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# 2. Principles for Assessing Analytical Quality Specifications ("AQSpecs") and their Use in Design of Control Systems

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Interpretation of clinical laboratory data aiming at improved patient care may be considered as a signal-to-noise problem, where the signal contains the information about the individual's state of health and the noise is due to a mixture of disturbing factors. These factors cover a wide range, from selection of measurands, over sampling and analytical performance, to interpretation of the obtained data (28, 44).

Selection of the relevant measurand for a specific purpose is the responsibility of the individual clinician, but the choice may be facilitated or aided by agreed protocols or national recommendations outlining strategies for this as well as for interpretation of the data.

Clinical chemistry as a discipline is often involved in the setting up of such protocols and recommendations, where valid contributions can be given. This activity seems to involve the discipline to an increasing extent, but the main duty of the clinical chemistry laboratory is still to handle samples and produce reliable results. The question is then, 'what is a reliable result' or 'which analytical quality is needed'?

## 2.1. THREE MAIN APPROACHES

Many proposals for 'quality goals' and 'analytical quality specifications' (AQSpecs) have been advocated since Tonks (61) in 1963 tried to establish a limit for acceptable analytical quality. The various postulates concern only analytical imprecision (reproducibility) or in vague terms an implication of analytical bias. Few define a clear relationship between requirements on imprecision and bias, and even fewer a relationship to analytical specificity or to preanalytical conditions.

The main approaches to analytical goal-setting have been based on:

- the assessment of the current quality of analytical performance, 'the state of the art' approach;
- estimates of biological within- and between subject variation, 'the biological' approach;
- assessment of the clinical usefulness criteria in a broad sense, 'the clinical usefulness' approach.

These three approaches may also be considered as successive steps in the process of achieving the most relevant basis for defining optimal standards of analytical quality from the point of view of clinical practice. For all three approaches it seems that they are highly influenced by the professional background of the advocates or the actual problems in their mind.

Thus 'the state of the art people' mainly represent individuals involved in external quality assessment (1,16) where they need a 'yardstick' for judging the quality of results obtained from control surveys, whether defined by legislation or other national or commercial control schemes. The intention is to improve the overall quality without discrediting too many of the participating laboratories. Even when other criteria are introduced they are adjusted to 'obtainable quality' if they are too demanding.

The biological approach is mainly advocated by people with a biological (44) or a statistical background (36). The general formulations of statistical models are very attractive, and the many data sets on biological within- and between-subject variation give the basis for an extensive application.

Proposals based on clinical usefulness criteria are mainly suggested by people involved in establishing 'recommended programmes for clinical actions or treatment' or theories of 'medical decision making' (11, 34, 39, 75), where the outcome from clinical strategies is the measure of quality, and analytical variation is considered as one of the noise factors. The close connection to the clinical evaluation makes this approach favourable for the investigated clinical situations.

This clear difference between the three approaches facilitates the understanding of the many principles for goal-setting, and explains why it can be difficult to reach a common

agreement on analytical quality specifications. It must be remembered, however, that some proposals for analytical goals are based on mixtures of these general principles. Further, there seems to be an increasing understanding for combinations, where specifications based on 'the state of the art' are substituted for more demanding specifications as interim proposals (22).

It is important to understand that the many approaches, principles, and models for goal-setting and elaboration of quality specifications may serve certain purposes and, therefore, be relevant for the application for which it is intended - even when it may be in conflict with other specifications - at least for a time. However, the clinical usefulness criteria must be the highest level for our endeavours.

A number of problems make the clinical approach to goal-setting and specifications for analytical quality technically more difficult than the biological approach (22, 44):

(i) it is often difficult to find clear situations - except for screenings - where one or more quantities are single determinants of the clinical outcome;
(ii) the same quantity may be used for several purposes resulting in different quality specifications;
(iii) clinical strategies may vary over time and geography; and
(iv) the models are often complicated, and difficult to apply in specific situations as several assumptions must be fulfilled.

Recent publications on analytical quality goals and AQSpecs have been written by Fraser *et al.* (16, 19, 22) Hyltoft and Hørder (44), and by Groth and de Verdier (7, 32).

## 2.2. PRINCIPLES FOR GOAL-SETTING AND AQSpecs

### A. The state of the art approach

Here the principle is to define a fraction of the "best performers" in terms of imprecision and bias, either as

(i) a small fraction of the laboratories (*e.g.* 0.20) which shall serve as a target to reach for the others (1); or
(ii) a broad fraction of the laboratories (*e.g.* 0.95) which are considered satisfactory according to current quality. The stated limits may be conveyed to be permanent (16).

This approach may be considered to be the simplest form of analytical goal-setting. It may help the single laboratory to disclose poor performance or it may be a governmental guarantee against unprofessional performance. Further, it may be a realistic way for improving analytical quality, when quality specifications based on other principles are very demanding.

There are several drawbacks:

i) the fraction is selected more by political than by scientific or clinical reasons;

ii) the target quality depends on current quality of performance and will vary over time;

iii) poor methods may be accepted if results from different products (equipment, reagents, calibrators) are grouped (so-called peer-groups) and thereby accepted;

iv) further, the AQSpecs are defined without any relations to the clinical use of laboratory results.

**B. The Biological Approach**

The basic principle is that the analytical errors should have a minimal influence compared to:

(i) the biological within-subject variation, $CV_{Bw}$ (11, 36)

(ii) the total biological (combined within- and between-subject) variation, $CV_B = \sqrt{CV_{Bw}^2 + CV_{Bb}^2}$ (5, 27, 37) or the reference interval for a healthy population (2, 26, 61).

Special glossary for different types of biological and analytical variations see ref. (8) (Chapter 11).

For biologically derived goals and AQSpecs the preanalytical factors contribute to the variation; in most evaluations these have been considered as part of the biological variation (20, 44, 50, 72).

The models for biologically derived quality specifications are general in nature and, thereby, applicable to any biological naturally occurring quantity, where values for $CV_{Bw}$, $CV_{Bb}$, and $CV_B$ (or at least a reference interval) are available. There are many data in the literature on $CV_{Bw}$ and $CV_{Bb}$ (1, 3, 4, 17, 56), and on reference intervals.

The approach is then to express:

(i) the coefficient of allowable analytical variation as a fraction of $CV_{Bw}$ :

$$CV_A \leq f \cdot CV_{Bw}$$

It is generally accepted to use f = 0.5 (11, 16, 36) which will increase the total coefficient of variation, $CV_{TBw}$, by a factor 1.12 at the most:

$CV_{TBw} = \sqrt{CV_{Bw}^2 + CV_A^2} = \sqrt{CV_{Bw}^2 + CV_{Bw}^2/4} = 1.12 \cdot CV_{Bw}$

(ii) the coefficient of allowable analytical variation as a fraction of $CV_B$ or of the reference interval. Different values of f have been proposed:

$CV_A \leq 0.5 \cdot CV_B$ (5) or $s_A \leq 1/8$ reference range (61) or $\leq 1/5$ reference range (26) or $s_A \leq 1/12$ of the reference interval (26).

(iii) a combined estimate of allowable imprecision ($s_A$) and bias ($B_A$):

$\sqrt{s_A^2 + B_A^2} \leq 0.5\ s_B$ has been proposed (37).

(iv) the combined estimates, of allowable imprecision ($s_A$) and bias ($B_A$), may also be expressed in terms of acceptable fraction of individuals outside each reference limit (27). Here the confidence interval around 0.025 fractile is 0.013 to 0.044, which gives

$B_A \leq 0.25 \cdot s_{Bb}$ for $s_A = 0$, and $s_A \leq 0.55 \cdot s_{Bb}$ for $B_A = 0$ (see Fig. 1).

(v) in an error budget allowing a 50 % increase in the false-positive rate for classifying healthy subjects (47) allowable $B_A \leq 0.36\ s_B$ ($s_A = 0$) and allowable $s_A \leq 0.13\ s_B$ ($B_A = 0$)

When the distributions defining the reference intervals are log-gaussian the approaches discussed here become more complicated (42).

The principles for deriving analytical quality specifications from biological variation are easy to grasp and the application is simple when the fraction is decided. Furthermore, the estimated CV-values seem rather constant from investigation to investigation (36), which make the quality specifications common for all applications for each quantity. The drawbacks are mainly related to the very general concept behind this approach, which makes it more or less irrelevant for the use of the data in specific clinical situations.

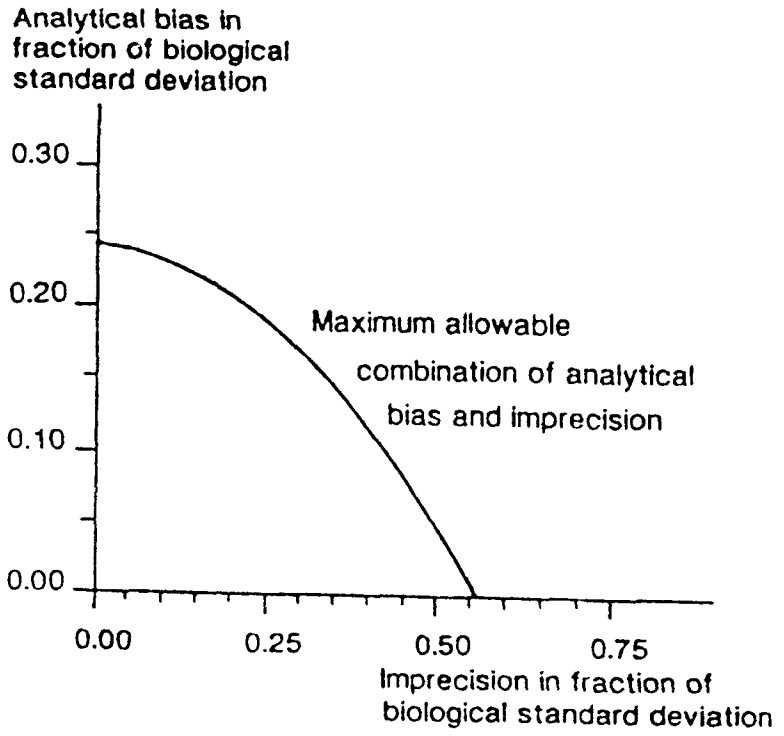


**Fig. 1.** AQSpecs for sharing common reference intervals. The figure shows the maximal allowable combination of analytical bias (y-axis) and imprecision (x-axis), both expressed as fraction of the total biological variation ($s_B$). The construction of the graph is based on IFCC recommendation for calculations of reference intervals using a minimum of 120 individuals, and the 0.90 confidence intervals of the estimated upper and lower reference limit. From (44) with permission.

### C. The clinical usefulness approach

There are two main approaches to the assessment of analytical specifications from clinical usefulness criteria:

(i) One is based on the 'clinicians viewpoint', as assessed with use of questionnaires sent to experienced clinicians, giving short descriptions of patient situations and where the clinicians then are asked to decide which change of a laboratory result would cause further investigations or treatment etc. (2, 12, 13, 58). The "median value for reaction", $\Delta_{med}$, is estimated and $CV_A$ is calculated as

$$s_A \leq \Delta_{med} / (1.65 \cdot \sqrt{2})$$

when a change is considered. This simplified model has been used and improved by Thue *et al.* (60), Linnet (50), Fraser *et al.* (21), and Magid *et al.* (52).

(ii) The other approach is based on clinical strategies or situations, where the specific use of a laboratory investigation is justified, *e.g.* in a reference care programme or a screening situation, or in monitoring of patients or follow up of a treatment, etc. (6, 21, 28, 34, 39, 41, 43, 44, 45, 51, 53, 54, 57, 72, 77). The principle is to express the clinical outcome in quantitative terms for an ideal errorfree situation - and to add increasing uncertainty ($s_A$ or $B_A$) to evaluate the effects on the clinical outcome. For a certain acceptable reduction in outcome the maximum allowable error can be estimated. For instance, the design of an optimal screening procedure (34) would consider the prevalence of disease, the relative importance of making correct classification, in addition to analytical imprecision and bias. The clinical outcome could be defined in terms of estimated costs due to misclassifications.

The clinical approaches have their advantages in their direct relations to the clinical use of laboratory data. They provide are the most relevant ways of defining quality specifications, but as mentioned before, the quality specifications derived in this way are restricted to the situations for which they were assessed. However, the models for assessment of specifications from clinical situations are general and can be applied when certain presumptions are fulfilled.

**D. Simulations of clinical situations**

Computers may be used to simulate the biochemical-physiological complexity behind clinical chemical measurement results - biodynamic modelling (29). Medical reasoning and decision-making processes may also be studied by various types of simulations (28). It is likely that computers will increasingly provide the means for documenting medical knowledge and for processing of procedures related to clinical decision making. Such "knowledge-base systems" (KBSs) will lead to more cost-effective diagnostic and therapeutic procedures. It is also obvious that the availability of such systems will increase the possibilities to assess quality requirements on laboratory data in a clinical context (28).

Systems and sensitivity analyses may be performed with use of biodynamic models and KBSs to investigate how various derived quantities (objective functions) are influenced by variation in basic input data (*e.g.* analytical imprecision and bias) and by the design of various procedures. Objective functions have to be defined to measure *e.g.* the gain or loss of information in different steps, or the benefit or loss incurred in making clinical decisions. Depending on the definition of the objective function one may perform

"suboptimizations" or more "total optimizations" of the use of clinical and laboratory investigations.

Some examples of this approach have previously been presented in detail elsewhere (28, 30, 33, 53, 64, 76), illustrating the potentials for assessing not only the analytical and pre-analytical quality requirements, but also the equally or more important aspects of selection and combination of laboratory investigations, frequency of sampling, the influence of incorrect conceptual models for interpretation of clinical laboratory results, and mode of presentation of results. The applications comprise design of procedures for measurement and interpretation of markers of acute myocardial infarction (33); and assessment of liver function with use of allopurinol loading test (64). In both cases biodynamic models were used for time-series analysis and evaluation of the influence of various factors on the diagnostic outcome.

Wiener *et al.* (76) applied sensitivity analysis to assess the analytical quality requirements related to the automatic interpretation of complement factors using a rule-based system. The influence of analytical variation was judged in terms of critical changes in the diagnostic comments produced by the system.

**E. Other approaches**

i) An often used pragmatic approach is to reach a consensus between clinical chemists in a laboratory and the users (48). This approach may result in useful specifications - and may lead to better understanding between the laboratory and the ward. The solutions, however, are local and may be decided too much from economical reasons - and may be considered more of a local 'state of the art' solution.

ii) Ross (57) have proposed "a general clinical model, which should be applicable to all clinical situations". However, the circumstance that it is based on are very special (prevalence 0.5 and defined distance between group means) makes it difficult to find clinical situations to which it can be applied.

iii) Models for evaluation of AQSpecs for drug analyses have been developed by Fraser (15, 18). The minimum time between collection of samples, $\Delta t$, depends on the biological half-life of the drug , $t_{½}$ , and $CV_A$:

$$\Delta t = (1/\log 2) \cdot t_{½} \cdot \log (2.33 \cdot CV_A + 1).$$

The interrelationship between $\Delta t$ and $CV_A$ is clear and the model is applicable when $t_{½}$ is known.

iv) Experimental variation of analytical quality was used by Wide *et al.* (74) in a study

on optimization of a TSH-method.

v) A single approach to quality specifications for specificity (23) might be the first step in a more intensive investigation of this field where Glick (25) has documented the problems for many analytical procedures.

### 2.3. FORMULATION OF AQSpecs

According to the overall strategy (scheme presented in Fig.1 in Chapter 1) the primary task is to try to formulate the 'clinical goal'. Most laboratory investigations are used in various clinical situations with different analytical quality requirements. Therefore, it can be difficult to state only one value for each analytical method. For instance, for diagnosis of hypothyroidism using S--TSH the analytical method must have a bias $B_A \leq 1.6$ mU/L and $s_A \leq 0.8$ mU/L at a S--TSH concentration of 5 mU/L (47). A S--TSH investigation may also be used for diagnosis of hyperthyroidism, the clinical goal will then be very different: $B_A \leq 0.26$ mU/L and $s_A \leq 0.13$ mU/L at a S--TSH concentration down to 0.3 mU/L (47). When the laboratory is going to set its AQSpecs the most stringent goal must in general be guiding. However, in the steps from the clinical goals to the AQSpecs the management of the laboratory has to decide what is possible from a measurement point of view and from a quality control point of view. This means that a list from the laboratory with its AQSpecs can only be prepared after considering data describing goals, measurement and quality control.
Estimates of allowable preanalytical errors should be possible to include both in the clinical goals and in the AQSpecs.

Clinical goals and AQSpecs should both be presented as a total allowable analytical error, $TE_a$, at a defined critical concentration/level for clinical decision. It is assumed that we are discussing the $TE_a$ of "the analytical procedure" which is equal to the total error of "the analytical measurement procedure" after having removed larger errors detected by the "analytical control procedure" (for explanation of terms see Chapter 11). The terms of error components suggested in Chapter 5.2 are not directly comparable with those used in other publications and in some of the contributions to this project report. In the two columns below we have tried to compare the concepts (*cf.* also different forms of errors defined in Chapter 10).

| **Frequently used terminology, *cp.* (65)** | **Terminology used in Chapter 5.2.** |
|---|---|
| Bias, measured ("stable inaccuracy") = $B_{meas}$ | Correctable systematic error = $SE_{corr}$ |
| Bias, matrix effect = $B_{matx}$ | Non-correctable SE = $SE_{noncorr}$ |
| Change in systematic error ("unstable inaccuracy") = $\Delta SE$ | Temporary change in systematic error $\Delta SE$ |
| Inherent random error of measurement procedure ("stable imprecision") = $s_{meas}$ | Inherent stable random error = $s_A$ |
| Change in random error ("unstable imprecision") = $\Delta RE$ | Temporary increase in random error = $\Delta RE$ |
| **Obs!** In ref. 65 the term "Inaccuracy" is used with another definition than recommended in Chapter 11. Ought to be replaced by bias. | $\Delta SE_{crit}$ and $\Delta RE_{crit}$ (see below) are derived from $TE_a$ |

## 2.4. USE OF QUALITY SPECIFICATIONS IN THE DESIGN OF QUALITY CONTROL PROGRAMS

**The use of quality specifications as a starting point for the design of internal quality control procedures** to assure the medical needs of analytical quality was first introduced in a paper by Westgard and Groth in 1979 (68), *cf* (70). This approach requires that a limit for allowable analytical error, AAE or $TE_a$ ,is specified and that the inherent method bias ($B_A$) and standard deviation ($s_A$) are known. Then the critically sized systematic and random errors that must be detected, $\Delta SE_{crit}$ and $\Delta RE_{crit}$ , can be calculated. Figure 2 presents a summary of the key determinants of analytical quality. Power function graphs for statistical control rules, introduced at the same time (66) to show the relationship between the probability for rejection and the size of the analytical error, are then used to choose control rules and number of controls which permit detection of the critically sized errors.

An instructive application of this approach to a multitest analytical system is found in a paper by Koch *et al.* (48).

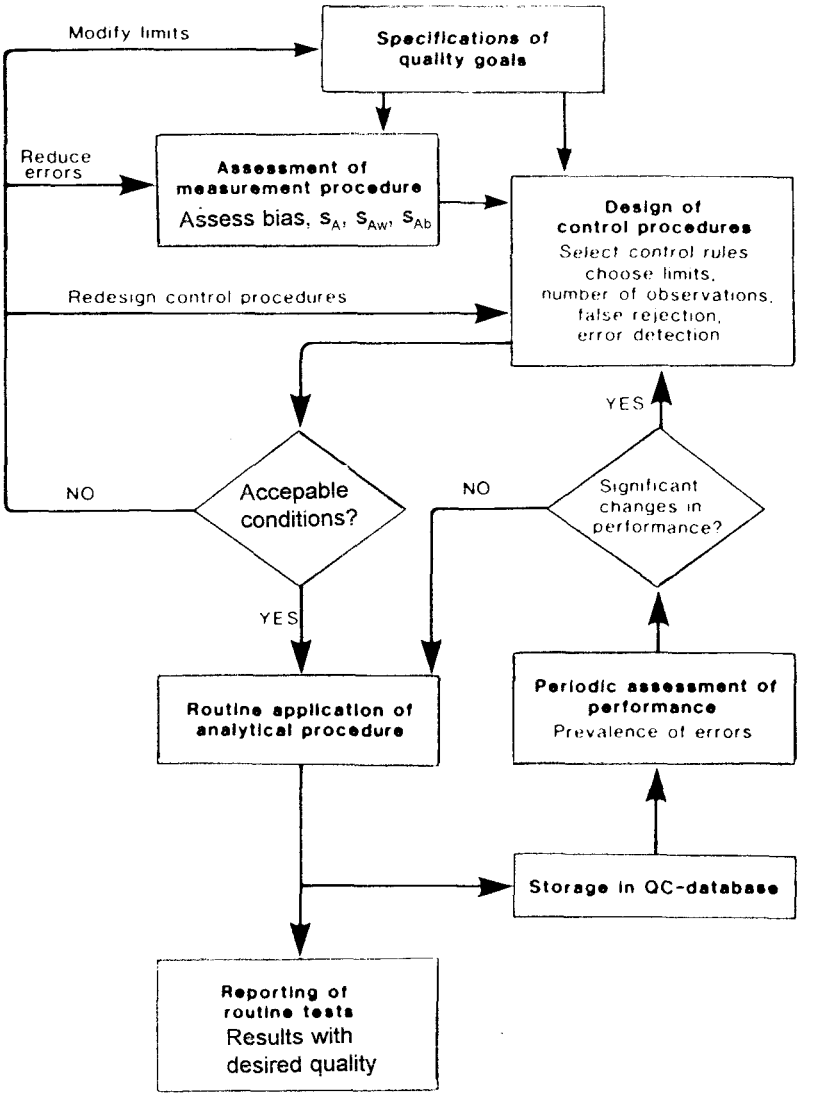


**Fig. 2.** A flow chart illustrating the connections between the clinical quality goals, the measurement procedure and the quality control procedure. Through quality audit and other steps the functionality of the control procedure will intermittently be revised. From Westgard, Groth & de Verdier (70) with permission.

"Quality Control simulator" programs are required to generate the power functions as influenced by several factors, which vary from one application to another (35, 67). These factors mainly describe characteristics of the control procedure (number of controls; choice of control limits and control rules), but may also include instrument characteristics

such as the number of significant figures in the measurement and analytical method characteristics as within-, and between-run components of analytical variation.

**Critical characteristics of unstable performance**, such as frequency of medically important errors, should also be considered in the design in order to achieve high predictive values of reject and accept decisions (69); otherwise time is wasted looking for problems when none exist, and runs are being accepted when errors are actually occurring.

So called "Quality Control Selection Grids" were developed by Westgard *et al.* (73) as "simple qualitative and semiquantitative planning tools that can be applied in today's busy service laboratories", "until improved tools are readily available".

A selection grid identifies QC rules and number of controls considered to be appropriate for measurement procedures having different "process capability" and "process stability", as characterized by the magnitude and frequency of medically important errors.

The grids were developed for single-rule fixed-limit procedures and multi-rule procedures, based on visual review of computer generated power function graphs.

**Quality and productivity cost characteristics should also be considered in an optimized design of QC procedures.** The test yield formulation of the "predictive value quality costs model" (71) provides a way to express quality-costs as a function of

* the measurement procedure's frequency of medically important errors,
* the control procedure's probabilities for error detection and false rejection, and
* cost factors for: incorrect analytical runs which are properly rejected; correct analytical runs which are improperly rejected; incorrect runs which are improperly accepted; and correct runs which are properly accepted.

The test yield, defined as the proportion of analytical measurements that are reportable as valid patient results, should be maximized with the constraint that the defect rate (falsely accepted results) should be lower than a specified value.

The application of these principles for selection and design of cost-effective QC procedures is limited by the access to QC simulation programs of the type described in ref. (35). Fig. 3 shows one type of output from this program, a plot of test yield and false accepts *vs* number of controls, that can be used to estimate the optimal number of controls.

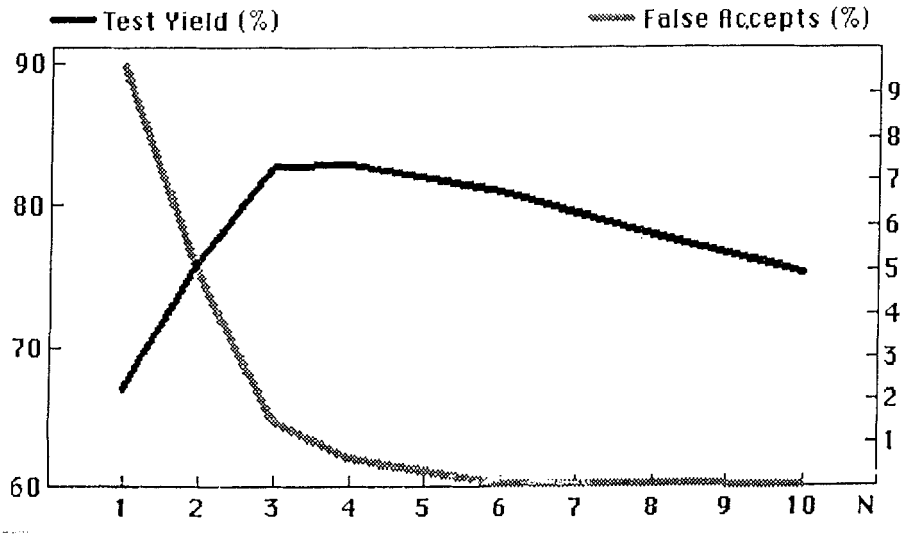


**Fig. 3.** An example of an output from the simulation program (35) for optimizing quality control design. A plot of test yield and false accepts *versus* number of controls.

So called Operational Process Specifications Charts ("OPSpecs Charts") have recently been introduced by Westgard (65) to be used to determine what QC procedure is appropriate, given a specified quality requirement, the observed "stable imprecision", and the observed "stable bias".

The total allowable analytical error $TE_a$ is expressed in %, and the OPSpecs Charts may be chosen for 90% or 50% analytical quality assurance. In view of the predictive value theory of quality control (69), a shortcoming of this procedure is that it does not include the frequency of medically important errors as an important design parameter. Furthermore, bias is generally not known or is difficult to estimate in lack of agreed "conventional true values". It could also be argued that measured and well-known stable bias should not be allowed to decrease the cost-effectiveness of the QC procedure. By following the metrological principle of correcting measured values for known bias the critically sized errors will be less demanding on the design of the QC procedure.

**Use of Quality Specifications in design of EQA programmes.** External "control samples" are traditionally distributed and processed within so called external quality control (EQC) programs (46). In Europe such programs are nowadays generally referred to as external quality assessment (EQA) programs, but in most countries analytical quality specifications are not used in the evaluation of the results. For a review see Libeer (49).

In the US there are governmental regulations and requirements for analytical quality of clinical laboratory investigations, and Proficiency Testing (PT) has been established as the approach for controlling that a defined quality is achieved in clinical laboratories. The minimum requirements are defined in the 'PT criteria for acceptable performance' as described in the Clinical Laboratory Improvement Act (63). The low number of control samples analyzed is a severe limitation in the statistical evaluation of the results. Laessig *et al.* have investigated various statistical rules for improved evaluation of interlaboratory performance data (10).

In Germany a "Ringversuch" approach has been implemented, based on quality requirements and "method-independent" reference method values as points of reference for interlaboratory surveys (24, 59).

In all the five Nordic countries EQA programs are running. It is stressed that information and education are important integral parts of well functioning quality assurance programs. For that reason the specialist organizations have assisted in selecting members of different expert groups (38, 55). One can assume that they in the future also will be engaged in guiding the laboratories about AQSpecs.

In a Nordic quality assessment program on plasma proteins (40) (Chapter 5.1), a series of well defined control materials are used for estimation of bias due to unspecific reactions, in addition to calibration bias. Limits for allowable analytical errors are used to evaluate the outcome, and make comments to the individual laboratories.

In another NORDKEM project on Transferability of Clinical Laboratory Data" (31) (Chapter 5.2) a linear regression approach has been applied for assessing analytical bias over a wider measurement interval, to be used for evaluation of compliance with specified analytical quality goals, and for correction of analytical bias. Given the allowable total analytical error $TE_a$, and the corresponding critically sized systematic error $\Delta SE_{crit}$, the acceptable region of the regression line $c = k\,c^* + l$, would be $|c - c^*| \leq \pm \Delta SE_{crit} \cdot s$, $c_{min} < c^* < c_{max}$, where c and c* denote the measured and assigned value, respectively, for reference material used for accuracy assessment of the bias of the analytical procedures.

In Europe there is an increasing awareness of the deficiencies and shortcomings of the design of most current external quality assessment schemes. There is also an ongoing discussion on "whether it would be appropriate to issue a protocol for how to run EQAS in laboratory medicine and what the content of such a protocol should aim at" (62). It remains to be seen if a CEN standard for such a purpose could be produced.

Certification and accreditation of laboratories have during the last two years been

intensively discussed. Both these processes require the writing of a quality manual with quality policy statements as a basic element (9, 14). It is our hope that the suggested procedure starting with 'clinical goals' and continuing to 'analytical quality specifications (AQSpecs)' will prove to be useful in this context.

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