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Opinion Paper

Collective opinion paper on findings of the 2009 convocation of experts on quality control

David Burnett[1], Ferruccio Ceriotti[2], Greg Cooper[3,*], Curtis Parvin[3], Mario Plebani[4] and James Westgard[5]

[1] Lindens Lodge, Bradford Place, Penarth, UK
[2] Diagnostica e Ricera San Raffaele, IRCCS H. S. Raffaele, Milan, Italy
[3] Quality Systems Division, Bio-Rad Laboratories Inc, Hercules, CA, Plano, TX, USA
[4] Department of Laboratory Medicine, University Hospital of Padova, Padova, Italy
[5] Westgard QC, Madison, WI, USA

Abstract

On May 28–29, 2009, a number of medical laboratory opinion leaders, pathologists and biochemists met in Sitges, Spain to discuss issues of interest to medical laboratory professionals. The meeting was sponsored by Bio-Rad Laboratories Inc. (Hercules, CA). Over 40 persons representing Austria, Belgium, Czech Republic, Finland, Germany, Great Britain, Israel, Italy, Netherlands, Portugal, South Africa, Spain, Sweden and the US participated in the 1.5 days meeting.
The intended purpose of the convocation was to give medical laboratory professionals from different countries and backgrounds an opportunity to share ideas, concerns and experiences in five areas of interest of the sponsor. These areas of interest included:

- a requirement for medical laboratory accreditation across Europe
- uncertainty of measurement in a clinical laboratory setting
- application of Six Sigma values to characterize laboratory quality
- effects of analytical errors on patient care and outcomes
- harmonization of allowable total error (TEa) specifications

The convocation began with a keynote speech by Dr. James Westgard on ''Managing quality vs. measuring uncertainty in the medical laboratory''. Dr. Westgard's presentation was thought provoking and called into question the utility and practicality of using uncertainty in a medical laboratory setting. This journal contains a companion article written by Dr. Westgard on this topic. After the keynote speech, the meeting adjourned into five discussion groups and reconvened the next day to hear the outcomes of the discussions by each of the working groups. This article provides a synopsis of the reports from each working group.
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Keywords: accreditation; allowable total error; measurement uncertainty; patient outcomes; Six Sigma.

*Corresponding author: Dr. Greg Cooper, Quality Systems Division, Bio-Rad Laboratories Inc, Hercules, CA, 3201 Technology Drive, Plano, TX, USA
E-mail: Greg_Cooper@bio-rad.com
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Introduction

This collective opinion paper is intended to document the proceedings and findings from a round of discussions held in Sitges, Spain on May 28–29, 2009 on accreditation, measurement uncertainty, the effect of analytical error on patient outcomes, Six Sigma metrics and harmonization of allowable total error (TEa) specifications.

Results

Pan European Medical Laboratory Accreditation: Pros and Cons

David Burnett PhD (Consultant, Lindens Lodge, Bradford Place, Penarth, Great Britain)

With the advent of a greatly expanded European Union (EU) (27 countries) and an increasing number of citizens moving within Europe for both work and individual healthcare, the requirement for transferability of results of laboratory investigations becomes paramount. The accreditation of medical laboratories provides an important mechanism whereby this can be ensured. There already exists an ''international model'' of proven value, which invokes the use of ISO standards in the accreditation and regulation of testing/calibration laboratories, which is increasingly being applied to medical laboratories worldwide. The model has three elements and five stages (A–E) (Figure 1).

The first and crucial element is an **internationally recognized standard.** Prior to the publication of the sector specific ISO 15189 (1) in 2003, medical laboratories sought to be assessed against the generic standard ISO 17025 (2).

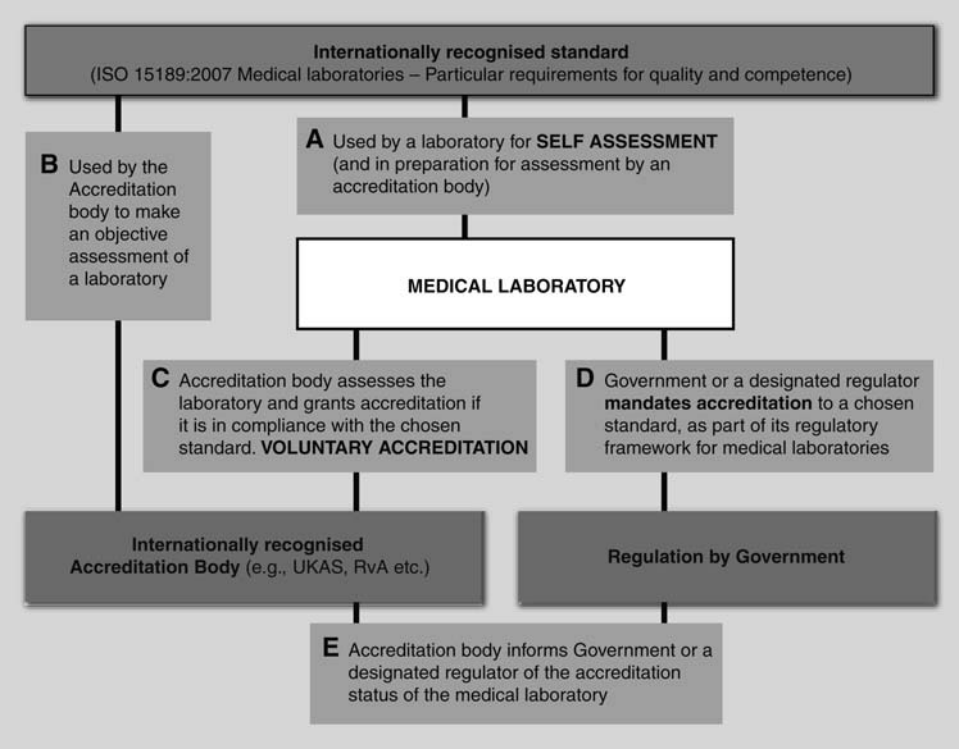

Figure 1 International model for standards, accreditation and regulation.

However, a recent survey of professional societies and National Accreditation Bodies (NABs) indicated that the sector specific standard is now the first choice (personal communication, Wim Huisman); for laboratories undertaking ''self-assessment'' and preparing for assessment by an accreditation body (Stage A), and for NABs making an objective assessment of a medical laboratory (Stage B).

The second element is an independent and **internationally recognized accreditation body** that assesses the medical laboratory. If the laboratory is working in conformity to the standard, accreditation is granted (Stage C). If this is the end point of the model, the process is termed ''voluntary accreditation''. Starting January 1, 2010, the EU Regulation 765/08 establishes a legal framework for accreditation services across Europe. This framework establishes rules for the organization and operation of accreditation of conformity assessment bodies (CABs). (For purposes of accreditation, medical laboratories are regarded as ''Conformity Assessment Bodies'' or CABs.) The regulation reinforces the role of the European cooperation for Accreditation (EA) (www.european-accreditation.org) in supporting and harmonizing the implementation of accreditation in the voluntary and regulated sectors. Each of the 27 member states of the EU is required to designate a single NAB. EA as a regional co-operation and its constituent NABs are also members of the International Laboratory Accreditation Co-operation (ILAC) (www.ilac.org). ILAC has a similar role to EA at an international level.

An NAB in full membership of EA and/or ILAC is required to operate in conformity with ISO 17011 (3), and thereby is a signatory to a multilateral agreement (MLA). This means the accreditation of a medical laboratory by one NAB is recognized by all countries who are signatories to the MLA.

The third element is **regulation by government.** This is where government or a designated regulator mandates accreditation to a chosen standard, as part of its regulatory framework for laboratories (Stage D). Finally, the accreditation body informs the government or designated regulator of the accreditation status of a laboratory and provides evidence of fulfillment of the regulatory requirement (Stage E). This is often called ''mandatory accreditation'', but it is important to recognize that the government ''mandates'' accreditation, not the accreditation body. At the present time, only France (4) mandates accreditation for medical laboratories. However, some other countries require accreditation to ISO 15189 for specific activities. For example, all blood bank laboratories in the Republic of Ireland must operate in accordance with ISO 15189 and also must comply with additional requirements relating to blood traceability and haemovigilance (notification of serious adverse reactions and events).

What is the value of laboratory accreditation?

The answer to this question depends on whether you are a member of the laboratory staff, a user or purchaser, or a

regulator. However, accreditation is important to all these stakeholders in that it represents formal recognition that a medical laboratory has been independently assessed by an authoritative accreditation body in the five key areas (5) concerning:

- Competence and experience of staff
- Integrity and traceability of equipment and materials
- Technical validity of methods
- Validity and suitability of results
- Compliance with appropriate management systems standards and is found to be competent to carry out its services in a professional, reliable and efficient manner

A further advantage to participating in accreditation is that a laboratory's management will benefit not only from identification of areas that need improvement, but that if members of staff also act as assessors, they will bring back to their own laboratories ideas for improvement.

The reasons for medical laboratories to seek recognition through accreditation range from a commercial imperative, such as, it being a precondition for a contract or license to practice, to laboratories wishing to practice in accordance with accepted norms. It should not be seen as a ''designer label'' but rather as assurance that the needs and requirements of the user will be met.

Finally, as results from medical laboratories are used in the diagnosis and treatment of patients, it follows that if patients are increasingly mobile in their receipt of healthcare, then HbA1c measurements for example, in one country must be comparable with those in another if a patient's needs and requirements are to be met. Requirements in ISO 15189 for calibration, traceability, internal quality control (IQC) and participation in external quality assessment schemes (EQAS) address some of the issues of transferability. However, other professional issues remain to be resolved, such as, units in which results are reported and the reference intervals against which the result is interpreted. Furthermore, the issue of traceability remains unresolved and, although the European Directive 98/79/EC on ''in vitro medical devices'' requires the use of metrological standards, there is no requirement for the use of recognized international reference standards or, with few exceptions, consensus among manufacturers.

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and laboratory accreditation

Back in 1999, the IFCC, in a policy statement on clinical laboratory accreditation (6), indicated that ''It is in the interests of patients, of society, and of governments that clinical laboratories operate at high standards of professional and technical competence…'' and that ''It is in the interests of competent laboratories that their competence is verified through a process of inspection, comparison against appropriate standards, and public affirmation of their good standing. Accreditation is an external audit of the ability of a laboratory to provide a high quality service''.

In June 2007, the IFCC published a further document (7) that states ''… an International Standard, ISO 15189:2003 (with minor revisions in 2007), has been published, that details the requirements for quality and competence in the medical laboratory. The IFCC recognizes that this standard encompasses all the assessment criteria specified in the policy statement and as such should form the basis for the accreditation of laboratories''. It then recommended some key principles to be followed by NABs accrediting medical laboratories:

- The scope of accreditation should normally cover a substantial majority of the overall service provided by the laboratory within a medical field.
- It is recognized that some accreditation bodies cannot enforce this. However, these NABs should encourage medical laboratories to cover the majority of their examinations within each medical field in their scope.
- The ''flexible'' scope of accreditation is preferred. The laboratory shall maintain a list of all individual examinations for which it is accredited.
- At the first level, the scope of accreditation shall be defined as a medical field or discipline, such as Clinical Chemistry, Hematology, Immunology, Microbiology, etc. It is accepted that on national level there may be differences in the way NABs and the corresponding medical professions define the disciplines.
- For each medical field mentioned in the scope, it is expected that the laboratory provides a full service. This includes all pre-examination, examination and post-examination aspects that are essential to provide an effective and efficient laboratory service to patients. Within this, it is expected that a medical laboratory is able to demonstrate its competence in interpreting the results of the examinations performed.

Other major organizations have supported the value of laboratory accreditation. A recent joint World Health Organization-Center for Disease Control (USA) conference on Health Laboratory Quality Systems (8) confirmed the importance of accreditation by stating that ''National Reference Laboratories should seek to be accredited by international bodies to internationally accepted standards. Other laboratories will require a staged or phased approach to achieve appropriate accreditation''. This staged approach is important for countries with less developed laboratory services. However, ''more advanced and national reference laboratories'' should be ''encouraged to aim at meeting internationally accepted standards such as ISO 15189''.

OECD Guidelines for Quality assurance in Molecular Genetic Testing (9) published in 2007 set out ''Principles'' of quality assurance systems on molecular genetic testing. It recommends that ''Governments and regulatory bodies recognize that accreditation of medical laboratories is an effective procedure for assuring quality''.

What are the problems of laboratory accreditation?

Some of the problems regarding laboratory accreditation are perceived rather than real. For example, it is still often said by laboratory professionals that the actual process of accreditation is very expensive. ISO 15189 was written by medical laboratory professionals and is regarded as the minimum standard for the proper functioning of a medical laboratory. If that is the case, then laboratories, whether in the public or private sector, have a responsibility to operate in compliance with the standard, and the costs of doing so are necessary costs. In comparison to the costs of compliance, the actual accreditation costs are relatively small. The funding of NABs varies from country to country, but they are essentially non-profit organizations, and as such should strive to keep the costs of accreditation as low as possible and develop equitable ways of charging for their services. Most laboratories would find it easier to have an annual charge than a large fee at the time of accreditation.

There are, however, a number of valid concerns that need to be addressed. If laboratories are to continue to participate in accreditation, then the process must be equivalent from country to country and there should be ''a level playing field''. There are two sources of concern. The first relates to additional requirements, which may derive from regulation or from the conduct of accreditation processes.

Regarding the first concern, a recent paper states ''Germany is perhaps the only state in the EU that has official and mandatory requirements for clinical laboratories. The German Physicians Board (Bundesärzetekammer; BÄK) has published requirements for day-to-day imprecision and error of measurement'' (10). For this discussion the important question is not the derivation of the requirements, but rather that it might make accreditation in one country easier or more difficult to obtain when such regulatory requirements are in place. The last section of these proceedings deals with harmonizing TEa specifications.

The second concern relates to the scope of accreditation, the conduct of assessments and subsequent decisions based upon those assessments. These are valid concerns and the dialogue required to deal with these problems is already taking place in the medical laboratory subcommittee of the EA Technical Committee on Laboratory Accreditation. This subcommittee is composed of representatives from the professions and NABs. All the NABs in the EU are represented, but not many representatives from the professions participate at the present time. The issue of the ''scope of accreditation'' has been discussed and led to the publication of the IFCC document mentioned above and to an EA paper EA-2/15 (11) on flexible scopes. The majority of medical laboratories will benefit from accreditation using a flexible scope, but a major limitation of the EA paper is in Section 3 Constraints, where it states ''it should be noted that it is not mandatory for EA members (NABs) to accredit flexible scopes''. This constraint is not reconciled easily with the quality management principle of ''customer focus'' (12), nor is it made any easier by the EU Regulation765/08 mentioned previously.

A further aspect of the concern regarding scope is that a laboratory may apply for and receive accreditation for a very limited number of the examinations that it actually performs. Not only does this contravene the spirit of ISO 15189 which looks to a laboratory to meet its requirements for the whole of the service offered, but also it can lead to intentional or unintentional misrepresentation with regard to its competency to provide a service appropriate to the needs and requirements of its users. This is neither in the interests of accredited laboratories nor accreditation bodies.

Further issues that are ongoing include questions such as: Do assessors in different countries interpret the standard in the same way? How are non-conformities classified? Is the time allowed for discharge of non-conformities similar in different countries? Are assessments focused not only on the examinations, but as well on the consultative and interpretive aspects of the service? Do assessors consider not only the mechanics of the quality system, but also its outcomes in terms of continual quality improvement? All these issues have the potential to affect whether the accreditation certificate granted in one country is comparable to that in another. As medical laboratory services become more specialized, there may be certain areas where assessors with sufficient knowledge are not available in a specific country, and exchange between countries is needed.

What should be done to encourage medical laboratory accreditation in Europe?

In the overwhelming majority of countries in the EU, accreditation is voluntary. However, there are a number of European Directives that have a direct impact on the work of medical laboratories. Also, in the future there might be EU directives concerning quality and competence of medical laboratories. At present, with the exception of France, accreditation of medical laboratories in the EU is voluntary. However, it is important that all professional bodies take a major role in encouraging individual members to be involved in accreditation by:

- Being members of their National Standards Bodies and thus being eligible to be represented on ISO/TC 212. This committee is responsible for review and revision of those standards which impact the provision of medical laboratory services (in particular ISO 15189).
- Participating in the work of their NABs and representing them on the EA subcommittee for medical laboratories.
- Encouraging members to become assessors for their NABs.

Professional bodies themselves should also seek to:

- Influence the decisions made by government in regulating medical laboratories
- Create interpretative guidelines for aspects of international standards
- Be involved in the training of assessors

The need for and the practicality of measurement uncertainty

Ferruccio Ceriotti MD (Diagnostica e Ricera San Raffaele, IRCCS H. S. Raffaele, Via Olgettina 60, Milan, Italy)

ISO 15189 states in subclause 5.6.2, ''The laboratory shall determine the uncertainty of its measurements, where relevant and possible. Uncertainty components which are of importance shall be taken into account'' (1). In addition, the ISO standard requires that clinical laboratories provide this information upon request, and that the laboratory information systems record measurement uncertainty together with the measurement result. The concept of measurement uncertainty is relatively new in clinical laboratory sciences. This concept was formally defined by the Bureau International des Poids et Mesures (BIPM) in 1981 (13), but there is not unanimous acceptance of it by clinical laboratories (14, 15). Measurement uncertainty, according to the International Vocabulary of Metrology, is defined as a ''non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used'' (16). In brief, it can be stated that the result of a measurement is only an approximation (or estimate) of a true value of the measurand, and thus is complete only when accompanied by a statement of the measurement uncertainty. However, the application of this concept to the results provided by a clinical laboratory may not be so straightforward.

How can we calculate the uncertainty of our measurements?

The basic reference is the *Guide to the expression of uncertainty in measurement* (GUM) (17), but several other documents are available (18–21), and a specific ISO document is under development (22). The GUM proposes the so-called ''bottom-up'' model to calculate the uncertainty. The model requires the identification of every source of variability that can affect a measurement, the quantification of the variability introduced by each and every source performing ad hoc experiments (type A – evaluated by statistical methods) or using available data (type B – evaluated by other methods, e.g., manufacturer declaration of the uncertainty of the value assigned to the calibrator); and the calculation of the combined standard uncertainty. Finally, the expanded uncertainty should be calculated multiplying the combined standard uncertainty by a ''coverage'' factor (usually 2).

Is the measurement uncertainty useful?

Measurement uncertainty is certainly useful for a number of reasons. It gives information about the quality of the measurements; it might help in comparing the metrological quality of several clinical laboratories (among accredited clinical laboratories, provided that it is calculated in the same way); it helps in interpretation of measurement results, especially when close to critical values (e.g., disease defining values, ethanol concentration in blood for drivers, etc.). In fact, when comparing a result with a decision limit (e.g., 7.0 mmol/L in the diagnosis of diabetes) we can give clear information to the clinician only if the limit is not included within the uncertainty around the result. So, there is no doubt that the concept is valuable.

Taking into account that some clinical laboratories are more familiar with the ''total error'' concept, a simple question arises: are the two concepts completely different?

Even though the approach and some mathematics are different, we can say that the measurement uncertainty is due to the sum of the errors we make during the measurement process. We make random and systematic errors. Systematic errors can and should be corrected if we have a defined reference from which to calculate the bias. But this clear reference most often does not exist or is questionable. The most significant theoretical difference between the total error approach and the measurement uncertainty model is the way to deal with the bias. In the total error model you just sum it. In the measurement uncertainty model you correct for bias and take into account the uncertainty introduced by this correction (i.e., the errors related to the definition of the reference and to the calculation of the bias). These two approaches are substantially different when the reference is clearly defined and the systematic component of our error is easy to calculate. However, this is never the case in the clinical laboratory. Thus, if you are not sure of the reference, the measurement uncertainty related to the correction practically equals the bias itself. In our opinion, the calculation of measurement uncertainty value is an alternative way for estimating the measurement error.

If the value of measurement uncertainty is clear, the way to calculate it is less clear. Is the ''bottom-up'' model proposed by the GUM (17) the best way to accomplish this task, and is it applicable to every test and in any clinical laboratory? There are three major obstacles to the application of this approach: 1, most of the information needed, is not easily available and would require new experiments; 2, the complexity of the mathematics involved is far beyond the usual basic level of knowledge; and 3, significant training and education is required because it is a totally new subject for clinical laboratorians. In addition, if some significant uncertainty component is overlooked, the resulting measurement uncertainty is underestimated (and some components are difficult to evaluate, such as, the effects of lot-to-lot variability of the reagents). The model proposed by the GUM is not the only one, and we believe that ''empirical models'' based on existing data of IQC and EQAS may be equally valid (18, 19, 21). The Australasian Association of Clinical Biochemists published a document that follows this approach (23). Combining the ''total error'' approach with the measurement uncertainty approach has the advantage of keeping the metrological quality references that were developed in the past. In fact, at present we do not have alternative approaches for setting goals for maximal acceptable measurement uncertainty.

In our opinion, clinical laboratories should gradually implement the approach providing measurement uncertainty for all their measurements. This should start from those with

a higher level of standardization, for which a reference measurement system already exists (reference measurement procedure, reference materials, reference measurement laboratories).

The final question is what to do with the measurement uncertainty statistic. Clinical laboratories do not produce ''certificates'' where the uncertainty can be easily stated, but reports often include tenths of measurement results. Should we report our data as a numerical result ± measurement uncertainty? Our belief is that laboratorians and clinicians are not yet ready for this. Substantial education is needed. Moreover, the quality of a significant number of our tests is relatively low (analytical coefficients of variation higher than 10%–15%, absent any recognized reference procedure of reference material). This would undoubtedly lead to very large uncertainty values that would confound the clinician. However, this is useful information, making us more aware of the limits of our results and of the needs for improvement. In addition, it can be provided to the clinician with a comment, putting some caution on the interpretation of some results or, conversely confirming their diagnostic value. Such comments would be especially useful when the measurement values are close to a decision limit.

In conclusion, we believe that the calculation of the uncertainty of our results is a great new opportunity to improve the quality of our services, but we perceive this development as an evolution of the ''total error'' concept, not as a revolution that wants to eliminate all of the past.

Utility of Six Sigma

James Westgard PhD (Westgard QC, 7614 Gray Fox Trail, Madison, WI, USA)

The concepts and principles of Six Sigma quality management are being readily accepted and applied in medical laboratories today. ''Sigma-metrics'' are found to be particularly valuable to normalize quality to a common scale, benchmark quality against other processes and other industries, relate quality to process capability indices and method performance, and to identify appropriate designs for IQC.

Education and training are important issues for advancing Six Sigma applications in laboratories. Fortunately, Six Sigma concepts and principles are readily applicable to the analytical process in the laboratory. Thus, it is possible to begin with a focus on analytical performance and quality control. Given that these are core competencies for a medical laboratory, there is a need to train laboratory analysts and technicians to effectively implement Six Sigma approaches such as, method decision charts and IQC selection tools. Such education is also essential for analysts to understand both the need and techniques for designing IQC to ''verify the attainment of the intended quality of test results'', which is a specific guideline in ISO 15189.

Applications with analytical processes require that laboratories define ''tolerance limits'' which describe the required quality or maximal allowable variation for a product or process. In ISO terminology, the term ''intended use'' represents the expected or required quality of a test. In practice, it is common to define an ''TEa'' as the analytical quality requirement for a laboratory test. Such TE requirements are available from national External Quality Assessment (EQA) and proficiency testing (PT) programs, or can be calculated from biologic goals for imprecision and bias for a wider variety of analytes. However, there is a lack of uniform practice in defining quality requirements from country to country and even within countries, thus, the definition of the tolerance limit is still a critical first step in characterizing method performance and calculating a ''sigma-metric'' for an analytical process.

The sigma-metric is commonly calculated as follows:

$$\text{Sigma-metric} = (\%\text{TEa} - \%\text{bias})/\%\text{CV}$$

where TEa represents the quality requirement in the form of an TEa, bias represents systematic error or inaccuracy and CV represents the random error or imprecision of the measurement procedure. All terms must be in the same units and it is convenient to work in percentages, as indicated in this equation.

There are issues with estimates of method imprecision and bias, since it is well known that performance may vary with concentration. One approach may be to develop ''sigma profiles'' analogous to the current thinking about ''precision profiles''. Bias profiles could, of course, also be accommodated in concentration related estimates of sigma. In addition, estimation of bias itself can become a serious limitation for many measurands where traceability and calibration are still serious problems.

This concentration dependency may also affect IQC designs, which may differ at different decision levels due to different quality requirements and/or different estimates of imprecision and bias. Different medical applications, e.g., emergency vs. routine testing, may also have different quality requirements. Thus, current practices of employing a single IQC design across different control materials may need to be developed further to better address the quality required at different concentrations and for different medical applications.

Also, there are practical issues in implementing different IQC designs for different tests and different analytical systems. Typically IQC designs involve changing the control rules and/or the numbers of control measurements. On multitest instrument systems, it is generally necessary to fix the number of control measurements for all tests, and vary only the control rules or statistics; additional preventive efforts may be necessary when detection is low. On multiple analytical systems, there is the additional issue of establishing IQC designs across or within analytical systems.

Six Sigma applications in medical laboratories are evolving and new and better strategies need to be developed to deal with the complexity of analytical systems. More widespread applications to preanalytical and post-analytical processes may also be expected as Six Sigma becomes more widely established and utilized in medical laboratories.

Effects of analytical errors on patient care and outcomes

Curtis Parvin PhD (Bio-Rad Laboratories, Quality Systems Division, 3201 Technology Drive, Plano TX, USA)

A range of issues related to the effects of analytical errors on patient care and outcomes were examined. The major discussion topics can be separated into two general themes; new or improved ways to reduce the magnitude and frequency of analytical errors in order to reduce the risk of adverse patient outcomes, and better ways to define and identify the analytical error conditions that lead to increased risk of adverse patient outcomes.

Ways to further reduce analytical error

It is difficult to directly link an analytical error in a reported patient result to an adverse patient outcome. However, while it may not be possible to precisely quantify the degree of impact, reducing the magnitude of analytical errors clearly will lead to reduced risk of adverse patient outcomes. With that in mind a number of opportunities to reduce analytical errors were discussed.

Many laboratories have more than one instrument that performs the same set of tests. This situation adds an additional source of unwanted variability which suggests the need for more stringent QC requirements. There needs to be a better understanding of how to design QC strategies that account for and can control this additional source of variability so that desired performance goals can be met.

There was general agreement that better use can be made of patient results as part of a laboratory's quality control strategy; not as a replacement for control-based quality control, but as a supplement to it. It was also reaffirmed that different QC strategies should be designed and implemented for quality control testing after a laboratory event such as, calibration vs. routine quality control testing over time.

Lastly, when a confirmed out-of-control error condition has been identified and corrected, more formal strategies are needed for designing optimal approaches to identify those previously reported patient results that should be retested and to decide which retested results should lead to an updated patient report.

Ways to better define and identify important analytical errors

Every reported patient result contains analytical error. The challenge is how to correlate the magnitude of an analytical error in a reported patient result with the likelihood of occurrence of an adverse patient outcome. Current practice is to define ''TEa'' as the magnitude of error that causes a result to be considered incorrect. TEa specifications are generally specified as an absolute or proportional error. A richer and more robust modeling of the relationship between the magnitude of analytical error and patient risk would be useful. TEa specifications that can vary with concentration and that allow more transition states than simply correct or incorrect could strengthen the association between analytical error and patient outcome. One example of this richer modeling technique is to define error grids (24).

It was felt that improved identification of important analytical errors can be facilitated with better integration of data across the healthcare enterprise (lab data, pharmacy data, data on working diagnosis and current treatment), and that appropriate reference values could assist in identifying large and important analytical errors. Finally, it was agreed that there would be significant value in creating shared databases that characterize identified analytical error conditions (magnitude, duration, concentration range, how identified, how corrected). This could substantially advance our understanding of the effects of analytical errors on patient care and outcomes.

No solutions to these complex issues were agreed upon in the short time allotted, but there was optimism that useful advances are within reach, and there was enthusiastic endorsement for any and all efforts to find workable strategies to address these important issues.

Harmonizing allowable total error specifications

Prof. Mario Plebani MD (Department of Laboratory Medicine, University Hospital of Padova, Via Giustiniani 2, Padova, Italy)

Although the concept of TEa specifications was introduced many years ago and a number of papers and books have been published on this issue, it still seems to be in its infancy with regards to the translation into every-day laboratory practice. In particular, some debating issues are:

- What are the uses for TEa?
- What are the published and unpublished sources of TEa specifications?
- Can/should TEa specifications be calculated for each laboratory based on biological variation and laboratory estimates of imprecision and bias?
- How can published sources of TEa specifications be harmonized?

Uses for TEa

Since the beginning, the concept and definition of TEa have been characterized by their practical utilization, namely their use in setting up specifications and the monitoring and improvement of quality in clinical laboratories. The main uses for TEa specifications achare summarized as:

- Defining quality specifications for many stakeholders (clinical laboratories, manufacturers, providers of EQA schemes, experts developing clinical guidelines)
- Setting quality control rules
- Providing laboratory staff with a consistent goal to achieve, maintain improving performance over time

- Define maximum bias and imprecision to maintain the application of a common reference interval across time and geography
- Providing information regarding change in patient health status by reporting the clinically significant change in serial results in the form of reference change value (RCV)

First, quality specifications based on TEa represent key concepts for managing and improving quality in everyday laboratory practice. The design and setting of analytical quality specifications, particularly bias and imprecision, are essential requisites for achieving quality. In particular, quality management and improvement is strictly related to the definition of analytical quality specifications and careful choice of analytical platform, which really complies with those quality specifications. For clinical laboratories, therefore, this is a fundamental step particularly in the current administrative environment in which tenders for diagnostic systems have to be based on objective quality specifications. For manufacturers, knowledge of evidence-based and consensually-accepted quality specifications represents a fundamental criterion for addressing the production of reagents and diagnostic systems, thus improving the quality of their products. For EQAS providers, the availability of reliable quality specifications based on biological variation is an objective criterion for setting targets and acceptable values for analyzing the data from participant laboratories (25).

Second, setting quality control rules based on quality specifications linked to TEas represents a major source of improvement for the daily quality control practices. In fact, the concept of a unique budget for managing random and systematic errors allows clinical laboratories to really control the analytical results on a practical basis by selecting the most effective rules (26).

Third, it provides laboratory staff with a consistent goal to achieve, maintain and improve performance over time. The eventual communication to clinicians and users of the observed total error should be an objective statement regarding the standard of quality achieved and maintained (27, 28).

Additionally, for networked laboratories that share a common reference interval the TEa specifications based on the biological variation model can be used to revise the reference interval and to apply common reference intervals across time and geography, thus leading to harmonization and higher comparability of laboratory results (29).

Furthermore, biological variation model can provide an objective approach to determine the sampling frequency that reflects the change(s) in a patient's health status and aids patient monitoring. This is an area where more dedicated studies are required (30, 31).

Finally, it should be used for reporting the RCV for serial measurements of laboratory tests used in patient monitoring and follow-up and for comparing the difference between two consecutive results with an objective criterion (RCV or critical difference). The RCV value is determined using biological variation derived from healthy individuals. However, for some tests, biological variation in a disease status differs significantly from that obtained in health. This raises the question about reporting disease specific RCV.

What are the published and unpublished sources of TEa specifications?

First of all, we should identify the criteria for defining how ''reliable'' the data for TEa specifications are, particularly when quality specifications are based on biological variation. For collecting reliable data on biological variation, well-defined protocols should be fulfilled, in particular:

- Health status of the subject must be known
- Predefined exclusion criteria must be applied
- Pre-analytical factors must be standardized and minimized
- Analytical variability should be minimized
- Defined statistical method for outliers exclusion and data analysis (based on ANOVA)

The suitability for inclusion of various sources of data in the biological variation database has been assessed by independent quality experts, namely, Carmén Ricos and colleagues. Therefore, reliable sources of information might be considered to be the publications by Carmén Ricos (32, 33), the Bio-Rad Laboratories Quality Systems Division website (http://qcnet.com) as well as the Westgard website (http://www.Westgard.com/biodatabase1.htm), but a careful review of the source of these data should be recommended, namely for some ''exoteric'' laboratory tests.

Can/should observed total error specifications be calculated for each laboratory based on laboratory estimates of imprecision and bias?

Successful experiences both from stand-alone institutions and networks of laboratories demonstrate the feasibility and usefulness of calculating observed total error based on estimates of observed laboratory imprecision and bias. Clinical laboratories may easily estimate bias and imprecision. Estimates of bias should preferably be obtained from EQA/PT programs, or alternatively can be calculated from a shift in QC mean. Imprecision can be obtained from the IQC system. For practical reasons, control materials should be obtained at concentrations near to the decision limit/clinically relevant values of the test. This practically means that the bias and imprecision that is nearest to the decision limits or clinically relevant values is what should be considered for the calculation of observed total error.

Conversely, the uncertainty approach is only available for a few laboratory tests for which reference methods and materials have been developed. In addition, even for those methods, quality control and EQA programs have to be implemented and sources of errors continuously measured. Moreover, the uncertainty at the level of the laboratory practice is certainly higher than the uncertainty of the reference method in use.

How can published sources of TEa specifications be harmonized?

In spite of the body of data accumulated on TEa specifications, there is a need to further harmonize the available information.

- Published data should be carefully reviewed, taking into consideration all possible sources of ''variation,'' including pre-analytical variables and methods used;
- Accurate meta-analyses, particularly for different diagnostic areas, should be promoted to obtain not only a collection of raw data, but reliable information; and
- Data should be released and published on an/the available website and continuously.

However, for allowing a better harmonization of currently available sources, it seems to be mandatory for more and more clinical laboratories around the world to adopt and utilize the TEa concept and to facilitate the comparison of experiences. By sharing data and the reactions of different professionals, it should be possible to achieve a higher level of quality in laboratory medicine.

Discussion

With the recent exception of France that will require laboratory accreditation beginning in 2010, voluntary medical laboratory accreditation is the norm among most of the countries represented at the Sitges meeting. Participants supported the concept of medical laboratory accreditation and felt that all European professional bodies should encourage medical laboratory accreditation by becoming more involved with their national accrediting bodies, their national standards bodies and the EA subcommittee for medical laboratories.

The discussion group on TEa recognized a number of uses for these specifications but recommended a careful review of the source of biological variation data, especially for less common tests. An interesting outcome of the working group discussion was a recommendation that laboratories should establish TEa specifications at clinical decision points using biological variation data and comparing these specifications to the observed total error based on laboratory imprecision and bias experienced at the clinical decision points.

Likewise, for estimates of Six Sigma, the working group found that there are issues with estimates of method imprecision and bias needed to calculate the sigma metric, because it is well known that performance may vary with concentration particularly at clinical decision points. One approach suggested by the discussion group may be to develop ''sigma profiles'' analogous to the current thinking about ''precision profiles''. Bias profiles could, of course, also be accommodated in concentration-related estimates of sigma. Knowing the performance at critical decision points, i.e., being able to characterize it, offers the laboratory the opportunity to better manage the quality of its outputs. One measure that would be directly affected by lack of quality and consistent performance is uncertainty.

Dr. Westgard's keynote address was aimed at stimulating a discussion of the practicality and suitability of uncertainty since some sectors of the industry question the concept. Participants in the discussion group on uncertainty seemed enthusiastic about the utility of this statistic as an evolution of the estimate of total error concept and framework. They also supported use of data derived from IQC schemes to estimate uncertainty and initiation of robust programs for laboratory education and training regarding this concept.

Uncertainty, Six Sigma, TEa and accreditation represent different approaches to assure medical laboratory quality and reliable patient test results. Laboratory activities begin and end with the patient, so it was important to have a discussion group consider the effects of analytical error on patient care and outcomes. The discussion group on patient outcomes felt it was difficult to directly link an analytical error in a reported patient result to an adverse patient outcome. However, while it may not be possible to precisely quantify the degree of impact, reducing the magnitude of analytical errors clearly will lead to reduced risk of adverse patient outcomes. With that in mind, a number of opportunities to reduce analytical errors were discussed. One approach suggested was better use of patient results as part of a laboratory's quality control strategy; not as a replacement for control-based quality control, but as a supplement to it.

Acknowledgements

Accreditation Discussion Group

David Burnett PhD (Group Leader)
Consultant in Quality and Accreditation Systems
davidburnett4@btinternet.com
Lindens Lodge, Bradford Place
Penarth, Great Britain

Francisco A. Bernabeu-Andreu PhD
fbernabeu.hupa@salud.madrid.org
Hospital Universitario Príncipe de Asturias
Ctra. Alcalá-Meco s/n
Alcalá de Henares, Spain

Adelina Gomes MS
M.Adelina.Gomes@insa.min-saude.pt
Instituto Nacional Saude Dr. Ricardo Jorge
Av. Padre Cruz
Lisboa, Portugal

Adrian Holt PhD
adrian.holt@cmft.nhs.uk
Manchester Royal Infirmary
Oxford Road
Manchester, Great Britain

Michael Hubmann PhD
mhubmann@mzl.at
Med. Zentrallaboratorium GmbH
Carinagasse 41
Feldkirch, Austria

Wim Huisman PhD
w.huisman@mchaaglanden.nl
Medical Center Haaglanden
PO Box 432
Den Haag, Netherlands

Solveig Linko PhD
solveig.linko@hus.fi
Helsinki and Uusimaa Hospital District HUSLAB
P.O.Box 340
Helsinki, Finland

Francisco Ramon Bauza PhD
framon@hsjdbcn.org
Spanish Society of Clinical Biochemistry and Molecular Pathology
Hospital Universitari San Joan De Deu
Passeig Sant Joan De Deu
2, Esplugues
Barcelona, Spain

Angel Salas Garcia PhD
asalas@cst.cat
Spanish Society of Clinical Chemistry
Padilla 3
Barcelona, Spain

Measurement Uncertainty Discussion Group

Ferruccio Ceriotti MD (Group Discussion Leader)
ceriotti.ferruccio@hsr.it
Diagnostica e Ricerca San Raffaele
IRCCS H. S. Raffaele
Via Olgettina 60
Milano, Italy

Niels de Jonge PhD
n.dejonge@hagaziekenhuis.nl
Haga Teaching Hospital
P.O.Box 40551
The Hague, Netherlands

Claudio Dotti PhD
dotti.claudio@asmn.re.it
Azienda Ospedaliera ASMN
Viale Risorgimento 80
Reggio Emilia, Italy

Paul Froom MD
paulfr@clalit.org.il
Clalit Health Services
Hataasia 47
Nesher, Haifa, Israel

Xavier Fuentes-Arderiu PhD
xfa@bellvitgehospital.cat
Hospital Universitari de Bellvitge
Feixa Llarga s/n
L'Hospitalet de Llobregat (Catalonia)
Barcelona, Spain

Rudolf Gruber MD, PhD
rudolf.gruber@synlab.de
Synlab Nürnberg-Weiden-Regensburg
Fürtherstr. 212
Nürnberg, Germany

Six Sigma Discussion Group

James Westgard PhD (Group Leader)
james@westgard.com
University of Wisconsin Medical School
Madison WI, USA

Jaya George MD PhD
jaya.george@nhls.ac.za
National Health Laboratory Service
7 York Road
Parktown, South Africa

Jeremie Gras MD
jeremie.gras@gmail.com
Cliniques du Sud Luxembourg
Rue des Déportés 137
Arlon, Belgium

Michele Mussap MD
michele.mussap@hsanmartino.it
University Hospital
Largo Rosanna Benzi 10
Genova, Italy

Dirk Peetz MD
peetz@uni-mainz.de
Universitätsmedizin der Johannes Gutenberg-Universität Mainz
Langenbeckstraße 1
Mainz, Germany

Tomas Persson PhD
tomas.persson@unilabs.com
Unilabs, Kärnsjukhuset
Skövde, Swedan

Douwe van Loon PhD
douwevanloon@planet.nl
Sint Antonius Hospital
Koekoekslaan 1
Nieuwegein, Netherlands

Effects of Analytical Error on Patient Outcomes Discussion Group

Curtis Parvin PhD (Discussion Group Leader)
Curtis_Parvin@bio-rad.com
Bio-Rad Laboratories
Quality Systems Division
3201Technology Drive
Plano, TX, USA

Frances Boa PhD
Frances.boa@stgeorges.nhs.uk
St George's Healthcare NHS Trust
Blackshaw Road
London, Great Britain

Paolo Brambilla MD
paolo.brambilla@uds.unimib.it
University of Milano Bicocca
Via Mazzini 1
Desio, Italy

Fernanco Cava-Valenciano MD
fcava@fhalcorcon.es
Hospital Universitario Fundación Alcorcón
C/Budapest 1
Alcorcon, Spain

Daniella Harell PhD
dharell@smile.net.il
Central Laboratory
Clalit Health Fund
27 Benjamin
Ramat-Gan, Israel

Matthias Nauck MD
matthias.nauck@uni-greifswald.de
Ernst Moritz Arndt Universität
Institut für Klinische Chemie und Laboratoriumsmedizin
Sauerbruchstraße
Greifswald, Germany

Cosimo Ottomano MD
ottomano@ospedaliriuniti.bergamo.it
Ospedali Riuniti Bergamo
Largo Barozzi 1
Bergamo, Italy

Janice Paiker MD, PhD
janice.paiker@nhls.ac.za
University of the Witwatersrand
Johannesburg and NHLS
7 York Road
Parktown, Johannesburg, South Africa

Eino Puhakainen PhD
eino.puhakainen@hus.fi
Helsinki University Central Hospital
P.O.Box 340
Helsinki, Finland

Jos Van Acker MD
jos.vanacker@azstlucas.be
AZ Sint-Lucas/Volkskliniek
Groenebriel 1
Gent, Belgium

Harmonizing Allowable Total Error Discussion Group

Mario Plebani MD (Discussion Group Leader)
mario.plebani@unipd.it
Department of Laboratory Medicine, University Hospital of Padova
Via Giustiniani 2
Padova, Italy

Emilio Ascari MD
ascarie@spedalicivili.brescia.it
Spedali Civili Brescia
P.le Spedali Civili 1
Brescia, Italy

Nathalie Durgniat MD
ndurgniat@unilabs.ch
Unilabs Lausanne
Rue de la Vigie 5
Lausanne, Switzerland

Pilar Fernandez-Calle MD
pfernandez.hulp@salud.madrid.org
La Paz University Hospital
Pso de la Castellana 261
Madrid, Spain

Nudhar Jassam PhD
nuthar.jassam@leedsth.nhs.uk
Leeds Teaching Hospitals Trust
Leeds General Infirmary
Leeds, Great Britain

Matthias Orth MD
matthiasorth@vinzenz.de
Marienhospital Stuttgart
Böheimstr. 37
Stuttgart, Germany

Carmen Perich MD
cperich.bcn.ics@gencat.cat
Institut Català de la Salut
C/ Mollerusa s/n
Barcelona, Spain

Marianne Philippe MD, PhD
marianne.philippe@uclouvain.be
Cliniques Universitaires Saint-Luc
Avenue Hippocrate 10
Brussels, Belgium

Rui Pimentel MD
rui.pimentel@joaquimchaves.pt
Dr. Joaquim Chaves Laboratório de Análises Clínicas
Av. General Norton de Matos, 71
Miraflores, Portugal

Thomas Plecko MD
t.plecko@klinikum-stuttgart.de
Katharinenhospital Stuttgart
Kriegsbergstraße 60
Stuttgart, Germany

David Rambau MD, PhD
rambau@lancet.co.za
Lancet Laboratories
cnr Menton & Stanley
Richmond, Johannesburg, South Africa

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