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3. Elements of Analytical Quality

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3.1 Model for Analytical Quality Achievement

General Aspects of Analytical Quality

Among the endless number of factors influencing on the quality of an analytical process, at least three main elements can be worked out as the basic factors in a model for analytical quality. These are (i) *Analytical Quality Specifications,* (ii) *Analytical Quality Creation,* and (iii) *Analytical Quality Control.*

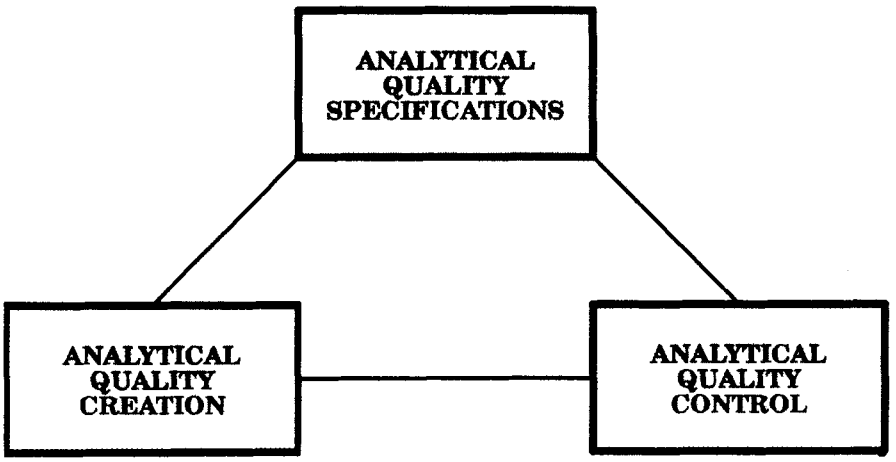

Fig. 3.1.1 Model for analytical quality illustrating the three basic elements.

(i) In order to judge analytical quality, knowledge about the required performance of the analytical procedure is needed. Without this information we can only talk about the relative quality compared to other procedures or have a vague feeling of whether the quality is good or poor. Therefore, *goals for its purpose* must be stated and *specifications of the needed quality* must be defined.

(ii) The indispensable elements of the creation of analytical quality relates to *standardization* and *analytical procedure.* The two elements are different in nature and to some extent interdependent as both are needed and each of them can spoil the good influence of the other if its quality is insufficient. The first relates to *traceability* of concentration values to *trueness* based on *definitive methods or international reference preparations* through *reference methods* and *calibrators,* to more or less extent, dependent on the quantity under consideration. The second part is more complex as the *analytical principle* determines the quality and thereby, the type of problems, whereas, *equipment* and *reagents* as well as the *actual performance* influence the extent of these weaknesses.

(iii) In contrast to the generally accepted idea, *control of quality* cannot by itself improve the quality of an analytical process. Control can at the best disclose or reject errors but these errors are at the most defined in relation to the current analytical level of quality, whether it is good or bad. However, the revealing of errors may be the first step in an *trouble-shooting* process which may lead to correction of the error, and thereby, to improvement of the analytical quality. The *design* of the control system determines its ability to fulfil this purpose, as control materials as well as interpretation of the results are decisive for the outcome. *External* and *internal* control systems are different in nature and should be designed and interpreted accordingly, as the external control should be related to an estimate of the stable analytical procedure and internal control should relate to deviations from the stable performance. Most important for control, however, is the definitions for the quality desired and the possibilities for establishing this analytical quality. Further, the external control seems to have two different and apparently incompatible purposes: Either as *external quality assessment* which provides the laboratories with informations or as *proficiency testing* which is a governmental safety of professional workmanship.

The three element outlined above may illustrate the idea of *quality assurance* but this concept is much wider also including the *general laboratory management* which is an other important aspect of quality, but independent of the analytical quality and not intended in this presentation. A more precise definition of the object may be *analytical quality management* as this concept relates to the analytical aspects - in a broader sense - to the elements needed for the establishment of analytical quality necessary for the *medical utility* of laboratory data. Therefore, the *model for analytical quality achievement* illustrates the analytical aspects including the *medical utility* and thereby, the *quality specifications,* the *factors involved in creation of the needed quality,* and the *control system designed for securing of the specified quality* as described below for the general principles. The more specified principles used in *The Nordic Protein Project* are described in chapter 6.

3.2 Goals and Specifications for Analytical Quality

In all analytical work a measure for good and poor quality is necessary for the judgement of the obtained result. Such a yardstick may be based on certain presumptions or a more arbitrary agreement about some common feeling of quality. Within clinical chemistry, however, it has been difficult to get to a general agreement on specification of acceptable analytical quality. Only within *proficiency testing,* PT, some rules or acceptability criteria have been established on national basis in a few countries. But, even few, they are all different and cannot be used for general specifications of good analytical quality.

In the individual laboratories the general picture is an internal control system based on the preceding analytical performance without real judgement of whether this quality is good or poor.

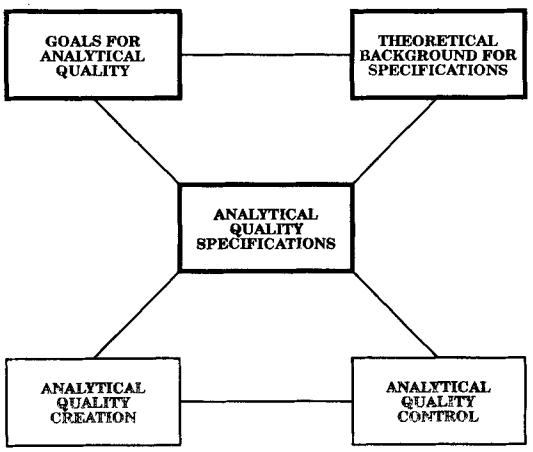

Fig. 3.2.1 *The model for analytical quality from Fig. 3.1.1 illustrating the expansion of quality specifications with goals and model for transforming into operational analytical terms.*

Therefore, a well defined purpose for the use of laboratory data, a *goal,* is needed in order to appraise analytical performance. When this is decided then the *specifications for analytical quality* can be evaluated based on more or less complicated models from which transformations of the more general goal to operative values for *analytical bias* and *analytical imprecision* can be done. These analytical quality specifications can then be used as basis for acceptance limits in control systems, whether external or internal. It must be remembered that acceptance limits in external control systems are not the same as the quality specifications.

Two main approaches to goal setting have been *the state of the art* and *medical utility,* where both can be subdivided into several subsets. All of these approaches, however, have their advantages and drawbacks - as seen from the following.

3.2.1 The State of the Art Concept

In this context the goal is bases on the current registrated analytical quality in external quality assessment schemes. There are two different approaches to the goal (i) to guarantee against unprofessional analytical performance and (ii) to improve analytical quality in general.

(i) This is the typical PT-concept where laboratories are licensed and the acceptance criteria are bases on legislation. Therefore, these criteria are outlined in order to accept the majority, e.g. 95% of the actual analytical performance. These criteria may be permanent or flexible according to the current performance. In control schemes where other criteria (biological or clinical) are also considered, they are adjusted to *the state of the art* if they do not correspond to current performance.

(ii) The other and more prospective attitude is to inspire laboratories to better analytical performance by defining the desirable quality as the quality obtained by the best performers, e.g. the best 20%. This, of course, is a guideline and cannot be used in any form for licensing.

As the goals in the two approaches are related directly to the current analytical performance the quality specifications are directly read from the decided percentage and no model or formula is needed for this. The advantage of the *state of the art* concept is that it is easy to apply and it is easy to grasp for everybody. The main drawback is that it is not related to the *clinical use of laboratory data* at all. More detailed information and critical evaluation of this concept is given in other papers, e.g. Ref. 9, 20, 21.

3.2.2 The Medical Utility Concept

Here there are several approaches to the goal setting and all are related to the clinical use of laboratory data. Two viewpoints have been dominating in the proposals, i.e. *the biological concept* and *the clinical concept* but the difference is more a question of *generalization* and *specific evaluation* than it has been a question of really conflicting approaches (9, 18, 19, 20). In reality and in spite of the many discussions there is only a vague and floating difference between the two concepts as seen from Fig. 3.2.2.

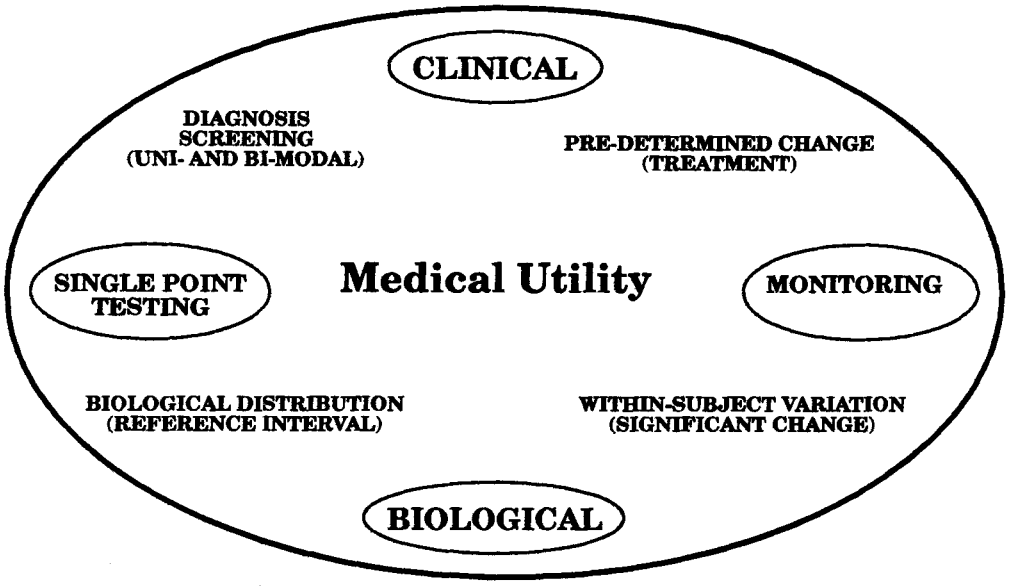

Fig. 3.2.2 Illustration of the overlapping between the biological and clinical concepts in relation to single point testing and monitoring of patients.

The most characteristic for the *biological concept* is the general background of *within- and between- subject biological variations* without specifying *the clinical situation,* whereas, the *characterization of the clinical problem* is the key-point for the *clinical concept.* In general the biological approach refers to *healthy individuals* and *the statistical H_0-hypothesis,* whereas, the clinical approach refers to *diseased* as well as *healthy individuals* and thereby to both H_0- and H_1-hypotheses. Another difference is that the *biological concept* defines models, which are applied to all quantities, whereas, the *clinical* defines the clinical situations and the quantity before the model is selected. This description, however, only covers the general approaches (26,27).

3.2.2.1 The Biological Concept.

There are two basic situations for which *biological goals* are defined (i) the influence of analytical imprecision on the measured within-subject biological variation and (ii) the influence of analytical bias and imprecision on reference intervals for healthy individuals:

(i) The goal is that analytical quality should not influence significantly on the *within-subject biological variation* and this is specified by the formula:

$$CV_A \leq 0.5 * CV_I$$

where CV_A is the analytical imprecision and CV_I is the *within-subject biological variation.* Thereby, the CV_I will only be increased by less than 12% (13). This formula can be applied to any naturally occurrent substance where CV_I is known. There are plenty of data on CV_I for many quantities in serum and urine (6).

(ii) Several proposals for "goals" based on reference intervals have been postulated, but only two are specifying the combination of analytical bias and imprecision (11, 12).

Harris (12) used a model comparable to (i) including the bias, B_A:

$$CV_A^2 + B_A^2 \leq 0.25*(CV_I^2 + CV_G^2)$$

where CV_G is the between-subject biological variation using the same principle of the total increase in the biological variance.

Gowans *et al.* (11) based the model on the concept of using common reference intervals where the population was homogeneous for the quantity. This concept is described in detail in chapter 4.

3.2.2.2 The Clinical Concept

This concept relates directly to the clinical use of laboratory data, whereby, it is the most relevant approach to evaluation of analytical quality specifications. The close relationship to the clinical use, however, makes it less general - as each clinical situation is particular and every clinical situation must be evaluated separately. The three main approaches are (i) the pharmacokinetic approach, (ii) the opinions of clinicians and (iii) clinical situations (strategies):

(i) *The pharmacokinetic approach* was evaluated by Fraser (5, 7) in relation to drug monitoring of patients. It relates to therapeutic interval or to sampling intervals in direct relation to the turn-over rate of the drug. The concept may be considered as something between the biological and the clinical concepts due to its general character and its relations to specific clinical situations as well.

(ii) A questionnaire with a number of simple case histories is sent to a number of clinicians in the *opinion of clinicians* concept. For each case and each quantity the value or the change for which the clinician would react is registrated and a fraction (often the median) of the answers is used for calculations of the quality specifications. This approach was introduced by Barnett (1), it relates directly to the use of data, but has some drawbacks. The best evaluations are performed by Linnet (23) and by Thue et al. (24).

(iii) The concept of *clinical situations (strategies),* investigates specific clinical strategies where an outcome can be quantitated on objective terms, such as the fraction of misclassifications in a decision situation (false negatives and false positives) or economically, e.g. in a screening situation, and even in monitoring of patients. When such clinical strategies can be described in detail, then the quality specifications can be elaborated according to models. A number of models and evaluations of clinical situations are described in two NORDKEM-projects (21, 26, 27). The monitoring model was introduced by Fraser *et al.* (10) and further evaluated by Lytken Larsen *et al.* (24) and by Hyltoft Petersen *et al.* (17).

3.2.3 Elements of Goal Setting and Quality Specifications

The *nomenclature* within goal-setting and quality specifications may seem confusing and sometimes contradictory. It is not possible to solve these problems here, but some of the aspects can be cleared.

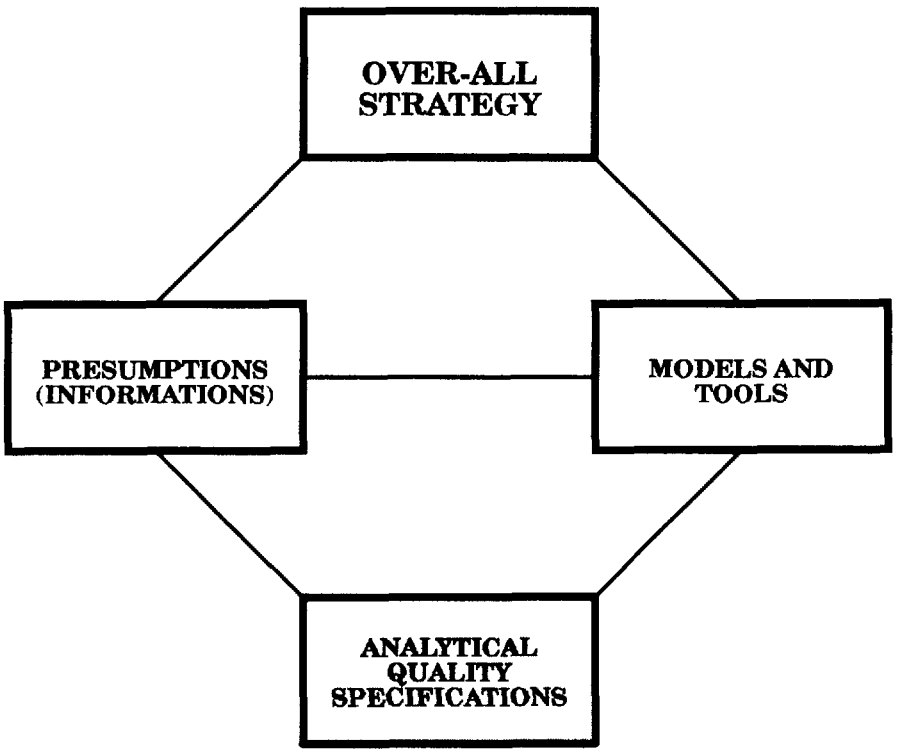

Fig. 3.2.3. An alternative model for describing the evaluation of analytical quality specifications.

Thus, *analytical quality specifications* always refer to defined values of *allowable/desirable/acceptable/needed* values for CV_A and B_A (on an operational level) for a defined quantity. Sometimes *goals* are used in the same sense, but most often in a more general meaning. Further, a *clinical goal* will include sampling error as well as other preanalytical factors from which the analytical quality specifications can be isolated when the other values are known or considered negligible.

The basic purpose for specifying the *allowable/desirable/acceptable/needed* values for CV_A and B_A has to be defined first, whether it is based on the state of the art, biology or clinic. This may be regarded as *The Over-all Strategy,* from which all other steps depend. It is described in general words and could be regarded as the *Overall Aim* or the *Overall Goal.*

In order to realize this over-all strategy both informations and models are needed. The informations must be related to the purpose, e.g. registration of current analytical performance, estimations of biological variation and knowledge of a clinical strategy. In clinical strategies further informations are needed. Then models or other tools are needed for the estimation of the analytical quality specifications. The process may be illustrated as shown in Fig. 3.2.3:

For the over-all strategy of sharing common reference intervals a separate chapter (four) is demonstrating the whole process, which is used further in chapter 6 and 7 in this book. Over-views are given by Fraser *et al.* (9), Hørder (21), deVerdier (26), deVerdier *et al.* (27), Hyltoft Petersen and Hørder (20), and Libeer (22).

3.3 Creation of Analytical Quality

Creation of quality is a complicated process involving a great number of factors, most of them individual for each quantity. Therefore, only the principles can be discussed here and a few examples can be used for illustration of the principles.

Today, most of the working out of methods within clinical chemistry is performed by the manufacturers, so the individual laboratory's problem is mainly to choose the method or rather the system from a company. This makes it easier but at the same time more complicated as it is difficult to get all relevant informations from the company. Therefore, the laboratory has to believe in the producer or published evaluations if it cannot evaluate the method itself.

Much work is invested in internal and external control by laboratories and national control organizations, whereas, only little time and money is used for creating the quality in the laboratory as well as on the national level. The quality is therefore just what the producers deliver. It cannot be better, but it can be worse in laboratories with poor performance. Recently the increasing interest for accreditation of laboratories according to EN 45001 or certification according to the ISO 9000-series has focused on the analytical aspects of quality, but much work has yet to be done on national and international level as well as in each individual laboratory.

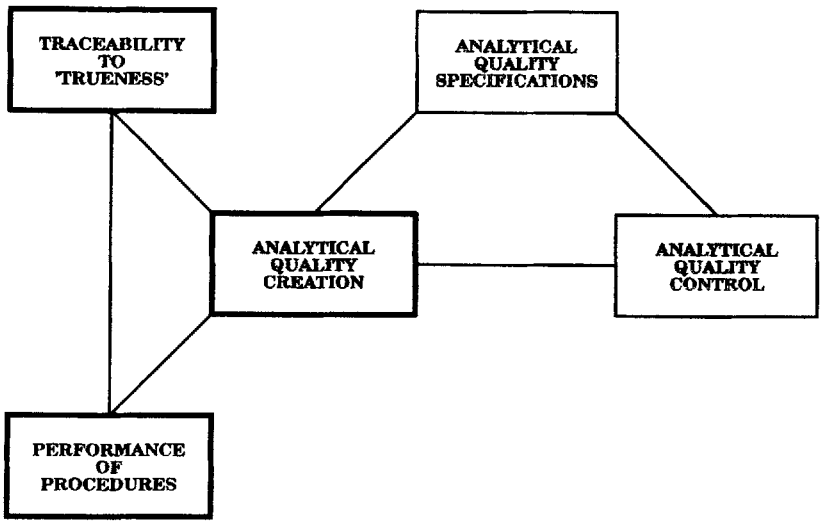

Fig. 3.3.1. The model from Fig. 3.1.1 illustrating the expansion of quality creation with traceability to "trueness" and performance of procedures.

As seen above, specifications for the needed analytical quality can be and have been stated for a number of quantities. These specifications must be the minimum level of quality to look for when buying methods, instruments etc. But all can benefit from better quality. So, if it is not too expensive, then the advantages from better quality are considerable as described for imprecision (8). In order to structure the problems the splitting up of the *sources of quality* in *standardization* with *traceability to "trueness"* and *methods* or *performance of procedures* is illustrated in Fig. 3.3.1. The standardization determines the common bias to all measured samples (patient and control) and the method determines individual bias (due to interfering substances, contamination and matrix) as well as imprecision, presuming error free performance.

In the following, commercial production of calibrators, equipments, reagents etc. is assumed. If some reagents or all are produced locally, then the laboratory substitutes for an external producer.

There are *external* and *internal* sources of quality and there are *permanent* as well as *variable factors* as earlier described by Hyltoft Petersen *et al.* (16) and by Libeer (22) and illustrated in Table 3.3.1.

Table 3.3.1 **SOURCES OF QUALITY**

	EXTERNAL FACTORS	INTERNAL FACTORS
PERMANENT FACTORS	**METHOD AND STANDARDIZATION**	**IMPLEMENTATION**
VARIABLE FACTORS	**BATCHES**	**PERFORMANCE**

It is important to know the sources of quality and where they come from - for which the producer is responsible and for which the laboratory. This is important, both for generating the quality of the procedure in the laboratory, where the quality is limited by the quality of the bought product, and for the internal as well as the external control as described below.

The external factors stem from several elements of different nature and relate to standardization as well as to the method and for the permanent external factors, both to the producers choice of basis for standardization and analytical principle and to the developments performed by the producer. Further, the variable external factors relate to batch-variations in calibrator and reagents as well as utensils as shown in Table 3.3.2:

Table 3.3.2 **EXTERNAL SOURCES OF QUALITY**

	PERMANENT FACTORS		VARIABLE FACTORS
	Principle Level of Quality	**Producer's Developments**	**Commercial Production**
Standardization	**Basis for Standardization (Traceability)**	**Calibration Material and Transfer of Concentration Values**	**Batch Variation**
Method	**Analytical Principle**	**Working out of Method, Equipment and Reagents**	**Batch Variation**

The *basis for standardization* may be *a definitive or reference method* or *the pure chemical component* or *an international reference preparation* dependent on the quantity under consideration. The producer is responsible for the choice of basis and for *the traceability* back to this. Further, he is responsible for the calibration material and the transfer of values to this. The uncertainty of the value(s) must be small compared to the quality specifications for analytical bias with a narrow confidence interval for location of the "conventional true value". The bias of the first part of this process is permanent, whereas, the production of calibrators and assignment of values result in minor variations, which should be kept very low, and still negligible compared to the analytical quality specifications. It is clear that the calibration material should be without matrix effects in the method.

The *analytical principle* determines the principle quality and the principle problems as limitations are inherently defined. Examples are *the Jaffe principle* for measurements of S-Creatinine, where presence of e.g. Glucose and Ketone bodies result in unspecific reactions, or *isotope techniques,* where the number of counts registered sets a limit for the obtainable imprecision. These effects may be reduced during *the working out* of the method performed by the manufactor. As for the calibrator, the batch-to-batch variation in reagents and utensils cause changes in bias. This effect is less when pure chemicals are used, but may be considerable for the use of polyclonal antibodies.

All these factors are outside the control of the individual laboratory which can only sometimes observe the changes through its control systems (see below). Further, the influence of interfering components may be reduced by measuring of a individual blank or when the influence is known, by a correction procedure, e.g. contamination from haemolysis by measuring S-Hb and correction by a factor.

The *internal sources of quality are permanent by implementation* of the procedure in the laboratory. Here the choice of *calibration function* determines a permanent common bias, and *the setting up and working out of the performance* including *instructions* determines the *individual bias-values* and the *inherent imprecision.* The *variable factors* are the *reproducibility* which depends on the *training, maintenance* and *monitoring of the performance* etc. as illustrated in Table 3.3.3:

Table 3.3.3 **INTERNAL SOURCES OF QUALITY**

	PERMANENT FACTORS	VARIABLE FACTORS
STANDARDIZATION	**CALIBRATION FUNCTION**	**REPRODUCIBILITY OF CALIBRATION FUNCTION**
METHOD	**SET UP AND WORKING OUT INSTRUCTIONS**	**TRAINING, MAINTENANCE MONITORING OF QUALITY**

Another and more systematic description of the elements of bias and imprecision (reproducibility standard deviation) is worked out by Dybkær (4) who further gives a vocabulary for the terms according to VIM and ISO.

The process of creating the analytical quality within the laboratory is a process of analytical quality management which has been described in detail by Westgard *et al.* (31) who go through the whole optimization process with check of each step in the procedure. In this procedure it is important to use the analytical quality specification for the quantity (see above) as they are objective parameters for the optimization process. However, it should be remembered that "space" should be left for more variation in the routine and for the control system which can only disclose greater deviations from the stable performance (see below).

As mentioned above efforts to prove analytical quality on a national or international level have been scanty. The effect, however, of a common calibrator as described in chapter 5 is tremendous as illustrated in chapter 6. Therefore, on international basis reference preparations should be available for establishment of national reference preparations or calibrators as intended in a NORDKEM project (2). Further, co-operation within regions on evaluation of new methods should be established.

3.4 Control of Analytical Quality

3.4.1 General Aspects of Control

As mentioned earlier the analytical quality cannot be improved by the control itself, only through the correction and prevention of the errors disclosed by the control system. And the quality cannot be better than the inherent stable performance, whatever the type of control system. Therefore, the analytical quality depends on proper methods traceability of concentration values etc. as described above.

Sources of errors are external and internal as well as permanent and variable as for the sources of quality (Table 3.3.1). So it is necessary to design the control systems according to the relevant problems as described below. Further, the control system should be worked out according to the analytical quality specifications defined by the over-all strategy (section 3.2).

It is important to distinguish between the possibilities for error detection by external and internal control systems. The external should disclose errors in the individual laboratory's stable performance, i.e. the chosen method with its standardization and implementation, whereas the internal control should disclose deviations from this stable performance. Therefore, the external system is mainly a registration of the stable situation and if the quality is unacceptable then the method or the calibration should be changed. The external system thus deals with the stable analytical bias, but in some quality assessment schemes it also deals with registration of imprecision in order to assist the laboratories in their internal system (but in principle this is superfluous).

The two types of external control systems are *the open system for quality improvement* and *proficiency testing,* PT, for licensing of laboratories. The open system may be a valuable tool for general quality improvement, whereas PT in spite of its intentions of protecting against unprofessional performance, has a tendency of preserving the quality at a certain level. Thus, the PT will not be dealt with here.

The internal control system should be able to distinguish between external and internal errors.

A third type of control system proposed by Adam Uldall, Herlev University Hospital (personal communication) is a system to control the manufacturers products. Such a system would solve the external problems for the laboratories. It would involve a close co-operation between laboratories within areas or at an international level. A single project on such a system is described by Hyltoft *et al.* (15).

3.4.2 "Fail-Safe" and Problem Related Control

It is better to solve a problem without control than to control without solving the problems could be the title of this clause. Again, if a problem is known efforts should be used to prevent its occurrence. By such a *fail-safe* procedure repeated work is prevented. It is easier, and you do not get frustrated by frequent trouble-shooting procedures and it is more economical. If you cannot prevent the occurrence of the problem, however, and it is not possible to change the procedure, then it is important to design your control system so that it will detect the error with a high probability or you must decide whether you will accept the size of the error, which means that your control system should not reject it. The problem is well known from measurements of hormones with commercial kits. In relation to batch-change the concentration level of the locally produced control materials suddenly changes (and the producer claims that nothing has been changed, and you are the only to complain). Then you must decide whether you will discharge the kit and stop production or you will accept the change. If you accept the change then you must readjust the control system accordingly as it does not help to reject a greater part of the runs. It only produces extra work, extra costs and frustrations.

Control systems are based on control materials and design of control rules as illustrated in Fig. 3.4.1

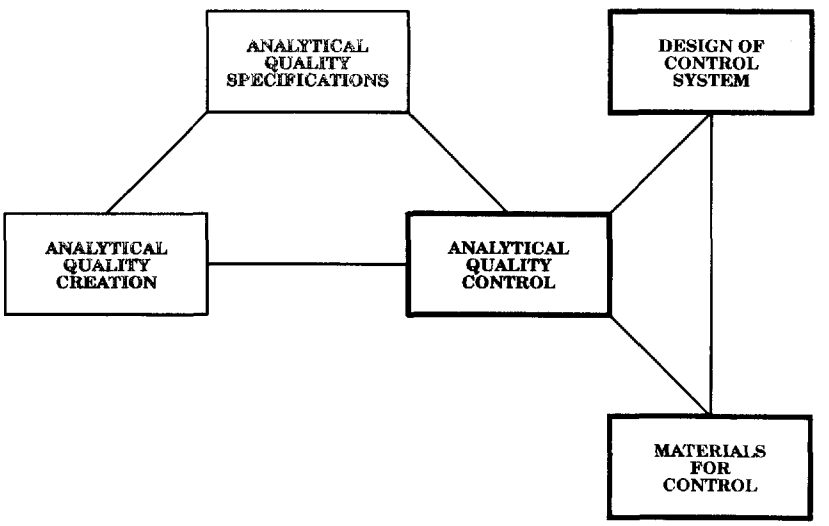

Fig. 3.4.1. The model from Fig. 3.1.1 illustrating the expansion of control with design and materials.

The design of system and the materials for control must be co-ordinated. Control of standardization (the common bias) must be performed with materials which approximate the patient matrix as close as possible, and with traceable assigned concentration values, and the design should be repeated measurements over several days in order to reduce the confidence interval around the measured mean. Control of individual bias (unspecificity) should be with sets of materials which are identical - two and two - except for the interfering component for which the procedure should be controlled. Here the measurements of each pair should be performed in the same run (to avoid between-run variation) and in several replicates in order to reduce the confidence interval around the mean difference. Control of the laboratory's analytical stability, usually does not need expensive control materials, but the reconstitution of freeze-dried materials must be very reproducible.

3.4.3. External control

External control systems should be quality improving, i.e. the registration of errors should be followed by an evaluation with guidelines for improvements. These guidelines could be advise for change of method, or in the case of laboratories using the same method advise could be given by one of the others using the same method for comparison of performance of certain steps in the procedure. Another model could be that the EQAS-organizers recommend *optimal procedures for quantities on different instruments* as DAKO for proteins. External control needs not to be frequent as it estimates the stable performance. Once a year might be appropriate. The stability is monitored in each laboratory anyway. The individual laboratory, however, should have possibilities for getting the "control materials" and advise at any time (when needed or if in trouble).

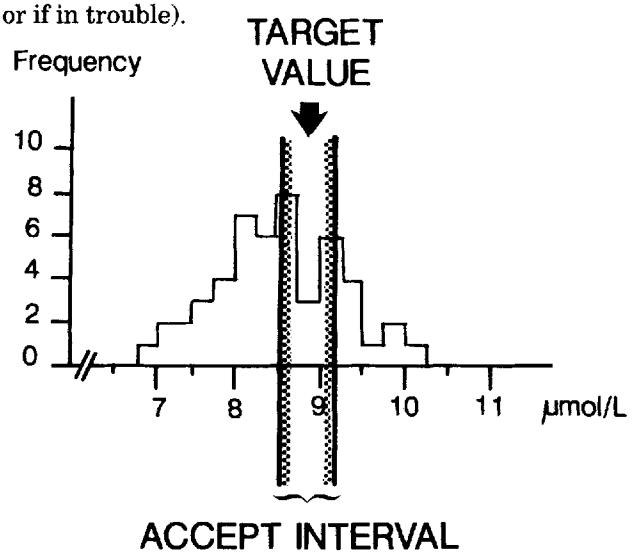

Fig. 3.4.2. Illustration of presentation of control results with indication of target value and acceptance limits.

The presentation of results are usually given in the form of histogrammes with indication of the laboratory in question. This form gives a good overview, but the target value (conventional true value) and the quality specifications for bias should be indicated as illustrated in Fig. 3.4.2.

Individual presentation of each laboratory's data may give better information as illustrated in Fig. 3.4.3:

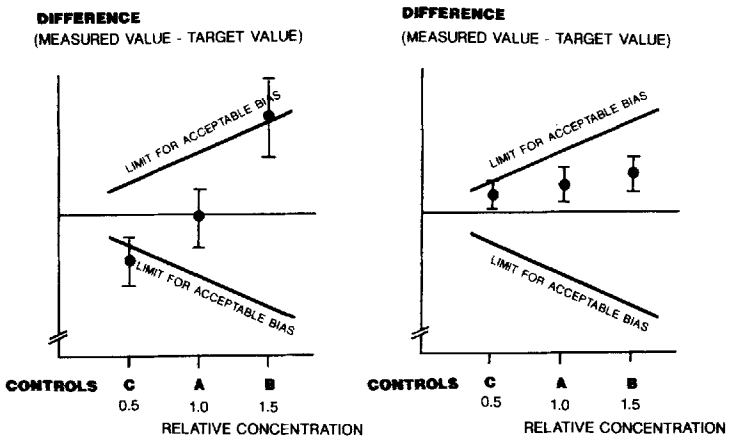

Fig. 3.4.3. *Bias-plot illustrating results for three control samples from a laboratory. Accept limits are indicated and each mean value is shown with it 0.90 confidence interval. From Hyltoft Petersen et al. with permission. (16).*

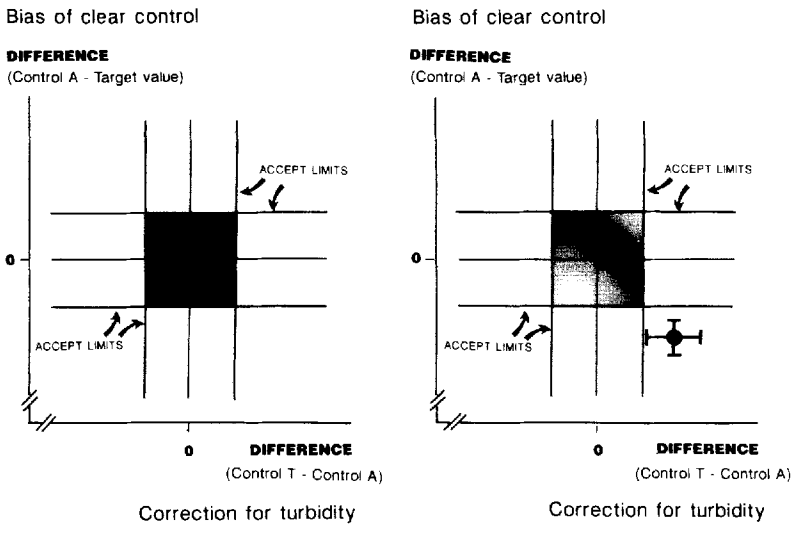

Fig. 3.4.4. *Double bias-plot illustrating the "common bias" and the "individual bias", here from turbidity. The accept limits are indicated. From Hyltoft Petersen et al. with permission (16).*

In the individual presentation it is further possible to combine informations about the standardization/calibration (common bias) and unspecificity (individual bias) when control materials are designed accordingly as illustrated in Fig. 3.4.4.

3.4.4. Internal Control

For internal control the statistics are very important for the design as demonstrated by Westgard, Groth, deVerdier and Aronsson in several publications (e.g. 28, 29, 30). The probability of false rejection, P_{fr}, and the probability of detection of errors, P_{ed}, of certain sizes are decisive for the control system. Systematic errors are change in bias from the stable performance and random errors are increases in standard deviation from the inherent imprecision. P_{fr} depends on the control rules used and on the number of replicates of the control in the run, whereas, P_{ed}, further depends on the type of error and its size.

The control rule "multi-rule Shewhart" (30) is relevant for multi channel instruments . For batch-wise analyses mean-rules are excellent for detection of systematic errors and range-rules are excellent for detection of random errors.

Most important, however, it is to minimize the number of reject-signals by working with very low P_{fr} (and fail-safe performance). For a quantity, run once a day, with a rule with $P_{fr}=0.001$ a false rejection will occur only once every third year. On the other hand it means that a rejection is identical with an error. This should be investigated by trouble-shooting and correction of the error (before a new run) and steps should be taken to prevent the same error to occur in the future (fail-safe).

An early warning of increasing systematic errors (or minor persistent systematic error) can be obtained by use of the Cusum-rule (30). Error-signals obtained by this rule should not lead to rejection, but to trouble-shooting by the first opportunity.

The registration of the actual analytical performance is difficult if based on control results as the control results are used in the monitoring of the same performance. Therefore, an independent pool (not used for validating the results) should be measured as an ordinary patient sample in order to get an unbiased estimate of the current imprecision.

In relation to the control system a trouble-shooting scheme should be designed based on experience from previous errors and common sense. New points should be added when new errors are observed. If the system leads to prevention of some of the errors these can get a lower priority in the scheme. It is important to evaluate the informations available from external as well as internal control in order to keep the quality and to improve it where possible in relation to the quality specifications.

3.5 Analytical Quality Management

Co-operation between scientists involved in the three different areas of analytical quality (Fig. 3.1.1) has been scanty until now. The model for analytical quality achievement, however, stresses the need for such a co-ordination of the many activities within each of the fields in order to obtain the sufficient analytical quality in all the clinical chemical laboratories. To our knowledge only two examples involve all three elements. One is the American *National Cholesterol Education Program* where the specifications for imprecision and bias are 3% and ± 3% respectively. The other is the *Nordic Protein Project* for nine plasma proteins which is described in detail in chapter 6, and with the additional establishment of common reference intervals for the proteins as described in chapter 7. The model may be extended according to the expansions described above as illustrated in Fig. 3.5.1:

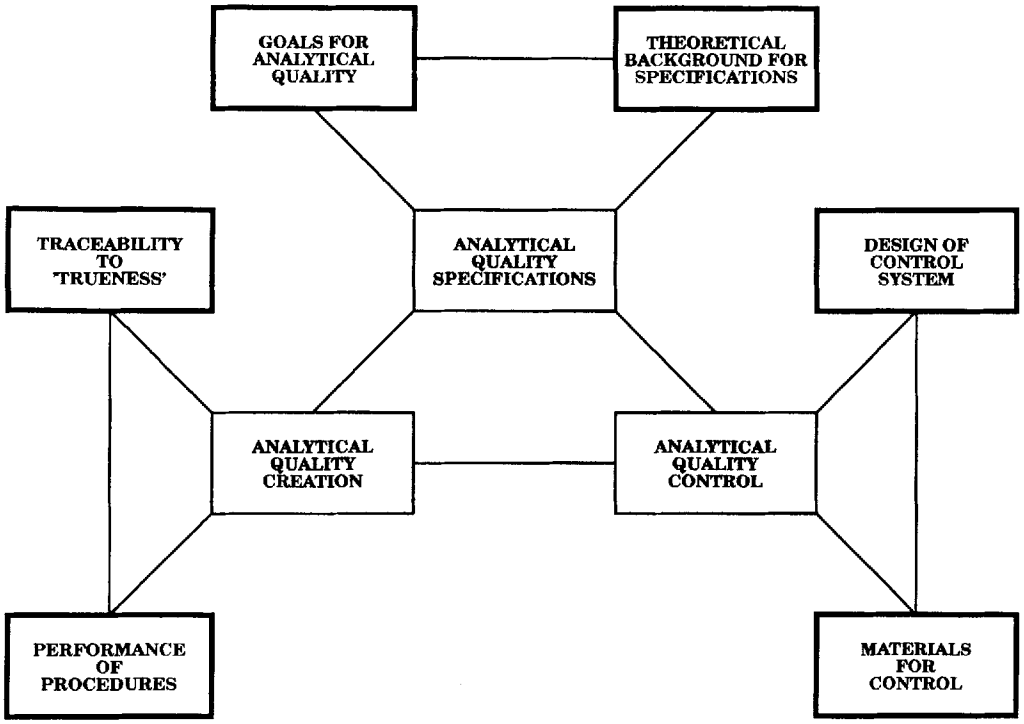

Fig. 3.5.1. *Extended model for analytical quality.*

New efforts for expanding the field of national EQAS-organizers (standardization, reference intervals) may, however, indicate that such projects (or even established co-operation with relevant groups) may occur within short as suggested by Libeer (22) and as proposed by the Nordic EQAS-organizers in chapter 8.

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