Review

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Contributions of CCLM to advances in quality control

Abstract

The discipline of laboratory medicine is relatively young when considered in the context of the history of medicine itself. The history of quality control, within the context of laboratory medicine, also enjoys a relatively brief, but rich history. Laboratory quality control continues to evolve along with advances in automation, measurement techniques and information technology. Clinical Chemistry and Laboratory Medicine (CCLM) has played a key role in helping disseminate information about the proper use and utility of quality control. Publication of important advances in quality control techniques and dissemination of guidelines concerned with laboratory quality control has undoubtedly helped readers of this journal keep up to date on the most recent developments in this field.

Keywords: Clinical Chemistry and Laboratory Medicine (CCLM); process control; quality control; quality improvement; statistical quality control; total quality management.

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Introduction

Attention to product quality and the concepts governing quality and process control can be traced as far back as approximately 2000 BC with the Code of Hammurabi, a well-preserved Babylonian law code. While most of the code deals with matters of contract law and punishment, it also establishes expected standards for quality. For example, one law states that “the mason who builds a house which falls down and kills the inhabitant shall be put to death”, while another establishes expectations for officials whereby “a judge who reaches an incorrect decision is to be fined and removed from the bench permanently”. Many of the great wonders of antiquity could not have been built without strict attention to quality and process control. The building of the pyramids in Egypt which have an average error of only approximately 50 mm in the entire length of each base could not have been accomplished unless there was strict adherence to process control.

The advent of manufacturing of consumer goods and services gave rise to the need for attention to the quality of the finished product. While cost is certainly an important consideration for any product, improving the quality of what is being produced, as well as improving the process used for making the product, can lead to efficiencies in production with resultant lower cost, as well as resulting in a product of greater quality and acceptance by the end user. The importance of process control is exemplified by the rise of medieval guilds during the Middle Ages. These guilds required long periods of training and oversight for apprentices. Those individuals who desired to become masters at their craft needed to demonstrate evidence of their abilities. Special measures were taken to inspect the work of apprentices in order to guard the Guild against claims of substandard work. The goal of this process was to ensure that the quality of the process being performed by the Guild was maintained at the highest possible level.

With the advent of the industrial revolution and establishment of factories to manufacture goods, the true beginnings of process control and quality control that we are familiar with today began to appear. The concepts of mass production and the interchangeability of parts necessitated that systems be put in place that would ensure the reproducible production of manufactured components. The need for skilled craftsmen to produce one-of-a-kind components of a complete product was slowly replaced by the need for individuals whose sole function was the inspection of components and finished product in order to ensure that minimum quality specifications be achieved. During these early years when mass production of products was relatively low, the process of product inspection
was not performed in a systematic way, but was adequate for the volume of product being produced. However, as mass production increased in size and complexity the need for more efficient control of product quality became increasingly evident.

The need for a specialized labor force dedicated to the principles of quality control was highlighted in 1911 with the publication of *The Principles of Scientific Management* by Fredrick Taylor [1]. The primary goal of this text was to improve economic efficiency, particularly through increases in productivity from the labor force. Taylor was one of the first to apply scientific principles in an effort to scientifically determine the optimal way to perform a task. One of Taylor’s primary means of achieving his goal of optimal performance was the use of time and motion studies. Using a stopwatch to time a worker's sequence of motions allowed Taylor to determine the single best way to perform various tasks. Following years of experimentation to determine optimal working methods, Taylor identified four principles of scientific management (see Table 1).

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<th>Table 1 Fredrick Taylor’s four principles of scientific management.</th>
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<td>1. Replace rule-of-thumb work methods with methods based on scientific study of the task being performed.</td>
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<td>2. Develop each worker following scientific selection and training of the worker rather than allowing them to train themselves.</td>
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<td>3. Follow-up workers to ensure that the scientifically developed methods are being followed.</td>
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<td>4. Make managers and workers share equally in the work so that managers can apply scientific management principles to planning the work and to ascertain that workers are actually following the scientifically prescribed work methods.</td>
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Inspection of product being produced was also an important component of these scientific principles. Inspections were performed to ensure that no faulty product left the factory. Inspections involved testing every item to make sure that product specifications were being met, and these inspections were performed at the end of the production process using specially trained inspectors. The importance of trained inspectors eventually led to the emergence of a separate inspection department within the workplace. The primary goal of this department was the prevention of product defects, which represented the early beginnings of workplace quality control.

While Taylor’s methods were indeed effective at improving worker productivity and the quality of the final product, these methods increased the monotony of the task being performed. The principles underlying Taylor’s approach to scientific management had the result of increasing the speed and intensity of work. The jobs that workers performed became more unpleasant and workers were viewed essentially as just another component in a larger machine. Jobs that once required skilled individuals to perform were broken into a series of simpler steps that could now be performed by less skilled and lower paid workers, or even automated. The net effect was competition between workers, resulting in depression of wages and job security. However, despite these drawbacks, scientific management principles demonstrated that improvements in workplace efficiency and product quality could be readily achieved and variations of these early principles are still in use today.

### Quality control and statistical theory

The historical growth and development of clinical laboratories as an integral part of clinical medicine parallels the development of quality control. A little over 100 years ago, the importance and necessity of clinical laboratories was not a view shared by all. An article appearing in the *Journal of the American Medical Association* in 1900 was written in an attempt to promote the utility of clinical laboratories, which were perceived by many to be non-essential to patient care [2]. The major points raised in this article were that:

1. Laboratories were not scientific luxuries;
2. Laboratories required little to minimal space to operate;
3. Laboratories were not expensive;
4. Clinical tests were not time consuming.

With respect to number 3 above, the author noted that maintaining a hospital laboratory could easily be accomplished on as little as $50 (US) per year.

The rapid growth in the role that clinical laboratories play in patient care becomes obvious when one considers the dim view that many had of laboratories just a little over 100 years ago. However, as the contributions to patient care provided by clinical laboratories was increasingly recognized, clinical laboratories realized that there needed to be ongoing commitment to improving laboratory performance. In order to maintain high standards, the accuracy of measurements needed to be monitored constantly and mechanisms for corrective modifications needed to be implemented [3]. The mechanism that was adopted was through the analysis of samples whose concentration was unknown to the analyst performing the measurement. The identification of these “blind” specimens was made only aware to the supervisor. The advantages of the blind
specimens were that since their identity was not made known to the analyst, they did not receive preferential treatment such as might be given to quality control specimens, thus enabling the laboratory director to assess the quality of work being performed by each analyst [4].

The use of the first control chart which gave rise to the discipline of statistical process control and quality improvement was launched by Shewhart in 1924. Shewhart went to work at the Western Electric Company in 1918 where his job was to assist in improving the quality of telephone hardware [5]. Working at Western Electric, Shewhart was a contemporary of and worked alongside a younger W. Edwards Deming, which significantly influenced the later work championed by Deming [6]. In addition to working with Deming, Joseph Juran also worked at Western Electric during this time, and like Deming, was also influenced by Shewhart. These three individuals, Shewhart, Deming and Juran, are considered to be the founders of the quality improvement movement. Shewhart contributions, such as control charts and the Plan-Do-Study-Act (PDSA) cycle, still influence quality control practices today.

Quality control practices were introduced into the clinical laboratory in 1950 by Levey and Jennings, with the goal of trying to improve analytical performance of laboratory methods [7]. Laboratory quality control as practiced by Levey and Jennings was somewhat different than that which is performed today. The original chart used by Levey and Jennings was a Shewhart chart on which was plotted the mean of duplicate measurements of a patient sample [8]. The use of duplicate measurements of quality control was subsequently modified a couple of years later to a single measurement of quality control material, and “single measurement” statistical quality control has become the industry standard [9].

The growth of the clinical laboratory and continued expansion of the variety of tests performed coincided with the application of automation. Automation enabled laboratories to perform batch measurements of a number of different analytes which quickly grew from one to three to six, to finally 20 analytes per individual sample. The increase in the number of analytes measured in a typical run, along with the continued use of control limits of two standard deviations, meant that the likelihood of false rejection increased dramatically. Also contributing to this growth was the development of computer-assisted processing of the medical laboratory. Early systems enabled the development of laboratory data processing. The significance of using laboratory information system for chores such as the placing of test requests, identification of samples, recording of patient data and quality control results helped to improve efficiency [10].

The problem of false rejection due to use of two standard deviation control limits applied to testing to multi-analyte panels led to what has been termed second generation quality control. Westgard and others sought ways to improve upon existing control practices in order to optimize the efficiency of quality control for detecting true errors. Through the use of computer simulation studies, a number of different control rules were developed for use in the clinical laboratory [11]. The application of these rules through the use of what was termed a “Shewhart Multirule Control Chart” was published in 1981 [12].

The use of multirule quality control has undergone gradual modifications over time due to improvements in the ability of automated analyzers to maintain measurement stability. The stability of these analyzers meant that quality control could be performed less frequently, enabling a modification in quality control practices. Thus, different quality control procedures and application of different rules could be employed.

**External quality control programs**

Laboratory improvement through the use of internal quality control programs continued to evolve through the 1940s, enabling laboratory directors to ensure that their own laboratories were performing adequately. However, there was no effort to ascertain the reliability and comparability of results obtained from different laboratories purportedly measuring the same analyte. In the US, the Sunderman Proficiency Testing Service was established in 1949 as a means for establishing the comparability of laboratory test results. Participants received two unknown samples each month, submitted the results of their analyses, and obtained a report that included a statistical analysis of the values reported by all of the participating laboratories, a review of the current methods used for analysis, a comprehensive bibliography, and validation of the results that a particular laboratory reported [3]. This early proficiency testing program serviced more than 2000 laboratories in the US and abroad. Results from each participant were maintained in strict confidence and this program was essentially self-auditing. Directors of laboratories whose results fell outside of the allowable thresholds were encouraged to take a constructive approach in determining the cause of these measurement errors. The Sunderman Proficiency Test Service provided proficiency testing services on a monthly basis for 36 years before being turned over to the American Society of Clinical Pathologists in 1985.
Following the establishment of the first proficiency testing program in 1949, it was soon recognized that standard reference materials were needed if many of the methods being performed in clinical laboratories were to report similar values for measured analytes. Up until this time, standard reference materials were available for analysis of pH and certain inorganic compounds present in blood, but reference materials for many others such as cholesterol and bilirubin were not available. The lack of standard reference materials persisted for a number of years in the US before the National Bureau of Standards recognized the need to help solve this problem in 1967. However, this problem of lack of standardization is one that still persists today for many analytes.

Proficiency testing is recognized as an important component of good laboratory practice and has been shown to be effective in characterizing analytical performance [13]. However, proficiency testing has several limitations including being insensitive to non-analytical process since it assesses only the analytical phase of testing, and has limitations in completely characterizing the appropriateness of analytical performance [14, 15]. Testing programs that use accuracy-based targets have since been shown to offer a much better assessment of interlaboratory accuracy. Although accuracy-based surveys are not yet a requirement for laboratories, and participation is currently optional, these surveys provide a basis for control of interlaboratory accuracy [16]. Proficiency testing, where performance is based only on peer group statistics, is relatively insensitive to errors in analytical methods and merely describes the performance of a laboratory relative to its peers.

The impact of Clinical Chemistry and Laboratory Medicine on laboratory quality control

Our journal has always actively promoted quality improvement initiatives through laboratory accreditation, development of reference materials, design of appropriate quality control rules associated with establishment of reference intervals and proper use and design of quality control programs [17–21]. Appropriate use of quality control requires first that appropriate analytical quality specifications be used. Publications by the External Quality Working group highlighted the importance that analytical quality specifications be biologically based [22]. For diagnostic testing, the goal is the achievement of accuracy, allowing for the use of common reference intervals. For patient monitoring, analytical performance should be concerned with stable operation with low imprecision when compared with within-subject biological variation. In addition, the use of a common control system that can be used for all quantities and analytical procedures is not practical. The publication by Petersen et al. was one of the first to demonstrate that each procedure needs to have its own particular quality control system [23]. They discussed this aspect of quality control, along with the publication of guidelines for statistical control rules.

Manufacturers play an important role in helping advance quality control. Feedback between users and manufacturers can lead to demonstrable improvements in analysis performance. Surveys published in this journal have concluded that both national and international quality control programs are useful for indicating the intrinsic quality of the quantities used in the clinical laboratory [24]. Problems with quality control materials and the lack of communicability have also been discussed [25]. Commutability depends both on the analyte being tested and the control material. No totally commutable material has been found for an entire set of tested analytes, and proposals have been made that laboratories verify the commutability of materials before use in external quality control assessment schemes.

More recently, CCLM has played a major role in advancing quality initiatives through the publication of opinion papers and conference proceedings on issues concerning laboratory quality and quality control. The convocation held in Sitges, Spain in 2009 resulted in the publication of a collective opinion paper from experts in the areas of laboratory accreditation, measurement uncertainty, the application of Six Sigma values to characterize laboratory quality, the effects of errors on patient care and outcome, and harmonization of allowable total error specifications [26]. With respect to the applications of Sigma Metrics to quality control procedures, the publication by Schoenmakers et al. provided a useful guide to the practical application of Sigma Metrics to the implementation of optimal Westgard quality control rules [27]. Also, in addition to issues concerning analytical quality, CCLM has been at the forefront in addressing issues related to improvements in preanalytical quality [28].

The setting of appropriate specifications for necessary analytical quality is noted to be difficult, with proposals for analytical goals based on biological variability considered to be the optimal solution [29]. Ceriotti et al. derived a risk-management approach for setting analytical quality specifications based on the evaluation of patient risk [30].
Total allowable error was based on biological variation. Using results from a ring trial with frozen serum sent to different laboratories for measurement of glucose and calcium, and on the basis of internal quality control data, these authors found that measurement of glucose could be accomplished with analytical quality associated with low risk to patients. However, for total calcium, interlaboratory bias made measurement of this analyte a relatively high-risk procedure for patients. Results from this study demonstrated the utility of a risk assessment approach for defining targets for analytical quality.

The international conference on Clinical Governance in Healthcare and in Laboratory Medicine held in Padova, Italy in 2005 led to the publication of a special issue of CCLM showcasing the state-of-the-art in quality and Clinical Governance. Manuscripts that reviewed the role that external quality assessment schemes play in the assessment and monitoring of all the elements that contribute to the formulation of laboratory information [31], as well as those that reviewed the causes and extent of laboratory errors, as well as mechanisms that can be used to mitigate such errors were published [32]. More recently, the collective opinion paper on findings from the 2010 convocation of experts on laboratory quality resulted in the publication of a summary of key findings on timely areas of interest including the use of biological variation, quality in point-of-care testing, assessing risk and mitigating sources of error and frequency of quality control testing [33].

Finally, CCLM has also been at the forefront in keeping readers up to date on the latest developments in quality initiatives in molecular diagnostics. Some have maintained that quality assurance and quality control is relatively underdeveloped in this rapidly growing area. A review published last year with an emphasis on issues relevant to quality assurance and quality control in the routine molecular diagnostics laboratory was timely and informative [34].

CCLM will continue to play an important role in quality control and quality improvement initiatives. A look back at the information contained in publications in the journal provide a glimpse at the past, present and future of quality control and quality improvement processes.

Future directions in quality control

The practice of quality control in clinical laboratories continues to evolve. The search for more efficient mechanisms for using quality control to detect true errors has long been sought by many investigators [35]. While a variety of forces are driving these changes in quality control practice, there are three primary factors driving these changes. These main driving forces are the implementation of laboratory automation by many laboratories, the continued growth in point-of-care testing applications, and cost considerations of performing quality control testing.

Automation of the total testing process, including specimen processing, delivery to the testing platform, analysis, automated evaluation of the resultant data and delivery of results is rapidly becoming the norm for many clinical laboratories. Automation of the testing process also implies automation of the laboratory quality control process. Re-analysis of samples with analytical errors or due to quality control failures is an inherent part of laboratory automation. Increased reliance on patient data to assess potential analytical problems is becoming more widespread [36]. The concept of using a moving average of patient data as a means of detecting errors was first proposed in 1965 [37]. Despite its publication over 40 years ago, the use of patient data as an adjunct to quality control is just now being adopted within the clinical laboratory. The availability of software able to monitor patient data in real time should now allow implementation of this adjunct to quality control. However, challenges remain in the implementation of the use of patient data for quality control purposes. Users must decide on what constitutes a meaningful change in patient mean values, how many data points should be used to establish a moving mean, and where to place truncation limits to maximize sensitivity and minimize the detection of false shifts.

Point-of-care testing devices are characterized by simplicity in their operation. While simple to operate, no point-of-care device is error free. The simplicity in point-of-care testing is in part achieved by the use of prepackaged individual reagent cartridges or reagent strips that are expensive on a per test basis. This expense is usually reflected in the desire to perform quality control testing as infrequently as possible. This simplicity also means that point-of-care testing personnel typically do not understand the importance of performing quality control, usually do not have time to perform quality control, and usually do not know what actions to take when quality control fails.

The costs associated with performing quality control testing and the costs associated with evaluating, reviewing and maintaining quality control records are not trivial. One study estimated that the costs of quality to be 22% of total direct laboratory expenses, with 89% of the costs for maintaining quality to be associated with calibration and analysis of quality control material necessary to confirm the accuracy and reliability of test results [38]. Quality
control practices have been found to vary widely amongst different laboratories [39].

Like quality control testing, the costs associated with proficiency testing are not trivial. One estimate from 1990 placed the cost of performing proficiency testing and maintaining and tracking these results for the 12,000 US laboratories participating in proficiency testing programs to be $3 billion annually [40].

Conclusions

Quality control is an integral component of laboratory medicine, helping identify errors that can adversely impact patient care. Quality control continues to evolve along with advances in laboratory techniques, automation of laboratory processes, and advances in data management through the use of information technology. *Clinical Chemistry and Laboratory Medicine* has, and will continue to, play an integral role in helping laboratorians keep up to date with the latest advances in quality control and quality improvement initiatives.

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