they cannot remove scatter in the average bias of the method (seen as drift, or scatter of a mean around its target mean).

In this paper we produce a simpler FMEA-like calculation based on the elements that laboratories can control that determine errors (Cp_a, SE_{drift} and P_{ed}), examine the influence of APS and use laboratory EQA data to compare participants performance using a standardised 'risk' that calculates error rates and a functional QC run length.

The basis of our approach is that, under stable conditions, errors may occur due to a combination of assay imprecision and drift. These parameters can be used to calculate the steady state error rate, which when inverted, gives a theoretical QC run length which will contain one error under stable conditions. Multiplying by P_{ed} of SE_{crit} results in a QC functional run length where critical shifts can be detected, on average, in the same number of samples containing one steady state error. We propose this as a practical way to standardize the calculation of the risk of a QC strategy against a common performance specification.

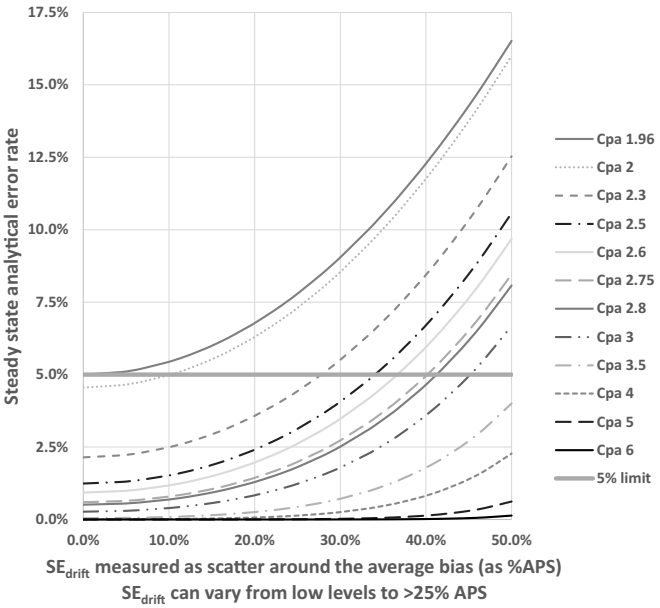

Fig. 2. Analytical error rates versus drift at various levels of imprecision, with boundary limits for 5% errors.

1. Methods

1.1. Model to calculate steady state errors from Cp_a and SE_{drift}

Cp_a is a simple metric equal to the APS expressed in assay SD [9]. Imprecision plus drift in the average bias affect the number of results outside the APS boundaries, ie analytical errors produced, under steady state conditions. Assay Stability (SE_{drift}) is the scatter around the average bias, not the average bias itself, measured as the SD of the differences between the mean of replicate results and the target at each concentration [10]. Cp_a and SE_{drift}, ie drift, can substitute in a normalized Gaussian distribution of APS-Z to calculate the rate of steady state errors (Fig. 1).

APS-Z represents the distance between the QC result distribution mean and the APS boundary after a shift of Z, hence it is the boundary value to use when calculating errors in that tail of the QC result distribution. The error rate for the top tail of the distribution (ie in direction of the drift/shift) can be determined using the Excel formula 1-norm.s.dist(APS-Z,1). At low Cp_a and for a small shift (Z) there are contributions to errors from the lower tail of the distribution. Errors in that tail are calculated at -APS-Z, ie APS + Z below the mean of the result distribution. So.

$$\text{error rate} = 1 - \text{norm. s. dist}(+\text{APS} - \text{Z}, 1) + \text{norm. s. dist}(-\text{APS} - \text{Z}, 1) \quad (1)$$

But, at steady state, Cp_a is the APS in SD and SE_{drift} (in SD)

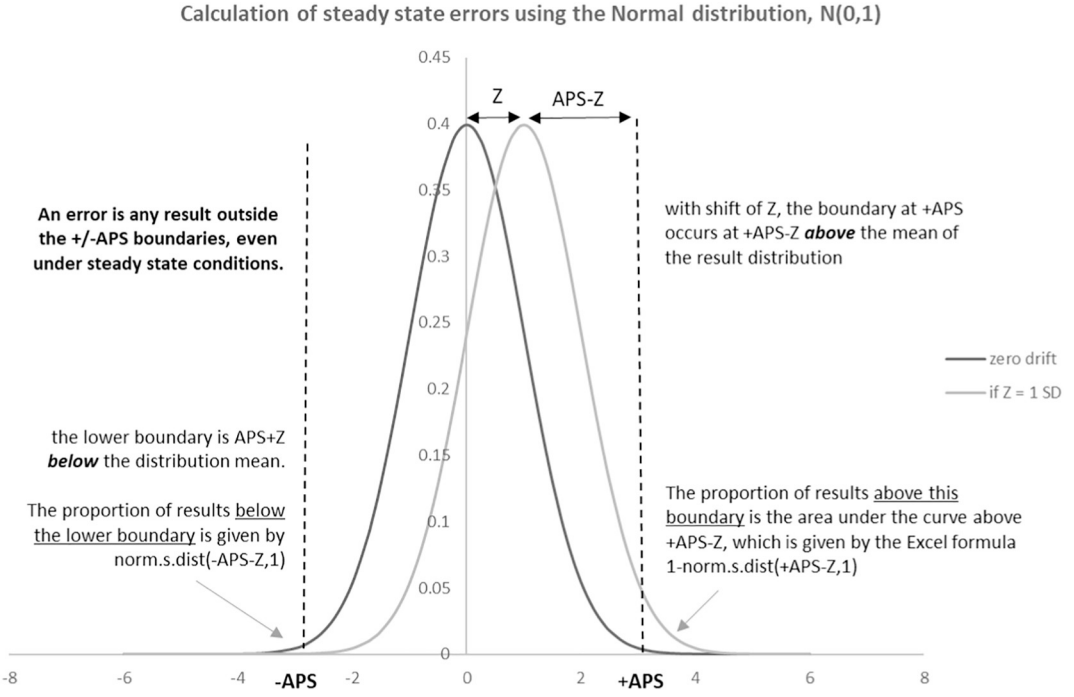

Fig. 1. The effect on the distribution mean relative to the APS caused by a shift of magnitude Z.

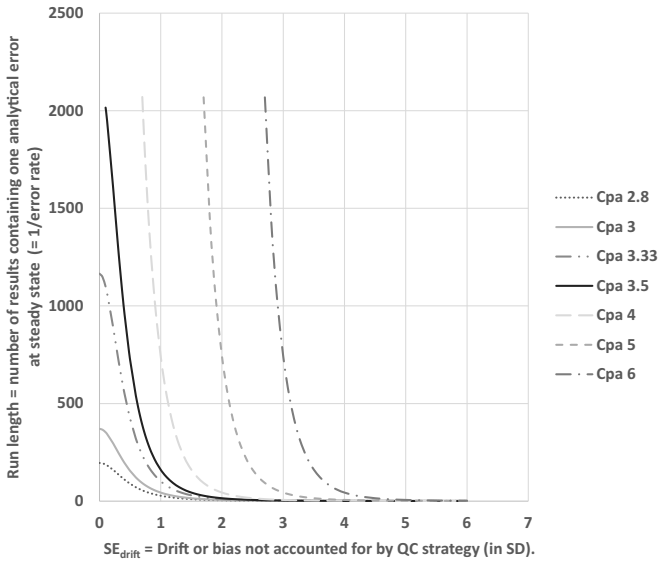

Fig. 3. Effect of drift on QC run length containing one analytical error at different Assay Capability assuming steady state.

represents drift which should be accounted for by the QC strategy, so.

$$\text{steady state error rate} = 1 - \text{norm. s. dist}(+Cp_a - SE_{drift}, 1) + \text{norm. s. dist}(-Cp_a - SE_{drift}, 1) \quad (2)$$

Fig. 2 shows the analytical steady state error rate versus SE_{drift} for different Cp_a.

Next, we invert the steady state error rate to calculate QC run length normalized for one steady state error. So.

$$\text{normalized run length} = 1/(\text{steady state error rate}) \quad (3)$$

Fig. 3 shows QC normalized run rate versus SE_{drift} for different Cp_a.

1.2. Functional QC run length combines error rate and error detection

We calculated the QC functional run length by multiplying the normalized run length by the QC algorithm P_{ed} for SE_{crit}, effectively standardizing the run length to detect a critical shift, on average, in the same number of samples that contain one steady state analytical error. If we don't apply this factor, then more steady state analytical errors will be produced before the QC algorithm detects the critical shift, if it occurs.

$$\text{functional run length} = P_{ed}/(\text{steady state error rate}) \quad (4)$$

We previously showed that $SE_{crit} = Cp_a*(1\text{-}SE_{drift}) - 1.65$ where SE_{drift} is drift expressed as % APS and 1.65 represents a shift for 5% errors [9] and published a table of P_{ed} and SE_{crit} estimated from Westgard Validator graphs [15] for some common QC algorithms with various Cp_a and levels of SE_{drift} [10].

Examples of these calculations are shown below using EQA data.

1.2.1. Risk analysis using EQA data

We used de-identified data from RCPAQAP General Serum Chemistry program [16]. Each cycle has 16 randomised linearly-related samples of 8 duplicate concentrations, tested over 8 weeks. Program instrument subgroup reports contain method medians for each sample, individual laboratory results, calculated parameters and their rankings across all cycle participants. Creatinine data for cycles 45 (1997) and 107 (2018) was transferred to Excel (suppl. file).

Assay Capability was calculated using reported data as $Cp_a = APS/CV_a$. To calculate SE_{drift} as % APS, the differences between the mean of laboratory duplicates and the corresponding method median were first converted to % APS at method median concentration before calculating the SD. To calculate steady state errors, this value was multiplied by Cp_a to express SE_{drift} in SD (because Cp_a is APS in SD).

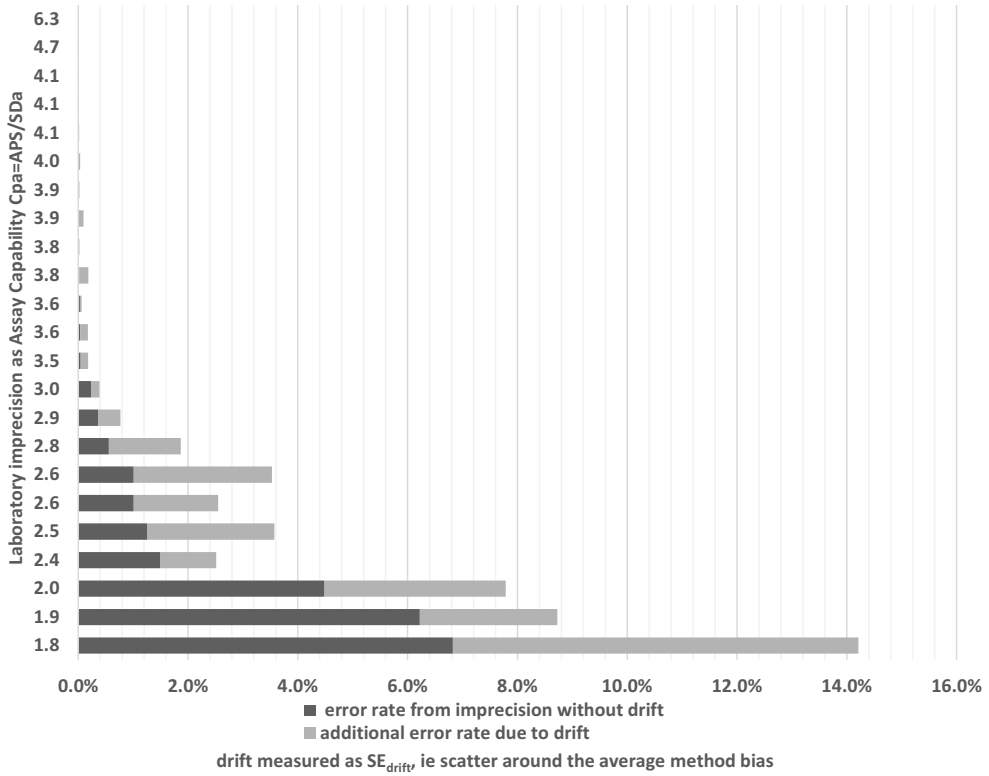

Fig. 4. Contributions of imprecision and drift to Steady State Analytical Error Rate from EQA data for serum creatinine in RCPAQAP General Serum Chemistry program cycle 107 [16].

Steady state errors were then calculated using Eq. [2], using both Cp_a and SE_{drift}, or Cp_a alone. The effect of SE_{drift} was estimated as the difference. Fig. 4 shows the data from cycle 107.

1.2.2. Example calculation using EQA data

To show the practical application of the method, we chose a laboratory in this subgroup that was the top 20th percentile laboratory for imprecision among all participants in the cycle. For serum creatinine RCPAQAP APS is 8 umol/L for concentrations up to 100 umol/L then 8% for values above 100 umol/L. For patient monitoring the clinical goal is CV_i which is 5.95% [17].

Laboratory CV_a of 2.1% is determined at the midpoint of the regression which is at > 100 umol/L. So.

RCPAQAP APS is 8%.

Cp_a = APS/CV_a = 8%/2.1% = 3.832.

SE_{drift} = 8.47% APS (from suppl file) and 0.0847*3.832 = 0.3245 in SD units.

Steady state error rate = 1-norm.s.dist(+3.832–0.3245) + norm.s.dist (−3.832–0.3245) = 0.02427%.

Normalized run length = 1/(steady state error rate) = 1/0.02427% = 4120.

If the assay is stable, and constant bias has been accounted for, eg by factoring, this number of samples contains one steady state analytical error.

SE_{crit} = Cp_a*(1-SE_{drift})–1.65 with SE_{drift} in % APS = 3.832*(1–0.0847)–1.65 = 1.86.

Westgard Validator critical error graphs give approximate P_{ed} as:

P_{ed} = 89% for algorithm $1\text{–}3_s$ $2\text{–}2_s$ $R4_s$ $4\text{–}1_s$ $8\times$ $N = 4$ $R = 2$ so functional run length is 4120*0.89 = 3667.

P_{ed} = 57% for algorithm $1\text{–}3_s$ $2\text{–}2_s$ $R4_s$ $4\text{–}1_s$ $N = 2$ R = 2 so functional run length is 4120*0.57 = 2348.

Using any of these combinations of run length and QC algorithm, the laboratory can detect on average, a shift causing 5% analytical errors within the same number of samples containing one steady state analytical error. For continuous workload conditions of 300 samples an hour, 2400 samples represent an 8-h shift. But for a high-volume laboratory it might represent only a few hours workload.

Note that if P_{ed} is not 100% there is a risk the shift causing 5% errors will not be detected at first QC challenge. This risk increases as P_{ed} declines. But there is no way to know if the shift will occur, let alone when it does.

1.3. Influence of performance specification on clinical and analytical errors

Clinical errors are more important than analytical errors and must be calculated by substituting APS with the Clinical Performance Specification (CPS), which changes with patient circumstance, e.g. monitoring or diagnosis. Analysing RCPAQAP cycle 107 data using different performance specifications (RCPAQAP, CLIA and Biological Variation) produced significant differences (suppl file). The effect is shown here in Fig. 5 which has theoretical creatinine analytical and clinical steady state error rates versus imprecision (CV_a) calculated using equ [2] and APS from CLIA (15%), RCPAQAP (8%) or biological variation for patient monitoring, CV_i (6%), standardised by assuming constant APS and zero SE_{drift}. Arrows mark error rates at CV_a for optimal, desirable and minimal imprecision performance for patient monitoring based on biological variation [18].

2. Results

2.1. Cp_a, SE_{drift}, steady state errors and QC run length

Fig. 2 describes the relationship between the analytical steady state error rate and SE_{drift} for different Cp_a. Given a particular Cp_a, increasing SE_{drift} increases the error rate in a non-linear manner, with the least capable assays most vulnerable to drift. The 5% limit line marks the required SE_{drift} to restrict errors to 5% for a given Cp_a.

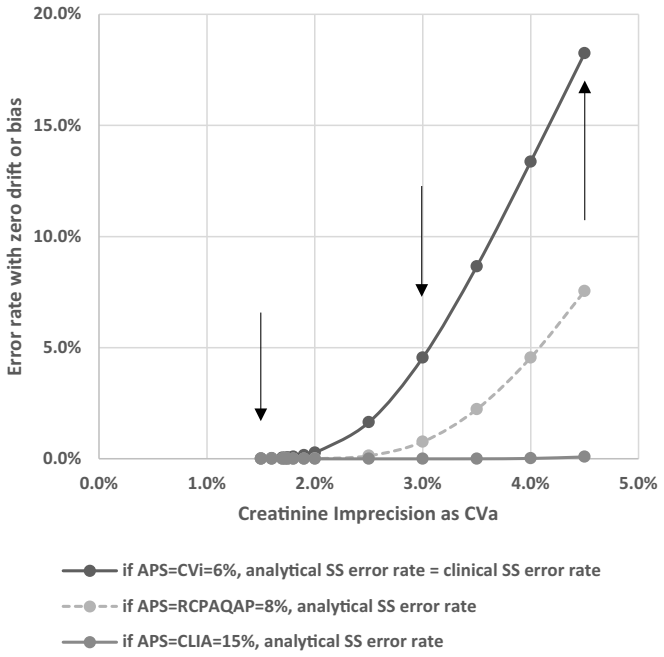

Fig. 5. Analytical error rates with different performance specifications versus clinical error rate.
Arrows mark error rates at CV_a for optimal, desirable and minimal imprecision performance for patient monitoring based on biological variation [18].

Drift (SE_{drift}) that is unaccounted for by the QC strategy has a profound effect on errors at low Cp_a and significantly reduces the QC normalized run length, while at high Cp_a moderate SE_{drift} can be easily accommodated allowing high QC run lengths per analytical steady state error (Fig. 3). Although these concepts are intuitive, our simple model describes them mathematically.

QC frequency based on a normalized run length, ie per theoretical steady state error, only manages analytical risk when assays are stable. Adding an error budget approach to detecting critical shifts, by multiplying normalized run length by P_{ed} of the QC algorithm, standardizes the risk approach for both stable and unstable situations. However, this requires that laboratories understand their QC algorithm P_{ed} for detecting SE_{crit} at their operating Cp_a and SE_{drift}. That is, understand the ability of their QC algorithm to detect critical shifts at their assay operating imprecision and drift compared to the performance specification. So, the choice of performance specification used is important in assessing risk.

2.2. Risk analysis from EQA data

The contributions of imprecision and drift to steady state analytical error rate are shown for serum creatinine from an instrument subgroup report of RCPAQAP General Serum program cycle 107 (Fig. 4). Using only Cp_a (imprecision) in the calculation, laboratories had steady state analytical error rates from < 0.01% to > 5%. Varied combinations of Cp_a and SE_{drift} contributed to total analytical steady state error rate which peaked at > 10% for the worst performing laboratory.

The single instrument type in this EQA subgroup report had performance over five orders of magnitude for steady state analytical

errors. This suggests that QC strategy and operation is just as critical to performance as an appropriate analyser. These data illustrate the importance of simplifying the relationships between performance specification, assay imprecision and stability (drift), analytical performance (error rate), error detection and QC run length.

RCPAQAP does not assess QC algorithm P_{ed}, so functional run length could not be analysed, only normalized run length. However, if standards were adopted for steady state errors, calculations could be made for P_{ed} required to meet them, leaving laboratories the choice of algorithm to achieve that P_{ed}.

2.3. Clinical versus analytical errors

Error rates, which are the area under the QC result distribution outside +/-APS, are not linearly related to the APS, so clinical error rates should be calculated with the relevant Clinical Performance Specification (CPS) replacing APS. Calculation of errors this way reveals large differences between analytical and clinical error rates under steady state conditions (suppl file), and the inherent trap if assays are managed using only analytical goals.

Fig. 5 shows imprecision versus steady state errors for the three theoretical, standardised situations where the performance specification for serum creatinine is either the clinical goal for patient monitoring, CV_i, or the APS specified by RCPAQAP or CLIA. A serum creatinine assay with CV_a of 3% performs with negligible steady state analytical errors calculated using CLIA APS of 15%, but produces almost 5% clinical errors, which is the desirable but not optimal imprecision goal for patient monitoring [18]. At the optimal imprecision for patient monitoring, $CV_a = CV_i/4 = 1.5\%$, error rates are similar, and negligible, for all the performance specifications. But as imprecision worsens, the more the APS differs from CPS the more dramatically analytical performance fails to reflect clinical performance.

3. Discussion

3.1. Model, steady state errors and run length

The model presented in this paper uses imprecision (Cp_a) and drift (SE_{drift}) to calculate the steady state error rate, which is inverted to produce a normalized QC run length containing one steady state analytical error. If imprecision or drift is higher, or residual bias exists, error rates will be higher and QC run lengths shorter. This suggests that QC should be run at least as frequently as the normalized run length. But P_{ed} of the QC algorithm detects critical shifts (SE_{crit}), not steady state errors, so P_{ed} should be 100% within the number of specimens in a normalized run length. Functional run length, ie normalized run length times P_{ed}, is the maximum QC run length required to manage a QC strategy and one way to standardize comparative risk.

It is important to understand that detecting SE_{crit} using an error budget only works for capable assays. Incapable assays will produce > 5% errors when QC flags (detects SE_{crit}), because errors in a low Capability assay are not restricted to the tail holding the single-sided calculation of the error budget. At the same time the calculated SE_{crit} is smaller and so P_{ed} decreases for the QC algorithm. This explains why the normalized run length increases significantly below Cp_a 4. Our approach is to calculate initial run length using total steady state analytical errors from Assay Capability (Cp_a) and Assay Stability (SE_{drift}), then multiply by the P_{ed} of the QC algorithm at steady state conditions. We summarise these concepts in Table 1.

Our simple approach uses well understood parameters to assess the minimum QC frequency required (functional run length), and so deals with variable workload. It works for both capable and incapable assays and addresses stable and unstable situations.

3.2. Functional run length and FMEA

There is little guidance available for laboratories to calculate a QC run length that is evidence-based, so consequently many use a time or convenience-based approach [19]. In a recent paper Westgard et al. [20] described a process linked to a Sigma-metric Statistical Quality Control process to determine a QC run length. The method uses P_{ed} as a component of the risk calculation but does not take account of the frequency of errors and hence is not a FMEA risk-based approach.

Using a QC functional run length based on steady state error rate and adjusted for error detection by multiplying by P_{ed}, amounts to using a standardised risk approach using the first two elements of a FMEA-like calculation. The normalized QC run length or steady state error rate is the first component of a FMEA-like model of risk, frequency of errors, but under steady state conditions. P_{ed} of SE_{crit} is the second FMEA factor, the ability to detect errors, operationalized as the ability to detect a shift causing > 5% errors. The functional run length combines the first two FMEA factors - the steady state error rate inverted to become a run length multiplied by P_{ed} for detecting a standardised shift in the QC that would produce > 5% errors.

To be able to have QC run lengths standardised for P_{ed} of SE_{crit}, the laboratory must know the P_{ed} of their QC algorithms, not just imprecision and drift relative to the APS. This also assumes that average bias has already been managed by the laboratory e.g. by applying a factor to the result [14]. If not, analytical errors will be higher, implying our proposed approach based on Cp_a and SE_{drift} is the minimum QC frequency required to manage the risk of a QC strategy.

3.3. Clinical and analytical error rates

Clinical risk is affected by the difference between clinical and analytical performance specifications, especially when achieved laboratory performance is sub-optimal. We expect expert bodies and regulatory authorities to review these differences when setting performance specifications, and that laboratories be aware of them.

Error rates for desirable imprecision performance based on biological variation for monitoring patient creatinine are almost 5% if drift is zero. However, anyone would agree that having almost 1 in 20 results in clinical error poses an unacceptable risk to patients. Laboratory steady state error rate can vary widely and has practical application in QC run length; it appears to be a candidate for grading performance.

4. Conclusion

The parameters Cp_a, SE_{drift} and P_{ed} inform us about the risk of a QC strategy including functional run length which is the minimum QC frequency and have been used as a *defacto* FMEA-like model of analytical risk combining the frequency of analytical errors and error detection. This strategy normalizes QC run length for steady state errors and standardizes run length for detection of critical shifts in QC. This functional QC run length allows direct comparison of analytical risk across any laboratories using the same APS and can be deployed in situations of variable workload.

Inevitably, some decisions will be made in operationalising these ideas, e.g. how to deal with different QC run lengths on one analyser. Assessing operational performance that reflects patient results is different to discussing a theoretical QC strategy. But if operational performance measures of Cp_a and SE_{drift} are robust, our simple calculations

Table 1
Summary of FMEA-like factors and their value.

Step	Factor	Factor description	Progressive expression as error rate	Progressive expression as run length	Explanation
1	Analytical Errors	Steady state errors only, as area under the curve outside +/-APS calculated using a normalized distribution using APS-Z with Cp_a = APS and SE_{drift} = Z.	**Steady state *analytical* error rate**	1/ (steady state *analytical* error rate) is ***Normalized run length*** *for 1 analytical error*	**Steady state *analytical* error rate** in % of all results or in practical terms a *run length containing one steady state analytical* error.
		Cp_a = APS/SD_a = APS/CV_a which is SD inside the APS SE_{drift} in SD = drift or scatter around the average bias.		… *1/0.2% = 500*	*Assumption is made that the average method bias is already managed,* e.g. *by factoring.*
		Applies when assay stable ie in control	*If error rate is 0.2% …*		***Can only compare laboratories using the same APS***
2	Error detection	P_{ed} in % is the ability of the QC algorithm to detect a specified error rate caused by a shift (SE_{crit}), the size of which can be calculated using Cp_a and SE_{drift}. SE_{crit} = Cp_a*(1-SE_{drift})-1.65 with 1.65 for 5% errors, SE_{drift} as a fraction of APS.	(steady state *analytical* error rate) / P_{ed} *If P_{ed} is 66% at Cp_a and SE_{drift} the functional error rate increases to 0.2%*3/2 = 0.3%*	P_{ed} / (steady state *analytical* error rate) is the ***Functional run length*** … *500*2/3= 333*	**Run length adjusted for Ped so a shift causing 5% *analytical* errors is detected at the same rate as steady state *analytical* errors are produced,** ie in the same number of samples that contain one steady state error.
		P_{ed} is standardised to a shift causing 5% errors.		*this should be deployed to reduce risk*	***Can only compare laboratories using the same APS***
3	Clinical errors	Calculate clinical errors after replacing APS with a relevant clinical goal (CPS), which depends on patient circumstance.	Calculated as for analytical errors above, but using the relevant clinical goal (CPS)	Multiplying by P_{ed} determined using APS is inappropriate	**Clinical error rate** inverted to reveal the run length containing one steady state *clinical* error.
					By using a universally accepted clinical goal this measure of clinical errors is comparable across laboratories regardless of the local APS used for assay management
	Clinical risk	*A clinical error rate, normalized for steady state clinical errors (stable situation), and standardised for detecting a shift causing 5% clinical errors (unstable situation).*		Standardised clinical risk is calculated as clinical errors multiplied by P_{ed}, but *Ped must be determined using CPS.*	*The comparative clinical error rate when detecting a shift large enough to cause 5% clinical errors (out of control - instability) matches the number of samples that produce one steady state clinical error (in control - stability).*

provide a way to compare both analytical and clinical risk of QC strategies across laboratories.

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