Mini Review

The History of Statistical Quality Control in Clinical Chemistry and Haematology (1950 – 2010)

Petros Karkalousos[1*], Angelos Evangelopoulos[2]

[1] *Technological and Educational Institute of Athens (TEI of Athens), Medical laboratories department, Greece*

[2] *Head of Professional Services & Communications at Roche Diagnostics (Hellas) SA, Athens, Greece*

Statistical quality control in clinical chemistry and haematology has a tradition of almost 60 years. The most important landmarks were the adoption of control charts by Levey and Jennings (1950), the use of different control levels by Henry and Segalove (1952), the preparation of specific control samples by Freier and Rausch (1958) and the invention of control rules by Westgard et al (1981). Other methods attempted to utilize patient samples; these include the invention of the average of normals by Hoffmann and Waid (1965), the moving average in haematology by Bull (1973), the delta check by Nosanchuk and Gottmann (1974), the use of the anion gap by Witte (1975) and the use of retained whole blood samples in haematology by Cembrowski (1988). The selection of the appropriate method is aided by the use of the power functions (Westgard et al, 1979), the Operational Process Specifications charts (Westgard et al, 1994), and the Six Sigma method (Westgard, 2001). All these tools compare the performance of an analytical method to relevant quality goals. For use as quality goals, either the analytical goals (USA) or the biological variances (Europe) are usually selected. The use of biological variances was introduced by Fraser (1969) and achieved widespread application since Ricós et al collected variance values for a large number of analytes (1999). Along with internal quality assessment, statistical methods for external quality assessment were also developed. Important landmarks were the first interlaboratory quality control procedure by William Sunderman in the USA (1949), the invention of the Youden diagram (1959), and the implementation of specific quality control rules in the external quality assessment schemes by Cembrowski (1997). The introduction of uncertainty in 1993 changed the way of the estimation of values' dispersion.

In conclusion, modern laboratories have a large variety of quality control methods to choose from. The choice of quality control goals and the abilities of their computer system will guide them to the appropriate methods.

Key words: Average of Normals, Control Rules, Statistical Quality Control, Power functions, Operational Process Specifications charts

List of abbreviations

AON: Average of Normals
OPspecs charts: Operational Process Specification charts
SQC: Statistical Quality Control
LIS: Laboratory Information System

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Correspondence: Petros Karkalousos, petef@teiath.gr
Sarantaporou 40, Athens - Halandri
152 31

Introduction

The penetration of information technology and automation in clinical chemistry and haematology is closely associated with the evolution of statistical quality control methods. Statistical quality control (SQC) is a field of statistics which appeared in the United Kingdom and the United States in the early 20th century. The involvement of these two countries in quality control is not unexpected, since they were the leaders in automated manufacture at the time. For the same reason, the principles of statistical quality control were also implemented successfully in post-war Japan many years later.

It is a given fact that man has been controlling the quality of the products he consumes or uses ever since the beginning of human civilization. The ancient producers had to learn to control the quality of their products before consuming, selling or trading them. An item's usability, strength and elegance were some of the features that were controlled by the craftsman or by the master of the laboratory.

Until the 19th century, each item produced was examined individually. This practice continued during the first few decades of the industrial revolution. In the early factories, each product was constructed almost entirely by one workman. Gradually however, in automated production, each workman was responsible for making only a part of the product, instead of a complete one. This part should meet certain specifications, in order to ensure for example that it will be compatible with and will fit on to the other parts during final assembly. As a result, quality control was transferred to the individual sections of the production line, where the quality officer would control specific features. These features were assessed using quantitative measurements instead of empirical.

Statistical quality control drastically reduced the cost of quality control because it introduced the concept of sampling. It was no longer necessary to check each unit produced; only a sample of these, taken at regular intervals, needed to be examined thoroughly.

Over the course of the 20th century, the science of statistical quality control managed to solve the problems of correct sampling and statistical processing of the samples in order to draw accurate conclusions about the quality of the entire population of the units produced. After the 1950s, it was also used very extensively in laboratory medicine.

The birth of statistical quality control in industry (1900 – 1940)

Statistical quality control (SQC) has its roots in the 1920s at the Bell Telephone Laboratories in the USA. This is where the two main branches of SQC, acceptance sampling and process control, were born.

Acceptance sampling is based on the assumption that it is practically impossible to examine all of the units in a production batch. For this reason, Harold Dodge and Harry Romig (Figure 1) suggested that a sample from the batch should be examined and the entire batch could be accepted or rejected depending on the number of defective items found in the sample.

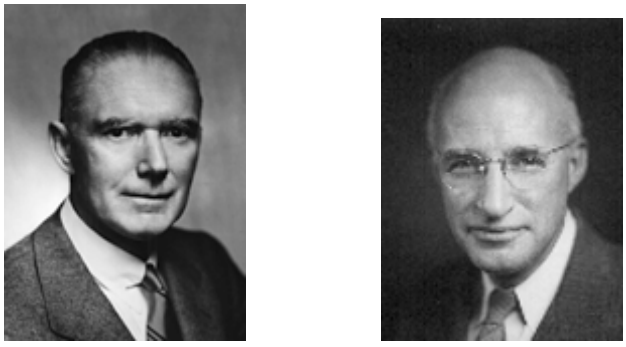

Fig.1 Pictures of Harold Dodge (left) and Harry Romig (right), pioneers in acceptance sampling. H. Dodge, H. Romig, W. Shewhart and E. Deming had worked together in the laboratories of Bell Telephones in the USA. That company's quality control methods were used extensively in the war industry during World War II.

Process control was developed by Walter Shewhart (Figure 2) in 1924 (1). Its primary goal was to prevent the manufacture of defective products, based on the assumption that variability due to random, non-systematic causes is inevitable. For that reason, Shewhart suggested statistical techniques and designed specific diagrams (control charts). The two control charts he created were based on the mean value of the samples ($\bar{x}$ Shewhart Chart or Average Shewhart Chart) and the range of the sample's values (R Shewhart Chart or Range Shewhart Chart).

In 1938, Edward Deming (Figure 3) published a list of 14 rules aimed at reducing product variability in accordance with the definition of quality control. These rules included a series of successive steps of testing, training, and retesting, which were implemented in the Japanese industries after World War II and contributed significantly to Japan's rapid post-war industrial growth.

Fig.2 The pioneer of statistical quality control Walter Shewhart and his wife Edna. His important work was recognized through the creation of the specialized Shewhart award, honoring scientists' contribution to the field.

Fig.3. A picture of Edward Deming from the web site of the W. Edwards Deming Institute in Washington, DC. Deming (1900 – 1993) contributed greatly to the dissemination of statistical quality control outside the USA and his name is now closely associated with the rapid post-war industrialization, through the well-known "Deming's 14 rules".

After the end of WWII, the first steps were made in organizing ring trials. These comparisons soon passed from the industry into clinical chemistry. In 1949, the first interlaboratory comparison scheme was implemented in a few biochemistry laboratories in Philadelphia, PA. Such interlaboratory comparisons were called "proficiency testing" in the USA and "external quality control" in Europe, where they were introduced soon afterwards. The first external quality control scheme was called "Sunderman Proficiency Practice Test", after the clinical chemist William Sunderman (Figure 4) who conceived it (2, 3).

Fig.4. A picture of William Sunderman (1898 – 2003) from the memorial article published by John Savoy in Clinical Chemistry (3). Sunderman was a clinical chemist and a pioneer in external quality assessment worldwide, both in clinical chemistry and in haematology. He died at the age of 104, having written 30 books and more than 300 papers on quality control, on toxicology (with pioneering work on nickel analyses), and clinical chemistry (where he invented a new method for glucose measurement).

The principle of statistical quality control in clinical chemistry (1950 – 1960)

In 1950 it was time to implement the principle of process control in medical laboratories. The American chemists Stanley Levey and Elmer Jennings adapted Shewhart's $\bar{x}$ control chart for chemical analyses in the medical laboratory (4). This new chart was called "Levey-Jennings chart" (LJ chart) (Figure 5) and is even now the primary quality control tool for automated analyzers. Before this chart was invented, good precision was ensured in many laboratories by double measurements.

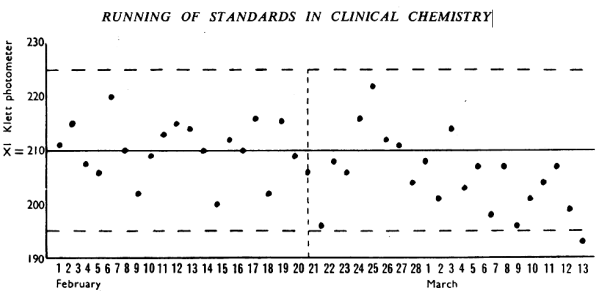

Fig.5. One of the earliest uses of the Shewhart control chart (or Levey-Jennings charts) in clinical chemistry (1952). Note that, at that time, control samples were called "standards".

In 1952 the first external quality control scheme (or external quality assurance scheme or ring-trial), was organized in Great Britain. The Netherlands followed in 1957 and the other European countries soon thereafter.

In the same year, the clinical chemists Richard Henry and Milton Segalove, working in the Bioscience laboratories (Figure 6), started implementing the Levey–Jennings chart on a daily basis using different levels of values (concentrations or activities) (5,6). A few years later, the use of the Levey-Jennings chart gained wider acceptance when Freier and Rausch suggested that serum pools be used instead of patient samples. These samples were first called "standards" and later "control samples" (7).

Fig.6. A commemorative photograph of the founders of Bio-Science Laboratories (Richard Henry is first from the left and Milton Segalove is third). These two scientists were the ones who suggested the use of control samples in clinical chemistry control charts. Henry in particular was one of the most important clinical chemists of the previous century in the fields of statistical quality control and biostatistics. He has published a plethora of relevant articles and the book Clinical chemistry: Principles and Techniques.

In 1954, the British statistician E. Page invented the "cumulative sum chart" (Cusum chart) (8). This is a specialized diagram adapted for the detection of small systematic errors which go undetected by the Shewhart chart. Despite this significant advantage, it was a long time before the Cusum chart was evaluated for possible implementation in the medical laboratory (J. Westgard et al 1977).

In 1959 the American S. Roberts (9) invented the Exponentially Weighted Moving Average (EWMA) chart. This chart uses a moving average of control samples in order to identify small systematic errors. The moving average is different from the normal average in that it includes a specific percentage of the mean values of the previous averages. It took some time for the moving average theory to be adopted by the medical laboratories. Some particularly important papers in this field were published by Brian Bull on the use of the moving average in haematology (1974) and by George Cembrowski on its use in clinical chemistry (1975). The EWMA chart itself would be evaluated for medical laboratory applications much later (Neubauer 1997).

In the same year, the American chemical engineer William Youden (10) presented the twin plot chart (quite often named after him as "Youden plot"), which is still used today in the graphical presentation of the results in which two different control materials are used (Figure 7).

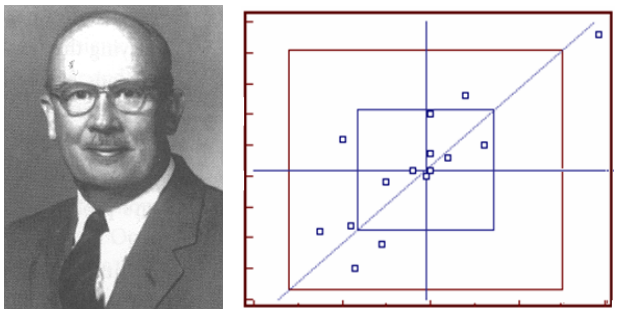

Fig.7. A picture of William Youden (1900 – 1971) from the web site of the American Statistical Association (ASA). An example of the chart named after him is also shown. Youden focused particularly on interlaboratory controls. The chart which he invented in 1959 is used in all interlaboratory control applications, as well as in external quality assessment schemes in clinical chemistry and haematology. In 1985, the ASA established the Youden award in his honor.

The first steps in the use of patient results for quality control (1960 – 1970)

In 1960 the cause-and-effect diagram was created by the Japanese statistician Kaoru Ishikawa. This diagram (also called "fishbone chart" because of its shape) is used to depict the variables related to the manufacture of a product or to the production of a result in a medical laboratory, as the case may be (Figure 8).

In the early 1960 the first observations were made on the possibility of using patient results for quality control of the first automated analyzers. These observations involved haematology and biochemistry laboratories.

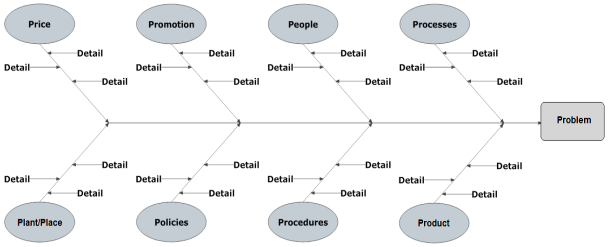

Fig.8. Representation of the cause and effect chart.

In 1963, Dennis Dorsey stressed the importance of erythrocyte indexes (MCV, MCH, MCHC) for quality control in haematology analyzers (11). In 1966, Frank Ductra suggested the repeated assaying of whole blood samples from two successive days as an alternative method of quality control in the place of control samples. These two seminal papers led to significant innovations over the following decades (12).

In 1965, Robert Hoffmann and Michael Waid (13) published the opinion that the arithmetic average of normal test results produced by biochemical analyses can be used to detect systematic errors. This method was named "average of normals" (AON). According to their theory, the average value of normal test results from successive days should lie within specific limits. If these limits are exceeded, then there is a systematic error. Numerous ensuing studies, especially by Westgard and Cembrowski, gradually solved all the problems of the AON method, and in fact many medical laboratory software applications list it among their features.

In another paper from the same year, Hoffmann and Waid (14) suggested that the median of the daily values can be used, under certain conditions, in order to detect the systematic errors for a biochemical parameter. This method was called "number plus method" but was never put into daily routine.

In 1967, discussion began on the quality goals (or quality specifications or tolerance limits). The incentive for this discussion was the application of the Clinical Laboratory Improvement Act (CLIA) quality standard. This standard is applicable to all types of medical laboratories (including histopathology, molecular biology etc.) and sets specific quality rules. Biological variations, analytical goals and medical decision limits were suggested as quality goals in the USA and in Europe.

Rapid development of automated analyzers and specialization of quality methods in clinical chemistry (1970 – 1980).

In 1970, the Americans Ernest Cotlove, Eugene Harris and George Williams studied the acceptable performance on imprecision and inaccurancy of various biochemical parameters based on biological variances (15).

In 1974, the American hematologist Brian Bull (Figure 9), based on observations by D. Dorsey and other researchers, invented a specialized moving average equation for quality control in haematology analyzers (16). This equation was initially used for erythrocyte indexes and was soon established as a reliable and cost-effective quality method; it is now called "Bull's algorithm" or $X_{\bar{B}}$. The innovative feature of Bull' algorithm is that, instead of control samples, it uses the patients' results without discriminating between normal and pathological values.

Fig.9. A picture of Prof. Brian Bull from the web site of the Loma Linda University in the USA, where Bull works as a professor of haematology. Bull's research work is extensive, but he became known mostly for his invention of a "moving average"-type equation which can be used in the quality control of haematology analyzers. This equation is used today in most haematology analyzers and is usually called "Bull's algorithm".

In 1974 an important tool was introduced in clinical chemistry: computer simulations, developed by the Swedish Torsten Aronson (clinical engineer), Carl-Henric de Verdier (medical doctor) and Torgny Groth (physicist) (17). That same year saw the publication of the first papers on the utilization of individual patient results (instead of averages) for detecting systematic errors. Specifically, Jerome Nosanchuk and Arthur Gottmann (18) suggested that each patient's results should be compared with previous results in a specific time frame in order to detect any analyzer errors. This method was called "delta check", when it involves only comparison with previous results, or "rate check" when it takes into account the time elapsed between measurements, and it has now been incorporated in most modern

laboratory information systems (LIS).

In 1975, the Canadian clinical chemist George Cembrowski (Figure 10) and the American clinical pathologist James Westgard (Figure 11) proposed the use of the moving average in clinical chemistry (19). One year later (1976), David Witte and coworkers suggested using the anion gap equation for quality control in automated blood gas and electrolyte analyzers (20).

Fig.10 A picture of Prof. George Cembrowski from the web site of the University of Alberta, Canada. Cembrowski is a clinical pathologist and he is specialized in biochemistry, statistics and medical informatics. He has been very effective in the documentation of many statistical quality control methods in collaboration with Westgard and other researchers. He has worked extensively on the moving average theory, as well as the "average of normals", the anion gap, Bull's algorithm and the selection of control methods. He has also worked on external quality assessment, where he suggested specific rules for the detection of systematic errors. He has authored dozens of articles on quality control and other subjects, and he has co-authored (with R. Neill Carey) the book Laboratory Quality Management: Qc and Qa (1989).

In 1977, James Westgard and his associate programmers Torgny Groth, Torsten Aronson and Carl-Henric de Verdier from Uppsala, Sweden, suggested using a variation of Page's Cusum chart in the field of clinical chemistry (21). This chart was called Decision Limit Cusum and, even though it is adapted to the requirements of clinical chemistry and has significant advantages, it was never established because it was overtaken by new developments in the field.

In 1979 the first paper of the so-called "power function" (Figure 12) was published by James Westgard and the Swedish specialist in medical informatics Torgny Groth (22). Many more relevant papers followed by James Westgard and other prominent researchers in this field, such as Curtis Parvin (Figure 13), Nathan Radin, Ross Wood, Sharon Ehremyer, Kristian Linnet and others.

Fig.11. A picture of Prof. James Westgard from the web site of the University of Wisconsin, USA. Until he retired, Westgard was a clinical chemist and a professor of clinical pathology at the medical school of the University of Wisconsin. Today he is the most famous researcher on quality control for automated analyzers. He has worked mostly on computer simulations, the Decision Limit Cusum chart, power functions, quality rules for the Levey-Jennings chart (multirule method), the Operational Process Specifications Charts, method validation, and the Six Sigma theory. He has worked with many scientists on the documentation of a number of quality control methods which use either control samples or patient results, such as the average of normals, the anion gap etc. The quality rules he proposed are used extensively in the construction of automated analyzers and have been named after him ("Westgard rules"). He has written six books as well as simulation programs for statistical quality control (the older QC Validator and the latest EZ Rules). His web site, www.westgard.com, is a rich source of information on statistical quality control.

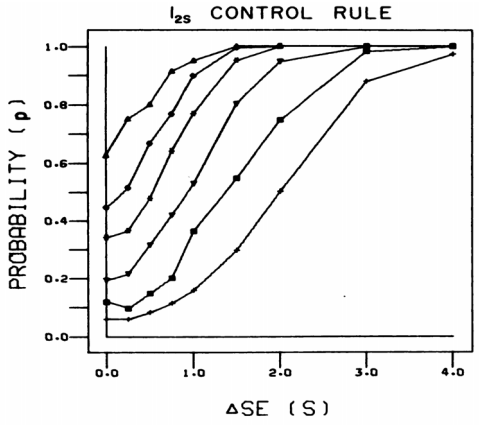

Fig.12. A power function chart, as published in the first relevant article by Westgard and Groth. Each curve represents the probability of detecting a systematic error of a certain magnitude (the error magnitudes are indicated as ΔSE on the horizontal axis) using a certain quality method (indicated as 1_{2s}) which uses a different number of control materials each time (represented by different curves).

Fig.13. A picture of Prof. Curtis Parvin from the web site of the University of St. Lewis, USA. Parvin is a biostatistician and specialist in medical informatics and teaches these subjects at the University of Saint Lewis in Washington. He has contributed significantly to the theoretic documentation of power functions and other statistical issues concerning quality control in clinical chemistry.

A landmark for quality control in clinical chemistry: the Westgard rules (1980 – 1990).

During the 1980's many papers attempted to establish Ductra's original idea, i.e. the repeated measurement of the same whole-blood samples on successive days. The most detailed methodology was proposed by Cembrowski and coworkers (23). In a major breakthrough in medical laboratory SQC, Westgard publishes his groundbreaking paper "A multi-rule Shewhart Chart for quality control in clinical chemistry" (24). This paper establishes simple rules by which medical laboratories can quickly interpret the Levey-Jennings chart. These rules allow analytical errors to be detected easily and random errors to be distinguished from systematic errors.

The 80s ended with an important innovation: the establishment of the first international quality standard for clinical laboratory operations. The EN ISO/IEC 45001 (ISO 45001:1989 General criteria for the operation of testing laboratories) standard stayed in use for many years until replaced by the EN ISO/IEC 17025 in 1999, which in turn was replaced by the EN ISO 15189, a specific standard for clinical laboratories.

The last decade of the 20th century: The quest for quality specifications (1990 – 2000)

During the 1990s, there was a lot of discussion on the so-called "quality specifications", a concept similar to that used in industry. The first specifications of this kind were instituted in the USA by the CLIA standard, with Europe following few years later. Many researchers undertook relevant studies, however particular mention must be made to the Scottish clinical chemist Callum Fraser and the Spanish pharmacist–clinical chemist Carmen Ricós.

Fraser and his coworkers (Figure 14) worked on the theoretical and practical application of biological variances as analytical targets in clinical chemistry (25). In this effort quite significant was the role of the American clinical chemist Eugene Harris (Figure 15), whose knowledge of statistics and informatics contributed greatly to the establishment of the theory of biological variances (26). On the other hand, Carmen Ricós (Figure 16) and a group consisting mostly of Spanish researchers collected data on biological variances and quality specifications for a large number of biological parameters (27, 28).

Fig.14. A picture of Prof. Callum Fraser from the biographical article in Clinical Chemistry. Fraser is a professor of clinical chemistry at the Universities of Saint Andrews and Dundee in Scotland. He has authored papers on many subjects, most of which are about quality control. He is one of the pioneers of the theory of "quality specifications" in the field of clinical chemistry, with significant work on equations and charts which use biological variances as a basic parameter for the selection of the most suitable quality control method.

Fig.15. A picture of Prof. Eugene Harris (1927 – 1997) from his biographical article in Clinical Chemistry. Harris was a bio-statistician specializing in biostatistics and informatics, which he taught at Berkeley University, California, USA. He was a consultant for public health organizations in his country, as well as for the International Federation of Clinical Chemistry (IFCC). He has contributed much to the theory of reference values, biological variances and biostatistics (multivariate analysis, survival curves etc.).

Figure 16. A picture of Dr. Carmen Ricós from James Westgard's web site. Ricós studied pharmacology at the University of Barcelona and works today in the biochemistry laboratory of the Vall d' Hebron Hospital in Barcelona. She has written many articles on the internal and external quality assessment in clinical laboratories, and is a member of quality committees for many international organizations. She is known especially for her initiative in concentrating biological variances for all substances measured at medical laboratories. These tables are used extensively today in the determination of quality specifications.

As a result of the debate on quality specifications, attempts were made to associate these specifications with the selection of the most suitable quality control method for each parameter. The first such attempt was the creation of the QC Selection Grids by Westgard together with Patricia Barry and Elsa Quam in 1990 (29). Four years later, Westgard proposed a much more comprehensive concept: the so-called Operational Process Specifications charts (Figure 17), which became known as "OPSpecs charts" (30). In the OPSpecs charts, the selection of the most suitable quality control method is linked to the quality specifications as well as the inaccuracy and imprecision of the analytical method (30). In creating the OPSpecs charts, Westgard used simulation software of his own design. This software, known as "QC Validator" in its first version and as "EZ Rules" in the final version, was used in many studies over the following years.

In 1993, the concept of uncertainty was introduced in metrology and in quality control in general. This concept was described in several publications such as the Guide to the Expression of Uncertainty in Measurements (31). In 1997 the German scientist Aljoscha Neubauer described a method of using the EWMA chart in biochemistry analyzers (32). Nevertheless, the EWMA chart is not used in medical laboratories because even small errors can usually be detected with the correct combination of Westgard rules.

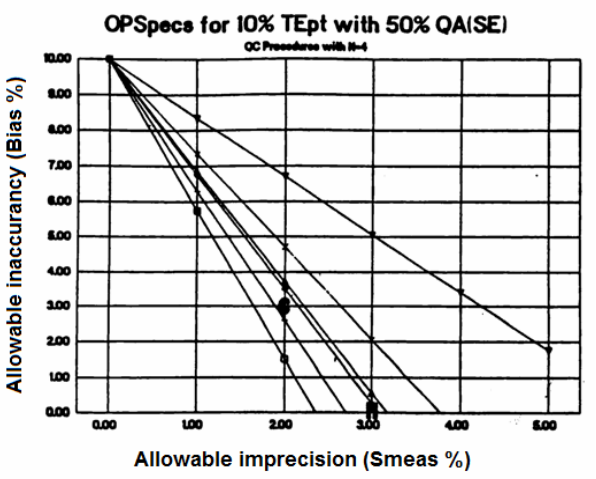

Fig.17. A representation of the OPSpecs chart from the first relevant article published by Westgard. This chart uses the values for allowable imprecision and allowable inaccuracy in order to identify the best quality control method which meets the "quality specification" 10% TE. Each vertical line corresponds to a different quality control method which can detect systematic errors with a probability of 50% QA. The dot in the chart corresponds to the values of the performing laboratory. The closest descending line corresponds to the most suitable quality control method for that particular laboratory.

In the 90s the first papers appear on non-analytical errors, i.e. errors that occur before or after analysis. Post-analytical errors and some kind of pre-analytical errors can be overcome to a large extent by developing, installing and configuring Laboratory Information Systems (LIS). Pre-analytical errors, however, cannot be dealt with so easily. Over the following decade, extensive literature – especially from a group of Italian scientists (Figure 18) – will examine all possible causes (33, 34). In the late 1990s and early 2000s a reduction in pre-analytical errors was achieved by the research & development departments of large diagnostic companies and smaller, independent manufacturers by the introduction of so-called pre-analytical systems. Soon these systems were further developed to cover post-analytical tasks and therefore are often called peri-analytical task management systems. Certain manufacturers have also developed consolidated sample management systems, which focus on the entire diagnostic process (pre-analytical, analytical and post-analytical steps).

Fig.18. A picture of Prof. Mario Plebani from the web site of the International Society for Enzymology. Although Plebani works mainly in enzymology, he is mentioned here because of his extensive work on pre-analytical errors, a subject on which he has written numerous papers and book chapters, either alone or in collaboration with his associates from the University of Padova.

The first decade of the 21st century (2001 – 2010)

In 2001, Westgard introduces the Six Sigma theory in clinical chemistry as another way of establishing quality specifications (34). This theory had already been tested in the industry for almost 20 years, with great success in reducing the number of defective products manufactured. The debate on the applications of the Six Sigma theory in the clinical lab setting is still ongoing. Closing the historical review on quality control, it should be mentioned that in 1999 the EN ISO/IEC 45001 quality standard was replaced by the ISO/IEC 17025 standard. A few years later (2003), a new standard was created exclusively for medical laboratories: the EN ISO 15189, which was revised in 2007 and 2012.

ISO 15189, from SQC theory to practice

ISO 15189 encourages the clinical laboratories to use state- of-the-art methods and follow the guidelines of international scientific organizations. For diagnostic purposes laboratories should use IVD reagents and equipment. Laboratory personnel must be familiar with any detail of its methods (i.e. principle, performance and interfering substances of the method) and to have them in mind in its daily practice. The use of proper methods of internal quality control and the participation of the laboratory in schemes of external quality controls remained one of the basic tasks of laboratory quality managers in ISO 15189. Furthermore, ISO 15189 brought some new concepts in statistical quality control of clinical laboratories. The estimation of the limit of detection, limit of quantification and uncertainty became some of the prerequisites for a clinical laboratory to be accredited. The determination of the sources of uncertainty and the estimation of its value for each test performed is an essential tool to compare testing values produced by different laboratories.

SQC evolution under the prism of technological advances

Quality control in clinical chemistry is mostly based on the theory of statistical quality control that was applied widely many years earlier in industry. The first control chart used in clinical chemistry, the Levey-Jennings chart, was adapted from the industry; even the Six Sigma theory used over the last few years also originated there. In addition to borrowing methods, many new proposals – especially in the last few years – have adapted statistical quality control to the new era of high technology.

The historical review presented previously can be divided for methodological reasons into five main stages illustrating the parallel evolution of statistical quality control and technology.

First stage: before the development of automated analyzers. This stage began when the Shewhart chart

was introduced into clinical chemistry by Levey and Jennings. The first applications of this chart in clinical chemistry used plotting paper, at first without different levels of values.

Second stage: the first automated analyzers. The first automated analyzers reduced random errors, so that focus shifted to systematic errors. The need to detect systematic errors led to the introduction of new control charts, such as the Cusum chart, and to the first attempts to use patient results, such as the average of normals.

Third stage: introduction of informatics. The combination of informatics and laboratory technology led to the development of automated analyzer models where quality control was performed by computers. The well-known Westgard control rules and Bull's algorithm were first used during this period. The multitude of quality control methods created the need for appropriate selection techniques. The first computer simulation programs reduced the need for complicated mathematical verification of the reliability of the various quality control methods.

Fourth stage: laboratory information systems. The unification of all laboratory operations into a single laboratory information system (LIS), often connected to the information system of a greater healthcare institution (e.g. HIS), brought about radical changes in statistical quality control. Methods based on patient results (average of normals, delta check) can now be implemented effortlessly in the lab. Laboratory information systems also achieved a significant reduction in post-analytical errors.

Fifth stage: automation of laboratory processes. Pre-analytical systems (or, more broadly, laboratory automation systems – "LAS") constitute the newest trend in laboratory technology, with great potential for future improvements. Such systems primarily reduce pre-analytical errors but also address aspects of the post-analytical tasks such as sample archiving.

Finally, new approaches permit the selection of the most appropriate quality control method in every case.

Conclusions

Today, statistical quality control is extremely widespread in all medical laboratories, whether in industrialized countries or even in the makeshift laboratories of humanitarian missions in the Third World. The reasons for its propagation are:

1. The developments in laboratory technology and more specifically the development of automated analyzers which facilitate the implementation of statistical quality control methods with built-in software.
2. The extensive use of laboratory information systems. The ability to directly store and retrieve patient results now permits the use of statistical quality methods based on patient results (e.g. delta check, AON), something quite difficult until previously.
3. Along with the developments in mechanical, robotic and information systems, the science of statistics has also progressed and has provided solutions for any quality problems occurring with each new device or technology.
4. There are also cultural reasons promoting the dissemination of statistical quality control in clinical chemistry. For example, the widespread use of the Internet allows laboratories to exchange information, to cooperate and to organize interlaboratory comparisons at a local or international level. The existing spirit of international cooperation allows the formation of scientific committees which propose international standards (such as the ISO standards). Finally, there are many instances in which it is necessary to provide patients who are away from their place or country of residence with reliable laboratory results, of a quality comparable to that which they would receive at home.

Global trends in statistical quality control in clinical chemistry today focus mostly on achieving three goals:

- Selection of the most suitable quality control methods by utilizing old and new statistical theories (power functions, OPSpecs charts, Six Sigma etc.). The goal is to limit needless expenses.
- Reducing pre-analytical and post-analytical errors by introducing automation, establishing appropriate and comprehensive quality management systems for this purpose and implementing statistical methods.
- Continuous improvement of quality standards employed at the national (e.g. CLIA) or international (e.g. EN ISO 15189) level. These standards are regularly updated to incorporate every new scientific development, focus on specific areas of laboratory medicine and set clear targets to be met.

Conflict of interest.

Angelos Evangelopoulos is employed by Roche Diagnostics (Hellas) SA. However, the authors believe that the nature of the article does not create any potential conflict of interest and its content has not been affected by this affiliation.

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