Quality Assurance for Clinical Laboratory

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Clinical laboratory faults may ascend mostly from the absence of awareness and implementation of the quality assurance program.
Nowadays, quality assurance is critical to encounter the needs of clients and customers satisfaction (patients, clinical personnel and researchers), those who responsible for the care of those patients.
Quality can be defined as responsiveness and conformance to the requirement standards. To expand on the definition, defined quality assurance as a means to guarantee the quality of test results and encompasses both quality assessment and quality control.

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2020

Dedication

To the souls of my parents

To my wife, sons & daughters

I dedicate this modest effort…

Siddig Bushra (**first author**)

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Introduction

The general concept of quality means the measure of excellence or state of being free from defect, deficiencies, and significant variations. However, there are many definitions of quality which include "the totality of features and characteristics of a product or service that bears on into ability to meet a stated or implied need", fitness for use and conformance to requirement, indicated that satisfying the customers' needs and expectations are the main factors in all these definitions [(1)].

Quality control *(*Q.C*)* is one component of the total quality management system which has been defined as all systematic actions necessary to provide adequate confidence to the laboratory services which satisfy given medical needs for patient care. By applying Q. C techniques in a laboratory one can minimize errors [(2)]. Quality Assurance (Q.A) is defined as all those planned or systematic actions necessary to provide adequate confidence that a product or service will satisfy defined needs [(3)]. Q.A has been summarized as the right result, at the right time, on the right specimen from the right patient, it involves all measures that can be taken to improve the efficiency and effectiveness of the laboratory and thus enhance the trust in the laboratory results [(2)]. Laboratory medicine has a strong impact in the prevention of risk to the patient and laboratories must implement procedures to minimize further risks of errors. Quality Assurance Programs (QAPs) represent an important tool that allows us to identify errors and pinpoint any need for further systematic investigations, [(4)].

The use of QAPs drives the search for solutions to deficiencies and requires the implementation of corrective action for quality improvement. Likewise, the professionals involved have to assume an implicit concern and accountability for quality, and they must also be able to make changes whenever necessary [(5)].

Laboratory professionals have long carried out activities intrinsic to QAPs, but they are now required to adopt a new approach: their accountability for healthcare provided has greatly increased. However, being accountable does not only mean being held responsible for one's own actions, but also accepting responsibility and acknowledging and honoring one's own duties [6]. Quality assurance involves all measures that can be taken to improve laboratory efficiency and effectiveness, with a view to the maximum benefit to the individual and community, [7].

After World War II, clinical laboratory medicine grew rapidly, but management primarily focused on only quality control. Quality control provides assurance that a laboratory functions properly for the benefit of the patient using daily or run-to-run data points plotted over time on charts [8]. However, there has been a major parading shift to business practice in the philosophy, and the role of the laboratory manager. Laboratory manager will respond to this issues by plotting the laboratory's financial data points as often as quality control and other performance indicator data points [9].

The mission of a medical laboratory is to provide a high quality service to meet the needs of Patients, Clinicians and Researchers. As well as to ensure that the Governmental receives accurate and reliable clinical laboratory services and test results by monitoring and evaluating medical test sites for compliance assurance for clinical laboratory testing [10].

And also is to provide information in answer to a clinical question to help clinicians to undertake the right action for each patient [11].

Overall notion of quality

Quality can be defined as responsiveness and conformance to the requirement standards. To expand on the definition, defined quality assurance as a means to guarantee the quality of test results and encompasses both quality assessment and quality control. A performance Management System poses the question: "Are we performing according to expectation [12]. To attempt an answer to this question from a clinical laboratory point of view, a survey on the laboratory performance would be necessary. A quality survey in Sudan based on external assessment reflected a significant percentage of results being statistically unacceptable [13].

The response to the performance management question from the laboratory point of view is therefore: "Not yet". Quality in most of the laboratories is still inadequate. Practical experience has shown that technologies and universities with their appreciable efforts produce clinical laboratory analysts who are lacking the necessary basic quality assurance knowledge, even after their internship training, Most of the analysts who have been in the clinical laboratories for some years are still struggling to attain the required quality standard. The practice of clinical pathology has been the area of pathologists with the rest of the laboratory staff playing lesser roles. Until about 55 years ago in South Africa, a discipline was identified as a discrete field of practice for the other analytical members of the laboratory staff, this was the area of laboratory technicians who were later through apprenticeship graduated as medical technologists, without writing any examination. Although this new area of independent practice was coined, it was not without uncertainties and deficiencies [12]. Quality assurance as one segment of laboratory practice still suffers appropriate methodological approach of presentation, this is why technologists and technicians of years in clinical laboratories are still lacking the necessary knowledge, this absence

of a systematic approach to quality assurance for many years is partly held accountable for the large amount of diagnostically poor results [14].

It is not what you find; it is what you do about what you find that matters most. All the planning, inspection, testing, measuring and other activities could be a waste of time if they do not lead to preventing the occurrence of poor quality. From laboratory perspective a systematic knowledge acquiring program in quality assurance could improve this level of performance. A critical problem facing mentors and other education facilitators in laboratory medicine, as in other fields of study, is how to transfer quality assurance subject knowledge successfully to learners. Traditional teaching methods have been used in tuition and are found lacking in many respects, such as emphasis, approach and objectivity [15]. For the laboratory to provide service of the required quality to the consumers, proper training of the laboratory staff is of the utmost importance recommends modular training for effective training and learning. Competency-based approach is recommended on the grounds of its advantages over traditional learning systems [16]. Quality assurance, according to some of the laboratory staff interviewed, is a difficult subject to master. This view necessitates a subject didactical approach. Unless and until the general problem, as it appears, is identified and the 'knowledge gap' is closed successfully, South African laboratories will not be able to attain the international standard of performance [15].

By the time stringent quality evaluation measures are applied in every laboratory, relegation will leave most of the laboratories with only a few tests permitted, jeopardizing patients of laboratory services [17].

The key to achieving true quality care lies thus, in the ability of an organization to develop and implement training programs, organize skills developing programs and developing preventative

and corrective programs. Provision of education should be aimed at achieving individual's highest ideals and at meeting the needs of the time simultaneously [18].

Quality assessment versus quality control

Quality assessment (QA) is a complete system of creating and following procedures and policies to aim for providing the most reliable patient laboratory results and to minimize errors in the Pre-analytical, analytical, and Post-analytical phases. QA also includes analyzing known samples called quality control (QC) samples along with unknown patient samples to test for analytical problems. When QC samples do not produce accurate and precise results, it can be assumed that any patient results, obtained at the same time are also erroneous. Following a set of guidelines for acceptance or rejection of patient results based on the QC results helps to assure reliability of the analysis. Specific rules for assuring quality regarding the patient specimen through collection, analysis, and reporting are also important aspects of QA. Thus, Preanalytical, Analytical, and Postanalytical variables need to be considered and minimized in order to have valid test results. Quality assessment is the term recognized by federal laboratory standards from the Clinical Laboratory Improvement Amendment of 1988 (CLIA' 88) Final Rule [19].

Until recently the abbreviation QA was used to represent quality assurance, which implied assuring quality but may not have placed emphasis on assessing and managing laboratory results. In the most recent interpretation of the CLIA '88 Final Rule, it was recommended that the term quality assessment be adopted since it places the focus on assessment of testing performance through all phases. The new interpretation of CLIA' 88 rules also places an emphasis on establishing and following written policies and procedures, taking corrective action, and making changes in policies and procedures to prevent problems from reoccurring. Assessment actually leads to assuring quality when actions taken to correct problems become permanent changes in policies, procedures, and behaviors. Similar terms that have been used in the past to represent quality assessment include total quality management (TOM) and continuous quality improvement (CQI). These terms may

also be more descriptive than the term quality assurance since they relate to assessing practices and applying management skills to aim for improvement in quality of laboratory work [19].

Many of the practices for assessing quality of laboratory results have been adopted from principles used in business and manufacturing. Thus, QC, TQM, and QCI may be familiar to you as a consumer. Another recent laboratory management procedure that has been borrowed and adapted from business is the Six Sigma process. The Six Sigma process is client oriented and uses facts and data to help make decisions about improving service. In the case of the laboratory, the patient, physician, other laboratory professionals, and other members of the health-care team are all considered clients depending on the situation. The main focus of Six Sigma is to help reduce turnaround time and provide better service with a focus on the patient to create a more satisfied health-care team through these processes. It is another TQM program that includes cost and waste reduction along with other aspects of QA. Aspects of Six Sigma include defining client needs and values with a focus on quality, cost, process, people, and accountability [20].

Quality assurance in clinical laboratory

An important prerequisite in justifying the inclusion of a subject in a curriculum is that there has to be an existing need for inclusion of such a subject. An example is a course in quality assurance in clinical laboratory practice, which should ensure the outcome to be of benefit to technologists and clients alike, when a subject is compiled, it should be indicated what the practical implications of such a subjects should be. Every conscientious worker in the laboratory will be able to realize and understand the role of quality assurance in clinical laboratory situations [21].

The importance of quality assurance in validating and controlling laboratory results makes it thus a very valuable subject in laboratory medicine and it should be mastered by all laboratory technical

workers' quality assurance must take its rightful place in laboratory, as in all aspects of life. It is desirable that all generated results be clinically acceptable [22].

Quality management program

The laboratory must have a documented QM Program designed to monitor, assess and correct problems identified in pre-analytic, analytic, and post-analytic systems as well as overall laboratory scope. A key component of the QM Program is the Quality Assurance Unit (QAU). The QAU must monitor for GCLP compliance, oversee the development of the QM Program, resolve quality related problems as described above, submit status reports to management, and prepare and respond to external audits [(23)]. The QM Program must include evidence of appropriate follow-up actions taken as a result of monitoring, as well as an evaluate the effectiveness of corrective actions [(24).] The laboratory must provide evidence of implementation of the QM Program (i.e., minutes of committee meetings, results of ongoing measurement, and documentation-related complaint investigations). The laboratory must be able to provide evidence of appraisal of its QM Program, (i.e., annual written QM Program and revisions to laboratory policies and procedures, and to the QM Program) [(25)]. The QM Program documentation must demonstrate regular (at least annual) review by the laboratory director or designee(s), the laboratory's monitoring of the QM Program must include an internal auditing program comprised of a comprehensive comparison of the actual practices within the laboratory against the laboratory's policies and procedures (e.g., personnel files, training documentation, QC performance, review of SOPs) or a standard set of guidelines or standards. All findings from the internal audit should be documented in an organized format to allow for appropriate corrective actions and follow-up through resolutions. The laboratory should enroll in EQA programs that cover all study protocol analytes, the laboratory director or designee must document review of all external quality assurance data , corrective actions taken and appropriate preventive actions in response to any unacceptable results must be documented [(26)].

The laboratory must have a documented QM Program which must incorporate the following elements: developed and maintained by the QAU staff; integrated with the institutional QM Program; describe the operational plan with QM Program's goals and objectives; accessible to all staff; designed to monitor, evaluate and correct problems in areas of quality; address monitoring to include complaints and incidents; include all aspects of the laboratory's scope of care; address problems that would interfere with study-participant care or safety while addressing risk assessment; describe procedures for collection and communication of quality and safety information; include control activities (e.g., QC and EQA); include key indicators of quality of laboratory operations that target improvement (e.g., test turnaround time, specimen acceptability, test order accuracy, and safety events) and; demonstrate regular review by the laboratory director or designee. The laboratory's QM Program must include results of ongoing measurement activities of key indicators of quality of laboratory operations compared with internal or external benchmarks and trended over time. The laboratory must be able to use the QM Program for guidance when conducting annual appraisals of effectiveness and must provide evidence of its implementation [23].

Standards for quality management

An overarching Quality Management (QM) Program is essential to ensure safety of study participants and maintenance of quality laboratory operations. The QM Program is a systematic approach to plan the achievement of quality objectives, comply with approved procedures, and assign specific functional responsibilities to laboratory staff. The QM Program should also include an External Quality Assurance (EQA) program, which is set up to externally evaluate the laboratory's analytical performance by comparing performance, using coded reagent panels with peer laboratories [27].

Quality System Essentials

The clinical laboratory standards has developed a guideline for clinical laboratories providing more information on the requirements of the ISO 15189 quality standard. It describes what quality management is and how a quality management system is incorporated in the routine laboratory processes. In this guideline the clinical laboratory standard uses a framework dividing a quality management system into 12 essential elements, the Quality System Essentials (QSE). These together cover all elements of the quality management system, facilities and safety, organization, personnel, equipment, purchasing and inventory, process control, information management, document records, customer service, assessment, occurrence management and process improvement [28].

Quality control program

The laboratory director or designee should be actively involved in the design, implementation, and oversight of a site-specific, written QC program which defines procedures for monitoring analytic performance and consistent identification, documentation, and resolution of QC issues [7,29]. This is so as to be able to detect immediate errors as well as changes that occur over time and hence assure the accuracy and reliability of test results, particularly if the data are used for patient management or product advancement decisions. In addition, the laboratory director and/or designee must determine the number and frequency of QC tests, as well as the appropriate QC materials to use , the quality control program supports functions in the following areas: Test standards and controls, reagents, test specimens, review of quality control data, quality control logs, labeling of quality control materials and reagents, inventory control, parallel testing, and water quality testing [30].

i. Internal quality control (IQC)

Operational techniques and activities within a production site that are used to fulfill requirements for quality of service, internal Quality Control comprises all steps of activity from assessing clinical needs, via collection of sample and measurement of a measurable quantity to reporting of results of measurement. Internal Quality Control is the set of measures undertaken by the staff of a laboratory to ensure quality from the collection of specimens of the test up to the analytical results, and the procedures being planned, ordered and followed up by to the staff itself the measures should include tests on control material and statistical or analysis of patient's data. The main object is to ensure day-today consistency of measurement or observation if possible in agreement with an agreed indicator of truth such as control material with assigned value [31].

Once a measurement procedure has been validated, the laboratory introduces it in to routine use and must establish a means of verifying its stability; in other worlds, the laboratory must verify that the accuracy is maintained, with in admissible limits, over time. This practice is known as internal quality control and internal control procedures differ from each other in the decision criteria employed and in the material that it used to obtain the control data. The most widely employed procedure uses control materials [32].

ii. External quality assessment scheme (EQAS)

The most common forms of external quality control are so-called inter-laboratory compression programs or external quality assessment program often known as external quality assessment scheme by the abbreviation (EQAS) which has been carry outside the laboratory (reference laboratory), necessary for long term 2-3 month, to minimized the variations between laboratories, based on a good internal quality control, to obtain the accurate method and to detect hidden problems. External quality assessment also for evaluates past performance, testing of unknown

samples, compare performance with others and provides a forum for improvements and correction of errors [33]. For understandable reasons the latter is even more difficult than the first. A large series of training session all over Europe on quality assurance for labs substantially increased the awareness for quality [34].

External quality assurance (EQA) programs serve three purposes: 1) To provide an internal measurement tool for ensuring that the information a laboratory generates and provides is accurate, timely, clinically appropriate and useful; 2) to provide the sponsoring and regulatory agencies with confidence that individual laboratories are generating data with a rigor that will support product licensure; and 3) to ensure that clinical trial volunteer specimens will be analyzed in a system that provides accurate and reliable information to ensure trial volunteer safety. This external evaluation of the laboratory's analytical performance is paramount to a complete quality assessment of laboratory operations. Therefore, it is critical that laboratories enroll in EQA programs that cover all study protocol analytes. The laboratory director or designee must review all external QA data and evidence of supervisory review of EQA program results must be available (e.g., signature and date of reviewed results and documentation of corrective or preventive actions taken upon unacceptable results) [14]. EQA specimens must be analyzed, quality assured and reported just as study- participant specimens are tested in the laboratory. As an example, most of the HIV-1 protocol-mandated safety assays are covered by EQA programs administered through the CAP and other organizations. Until recently no EQA programs existed for immunogenicity endpoint assays. Through efforts pioneered by the Division of AIDS, EQA programs for ELI Spot and intracellular cytokine flow cytometry have been established for laboratories involved in the testing of HIV-1 vaccines , the results of ELI Spot and ICS EQA programs have been published, are continually being refined and are becoming open to more participants via commercialization [35].

Eventually these EQA programs will mature and participating laboratories will be assessed bi-annually and provided feedback on their performance [36].

iii. External quality control with standard deviation index

There are two ways important to evaluate the results of external quality control are : Method of Standard deviation index (SI) and Variance index (VI).

The application of the National Programmer for External quality control in Syria is going to be important for improving laboratory performance; and thus began a new phase characterized by tangible progress in the quality of laboratory performance must be a catalyst for the introduction of programs for internal quality control in each laboratory, and make these programs permanent practice, because of their deep reflection importance on the accuracy and control of laboratory results. According to the quality assurance program mentioned, the quality index, which therefore assess the results of laboratories participating in the program, known as Z (Z-score), which represents the absolute value of the index Standard deviation: $Z=|SI|$, any result that represents the absolute value, of each participant laboratory for the average result value. The evaluation of results has follows: Excellent: $0 < Z \geq 0.5$. Very Good: $0.5 < Z \geq 2$. Good : $1 < Z \geq 1.5$. Acceptable: $1.5 < Z \geq 2$.poor: $Z > 2$ [37].

Preanalytical variables

Preanalytical phases are included, preparation of patient and patient identification, collection, transport and storage of specimens.

Preanalytical refers to everything creating an impact on the patient specimen before it is tested for the analyte. Many things can go wrong with the specimen while it is collected from the patient and sent to the laboratory for testing. If the patient and the specimen aren't correctly identified, and the specimen isn't collected or handled properly, the specimen won't be worthy of testing. Suitable

transport conditions such as in ice water or with protection from light may be necessary in order to preserve certain analytes in the specimen prior to testing. Other aspects of the Preanalytical phase include training of personnel for proper collecting and handling of samples, including adherence to specific steps and maintaining turnaround time involving sample receiving and accessioning. Use of well-written procedures and policies can help to minimize Preanalytical errors. Specific information about avoiding Preanalytical errors while collecting, transporting, and processing blood and other body fluid specimens will be discussed later in this chapter [38].

i. Blood specimens

The body fluid most commonly analyzed in the clinical laboratory is blood. Whole blood can be allowed to clot in a clean plastic collection tube and then be centrifuged and the serum removed for testing in clinical chemistry. Conversely, clotting can be prevented by allowing the whole blood to mix with an anticoagulant such as lithium heparin so that it can be measured as whole blood or centrifuged to obtain the plasma for analysis. Other types of testing performed in the clinical laboratory, such as the complete blood count, require anticoagulated, well-mixed whole blood. Serum specimens obtained from venous circulation are most commonly used in clinical chemistry. Therefore, proper collection technique is needed in order to obtain an acceptable specimen, which minimizes Preanalytical errors. Standards or practice in blood collection are found in other resources as those published by the Clinical Laboratory Standards Institute (CLSI; formerly the National Committee for Clinical Laboratory Standards [NCCLS]). A tourniquet typically is used in order to cause short-term venous occlusion, allowing palpation of the veins in the antecubital fossa prior to venipuncture. If the tourniquet is maintained longer than 1 minute, a relative hemoconcentration occurs due to fluid changes. Low molecular weight compounds such as potassium leave the capillaries and pool in the interstitial fluid region during hemoconcentration,

while proteins tend to be increased in the remaining plasma. Clenching of the first prior to venipuncture is a common technique. However, the technique should be avoided prior to collection of specimens for clinical laboratory analysis due to the changes that can be initiated. Fist clenching tends to increase lactate, phosphate, and potassium as well as lower pH. Secondarily, ionized calcium increases due to the transient lactic acidosis [39].

ii. Hemolysis of specimens

Hemolysis is generally a Preanalytical problem that can be avoided. It is graded based on visible presence of hemoglobin, when greater than 20mg/dL and it is often graded as mild, moderate, or gross Hemolysis [39]. Gross Hemolysis will often impact on almost every test method due to release of intracellular constituents into the serum and colorimetric interference due to pigments. Grossly hemolyzed specimens should always be rejected. Lysis of blood cells makes a serious impact on many chemistry tests. For intracellular chemicals such as potassium, phosphates, lactate dehydrogenase (LD), and Aspartate transaminase (AST), Hemolysis will directly increase serum levels. For other analytes such as creatinine kinase, glucose, and bilirubin, Hemolysis will cause chemical interference, which may increase or decrease the results. Mild to moderate Hemolysis may necessitate specimen rejection or at least a qualification statement for particular test results that are positively or negatively impacted. Older whole blood or clotted blood samples will become hemolyzed within 24 hours of the collection time, especially at 24°C and warmer temperatures [39]. Hemolysis can because by a variety of conditions during the collection and processing steps. Difficulty with phlebotomy procedures can cause Hemolysis. Examples include poor placement of the needle into the vein, pulling back the plunger on a syringe too quickly, and allowing air leakage due to a poorly fitted needle. Poor specimens are likely to be obtained and should be discarded when the blood container is only partially filled or fills slowly. Problems during

specimen processing can also lead to hemolyzed samples. For example, wringing out a blood clot prior to or after centrifugation or rough handling during transport are common causes of Hemolysis [39]. Using a small-bore needle when compared to the size of the evacuated tube or forcing blood through a stopper into the evacuated tube is likely to cause Hemolysis as well. Sample indices are measured by some automated chemistry analyzers and can be used to estimate the amount of free hemoglobin in the sample. These indices can be used to establish a criterion for unacceptable specimens. The indices are calculated from multiple wavelength readings of a patient sample diluted in buffer or saline. The calculated results are represented as an approximate hemoglobin concentration or as a semi-quantitative value. The same absorbance readings are also used to estimate relative icterus and lipemia. Some analytes, such as potassium, can demonstrate an almost linear relationship between the amount of Hemolysis and the increase in analyte. This near-linear relationship has led to the suggestion that the indices should be used to correct results for the false increase (or decrease) in analyte concentration that is caused by the presence of hemoglobin. These calculations are not recommended because factors other than hemoglobin. These calculations to altered test values. For example, hemolyzed heel stick specimens from neonates can contain increased amount of colorless intracellular fluid with increased potassium. However, the indices can be used to apply appropriate modifying statements to those samples that the health-care staff chooses not to re-collect. Chemicals leak from the cells in older specimens in which the serum was not separated from the clotted blood cells. Although the serum from old specimens may not appear hemolyzed, the effect may be the same as mild to moderate Hemolysis. Old specimens should be rejected for patient initial reporting. Retesting older sample may be necessary for internal QA practices. The effect of Hemolysis on sensitive results such as potassium, glucose, bicarbonate, and carbon dioxide and most serum enzymes must be considered. An alternative to clotted tubes

that are held for later retesting is the use of serum separator tubes. These contain an inert polymer that moves between the clotted blood cells and the serum during centrifugation. This gel barrier can prevent release of intracellular constituents for several hours. However, gel barriers can't be used for therapeutic drug monitoring since they can interfere with specimen testing. Separated blood, serum, or plasma is commonly held for up to 12 hours at room temperature or for 1 week in a refrigerator for repeat testing. This type of repeat testing, or internal QA practice, will be discussed more thoroughly in later portions of this chapter [39].

iii. Sample preparation

Sample preparation involves processing of the blood sample prior to and in preparation for analysis. Processing involves centrifugation, removal of protein (if applicable), and making an aliquot of the specimen in a test tube or sample cup so that the remaining specimen can be shared with other testing areas. Centrifugation is a common sample preparation technique since most clinical chemistry analyses are performed with serum or plasma. Keep in mind that clotted or whole blood cells can affect chemicals in the sample over a period of time, such that additional chemicals a rise or some chemicals are consumed. Therefore, centrifugation should be timed to occur so that the testing can begin within an hour of collection. Some newer analyzers will perform this step as part of the automation, but for the most part is a separate and important step of sample preparation. Standards of practice in specimen handling and transport may be found in other resources such as Governmental by CLSI/NCCLS [40].

iv. Transport of specimens and management

The accuracy of all laboratory test results depends on the identity and integrity of the specimen submitted. The establishment of a sound specimen chain of custody from collection through to reporting of test results is paramount in ensuring quality data [33]. The laboratory must have

documented procedures for collection, transportation, and receipt of specimens because the accuracy of all laboratory tests in dependent on specimen quality , a laboratory can only ensure specimen integrity when following appropriate specimen management and transportation procedures. A properly completed request form must accompany each study-participant sample to the laboratory. The request form must document unique study-participant identifiers, specimen collection date and time, study participant demographics, specimen type, and the collector's (phlebotomist's) identity. The specimen inspection process must involve verification of the specimen container label information with the request form or log sheet [41]. Any discrepant or missing information must be verified promptly, before specimens are processed or stored by laboratory personnel. The laboratory must have documented Specimen Acceptance/ Rejection Criteria for evaluation of sample adequacy and integrity. The laboratory must maintain an audit trail for every specimen from collection to disposal or storage. Audit trails must verify the date and time an activity was performed and the personnel responsible for that activity. All audit trails must be documented. A shipping procedure must be documented that addresses preparing shipments by following all federal and local transportation of dangerous goods regulations (e.g., International Air Transport Association (IATA)) by laboratory personnel who are certified in hazardous materials/dangerous goods transportation safety regulations twenty-four-hour monitoring of storage conditions (using personnel and/or electronic monitoring with alert systems) and SOPs for response to alerts must be in place to ensure the integrity of samples is maintained [41].

v. Preanalytical errors and specimen problems

Some specimen variations can be controlled through proper patient identification, collection, and handling and strict rejection policies. Light, heat, evaporation, and exposure to the atmosphere will

change many substances in routine clinical chemistry testing. Examples include the photo degradation of bilirubin by light exposure and the heat liability of enzymes. Exposure of plasma samples to high temperatures can significantly lower potassium concentrations [42].

The laboratory or health-care team can be trained to avoid misidentification, Hemolysis, atmospheric exposure to light and heat, and evaporation of blood specimens. Accurate patient identification, specimen identification, and sample aliquot identification are necessary from the time of collection until testing is completed and the result is reported. If there is any question as to the integrity or identification of the sample, the laboratory should reject the sample and request that it be recollected. Supervision of policy adherence and periodic training may be necessary in order to implement and maintain laboratory specimen QA. Specimen collection and handling procedures must be explained to all parties involved in the processing of specimens. It has become increasingly common for nursing personnel, physician assistants, and health-care professionals other than laboratory personnel to collect blood samples. Although laboratory personnel may not be directly involved in the collection of specimens, they are responsible for minimizing Preanalytical errors based on acceptance or rejection of the received specimens. Laboratory personnel are also responsible for training other personnel involved in specimen collection and transport and for communicating effectively in order to maintain optimal quality of specimens for laboratory testing. Since Preanalytical errors seem to make up the majority of most laboratory test problems, proper training is an important area to address [43].

Some Preanalytical problems may or may not be controlled directly by laboratory personnel, but information about such problems should be made available to health-care providers. These problems include patient-related factors such as ambulation, lying down or standing prior to collection, and biological differences, such as time of day, age, gender, and intake of certain foods

or herb supplements. Ambulation prior to specimen collection can impact upon total proteins, lipids, and other protein-bound substances. Levels of cortisol and many other hormones very throughout the day, so collection needs to be timed according to physician orders so as to provide the most accurate information. Intake of food greatly impacts on glucose, triglycerides, certain hormones, and electrolytes, so length of fasting prior to specimen collection is a Preanalytical factor that is commonly addressed prior to specimen collection and testing [39]. Intake of certain foods or herbs may impact on therapeutic drug testing or other laboratory results but often is not within the control of laboratory personnel prior to specimen collection. The age of the patient may be an important variable for the test result. For example, bilirubin and alkaline phosphatase values are different in pediatric patients than in adult populations, so coordinated reference intervals are needed. This variation is addressed through the use of age-appropriate reference ranges, but the information on patient age is often obtained at specimen collection, in the Preanalytical phase [44].

Analytical variables

Chemical analysis involves many steps and components. These include specimen measurement, sample pre-treatment, reagent volume measuring, sample and reagent mixing. Accuracy and reproducibility of the analysis involves following precise steps within a procedure, maintaining the function of an instrument, and testing known or QC samples along with unknown samples. QC practices include the use of QC sample, which are analyzed in conjunction with patient samples and following specific rules for acceptance and rejection of analytical runs. Using analytical methods with a high degree of accuracy and precision as well as maintaining optimal operational conditions of instruments also help to minimize analytical errors. The use of QC samples, following a program of error detection, statistical calculation, error correction, and method evaluation, will be discussed in more detail later in this chapter.

i. Analytical performance

From the medical laboratory perspective, information on the reliability of results is necessary for several reasons. First, a laboratory professional has to evaluate the fulfillment of quality goals in method validation, establishing of IQC or in running daily quality control secondly, it is important that the result of a measurement is accompanied with information of the error or uncertainty (within a defined confidence interval). Thirdly, the competence of the laboratory may be, and is often judged against the analytical performance in EQA or third party assessment according to available international standards. Common understanding and expression of terms is important in any field of science and technology. The pivotal ISO definitions characterizing analytical performance exist as the following concepts, trueness- the closeness of agreement between the average values obtained from a large series of test results and an accepted reference value; precision- the closeness of agreement between independent tests obtained under stipulated conditions; accuracy-the closeness of agreement between a test result and the accepted reference value; uncertainty- An estimate attached to a result, which characterizes the range of values within the true value, is asserted to lie. All testing from pre-analytic phase to the reporting involves with error and uncertainty sources. In quantitative analyses, the reliability of the measurement quality is expressed as random error (i.e. precision) and systematic error (i.e. trueness, or bias). The combination of these two errors is comprehended as total error, TE (i.e. accuracy). For this reason, it is important to distinguish the difference between error and uncertainty as stressed in the available guides. Current international standards applied to medical laboratory accreditation and quality management describe clearly the requirements for evaluation and calculation of the uncertainty of measurement whenever possible. In modern laboratory practice, the expression of the uncertainty of measurement has become an inevitable concept. Uncertainties of non-

quantitative tests in many areas are, expressed as alternative reliability measures such as; false positive rate; false negative rate; sensitivity; specificity; efficiency [45].

ii. Traceability in laboratory medicine

The term "traceability" originated in the metrological community, where it was first defined in 1993 in the International Vocabulary of General and Basic Terms in Metrology [46]. The same year, the Cooperation on International Traceability in Analytical Chemistry was formed to encourage the broad realization of traceability in analytical chemistry [47].With the implementation of the European Union Directive on in vitro diagnostic devices [48], establishing traceability of measurements performed with in vitro diagnostic devices became mandatory and had a worldwide effect on clinical laboratory measurements.

The aim of traceability in laboratory medicine is to link measurement results from a patient sample to a commonly accepted reference, making them comparable across measurement systems, location, and time [49]. The goals and principal approaches for establishing traceability are the same as those described over the last 50 years for standardizing clinical laboratory measurements [(50),(51),(52),(53),(54)]. Such activities include the CDC Lipid Standardization Program [55] and the National Glycohemoglobin Standardization Program [56]

iii. Analytical variables and quality control

Quality control (QC) is an aspect of quality assessment (QA) that is used to assess the analytical phase of patient testing. QC samples are solutions or chemicals of known concentration that mimic a patient's specimen. They are tested along with patient specimens to monitor the validity of the analysis. Usually QC samples are collected, processed, and manufactured commercially. QC samples are often preserved and stored in a manner different than patient specimens, so they bypass the Preanalytical phase of testing. QC results are not used to track the post analytical phase of

testing because they are not reported to physicians. They are very important, however, in helping to determine if current test results are validly measured in the testing phase. Federal regulations require that two QC samples be analyzed at least once per day for each analyte using control procedures and rules that monitor the entire analytical process to detect immediate errors. The measurement of QC of QC samples will detect problems of precision and accuracy over time. Interpretation of control results is based on using specific rules for acceptance and rejection of QC results, documenting results and decisions, and having a process for resolving problems that result in rejection of results. QC consists of various samples and procedures used to detect errors that occur due to test system failure, changes in environmental conditions, and differences in operator performance. Some instruments provide QC results from electronic detector output, known as "electronic QC" (EQC). These electronic performance indicators are acceptable to supplement analytical validity testing but cannot take the place of running QC samples along with patient samples to test all aspects of the analysis. QC rules should also monitor t accuracy and precision of the test performance over time.

Accuracy is the comparison of a result with the true value, while precision is the comparison of results with each other. A small amount of inaccuracy and imprecision is inevitable and accepted, but limits are set through federal regulations by the Clinical Laboratory Improvement Amendment [57].

iv. Quality control program

The goal of a well-defined QC system is to detect immediate errors in an analytical run while minimizing the number of false rejections. The simplest type of QC procedure uses one rule to reject the analysis based on QC results falling outside of a range such as the 95% range. If this is used, 5% of the time, a result that falls just outside of the 95% range would be falsely rejected.

Likewise, 5% of the results that are accepted within that range would also be a false rejection. These facts are based on probability that the correct decision was made 95% of the time when results that fall within this range are accepted. When testing is qualitative- that is, positive or negative- a simple one-rule policy is acceptable. Historically, manual testing was assessed with a one-rule rejection policy, tracking results over time to observe for errors.

False rejections are false alarms. They refer to the situation in which the testing process is actually acceptable but one QC result is occasionally and slightly outside of acceptable limits due to chance alone. Using multiple rules for acceptance and rejection, including some rules based on previous results, can lower the false rejection rate. This is especially important when automated testing is used, as in mort clinical chemistry testing. Adherence to a QC program with specific rules will help to achieve analytical goals during routine laboratory operation. As was mentioned earlier, QC samples may be purchased with known values for each analyte based on reported mean and SD. These are called assayed QC sample. QC samples may also be purchased without known values. Control materials should resemble as closely as possible the human materials to be analyzed, with the same general makeup or specimen matrix. Controls may resemble calibrators provided by a vender but are used differently. An assay should be calibrated with different material than the QC samples. Control materials should be tested in the same manner as patient samples so all steps of the analytical process are checked. Two control levels for each analyte are recommended, and there are sometimes used. QC levels may be chosen based on the clinically useful limits of the analyte, medical decision levels, or an analytical measurement range. Additional controls should be utilized as necessary to challenge the entire analytical range. These samples are internally evaluated within the laboratory [58].

Internal QC is performed daily in the laboratory, whereas external QC or proficiency testing (PT) is performed only occasionally as a test of competency. An outside agency provides samples and evaluates the results of testing. PT samples must be tested using the same procedures that are used for laboratory testing of routine QC and patient results. The results obtained from testing the PT samples are reported to the outside agency. The agency then provides a report of acceptance or rejection of the PT sample results for the participating laboratory based on the expected mean and SD testing results from all participating laboratories. Both types of QC, internal and external, are an important part of TQM and are required by federal regulations and voluntary accreditation bodies such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and the College of American Pathologists (CAP). A single lot number of control material should be purchased in quantities large enough to last 1 year. Adherence to manufacturer's storage requirements should increase the stability of most constituents. Most liquid controls are stored frozen at-10º to -20ºC. Storage in a frost-free freezer, one that has repeated freeze-thaw cycles, should be avoided. Lyophilized material must be reconstituted according to the manufacturer's guidelines using the recommended diluents and a highly accurate (class A) volumetric pipette. When a new lot number of control material is received, even when the mean and SD are provided by the manufacturer, each analyte should be assayed on 20 or more separate runs. A minimum of 20 data points is needed to establish a new mean and SD. These assays must be analyzed in parallel with the previous lot number control material [59].

A new mean and SD should be established if the control is unassayed or if it is different than the control data provided by the manufacturer. QC ranges can be set using several methods. Ranges can be set from the measured or provided SD so that statistically significant errors are detected, but they should comply with the federal guidelines for allowable SD. Federal guidelines also set

fixed limits for precision, based on the SD and on total error. Statistical analysis of control samples is based on the assumed Gaussian distribution of the data. Figure 2-2 shows a typical Gaussian, or bell-shaped, curve. With a Gaussian curve of the population, 68% will be within 1 SD, 95% within 2 SD, and 99.7% within 3 SD of the mean. This means that 95% of acceptable QC results should fall within 2 SD of the mean. The following statistics are calculated from the collected data and applied to QC rules to judge for analysis acceptability [60].

v. Quality Manual

The quality manual of a laboratory is a document or a set of documents describing the organizational structure, responsibilities, procedures and processes by which the laboratory achieves its objectives and gains confidence in its work. The manual is indispensable for achieving and maintaining good overall quality. Furthermore, the preparation of a quality manual may induce the laboratory to improve quality. Even a non-mandatory quality manual may be a valuable document for a clinical laboratory in demonstrating to clinicians and the hospital administration a commitment to quality. The laboratory shall define and document its policies and objectives for, and its commitment to, good laboratory practice. The hospital management shall ensure that these policies and objectives are documented in the quality manual and communicated to, and implemented by all laboratory personnel concerned. The quality manual contents are as follows, quality policy and quality system, organization, quality control, personnel, accommodation and environment, equipment, reference materials, test procedures, handling of reagents, sample collection, storage and disposal, maintenance of records and laboratory reports and dispatch of reports [61].

vi. Standards and controls

Individual assay controls must be in place to ensure assay performance. Control activities must be well defined and managed through an ongoing quality control (QC) program to capture immediate performance issues, as well as assay problems that can occur over time [(62)].

vii. Method Validation

According to the standardized definition, used for validation, this evaluation process is confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use are fulfilled. A process very close to validation, i.e. verification is performed when a laboratory wishes to confirm that specified requirements have been fulfilled. In laboratory medicine, validation can be understood as an adequate examination of a laboratory or a POCT method of measurement intended for a clinical investigation, i.e. monitoring or diagnosis. Clinical laboratory professionals meet the need for selection and evaluation of either new or modified methods recurring. At the time, both standardized and non-standardized methods shall be covered. Good laboratory practice postulates well established processes prior to method adoption to routine use. According to the modern approach of a new method introduction begins with establishment of need, method selection, and quality goal setting. The six valid analytical method principles have been introduced in the EURACHEM Guide for the Fitness for Purpose of Analytical Methods. The first principle stresses that analytical measurements should be made to satisfy an agreed requirement regarding measurements made under well-defined quality control and quality assurance procedures. Thus, an operational definition is needed first to agree on [(18)].

Due to its demanding nature, the outlines of validation (and verification) shall consist of: Planning, timing and follow up; Performance according to reasonable schemes; documentation; reporting; acceptance and in the laboratory medicine field, the first method evaluation schemes were

introduced in the 1970s. Several experts and expert groups have since then worked out evaluation protocols for medical laboratories and IVD manufacturers [2].

viii. Calibration materials in clinical laboratory

Calibration is a measurement process that assigns values to the property of an artifact or to the response of an instrument relative to reference standards or to a designated measurement process. The purpose of calibration is to eliminate or reduce bias in the user's measurement system relative to the reference base. Calibration refers to a set of operations that establishes-under specific conditions-the relationship between indications of a measuring system, or values represented by a material measure or reference material, and the corresponding results (values of quantities) obtained using measurement standards and quantitative measurement procedures are based on calibration materials (calibrators) are reference materials, which are used exclusively for calibration purposes. They must not be used for controlling analytical procedures; control materials, such as control sera, should not be used for calibrating methods or test systems. Solutions of calibration materials should never be used for supervising the analytical procedures in quality control. When introducing a new method or training new laboratory staff, solutions of calibrating material should be, assured in dilution series of 5, 10 different concentrations. The "calibrating curve" obtained in this manner is used for control of linearity. Limits of detection and working range within lower and upper limits and in routing work, usually a "one point calibration" may be satisfactory, using a concentration of calibrator at the upper range of expected values. For some analyses, e.g. protein to the quality control charts for accuracy. Self-calibrating instrument devices should be checked by manual calibration at least once a month [63].

Calibration and calibration verification-calibration is defined as procedure which uses known quantities of analyses to adjust the analytical system to ensure that result will be accurate. There

are two types of calibration, primary standards are usually aqueous-based and consist of weighed-in amounts of pure material. Secondary calibrators are usually serum-based and the analyte concentration less precisely determined by running many times against a former secondary calibrator or a primary calibrator [31].

Calibration verification grew out of the original regulation on linearity testing. Calibration verification consists of running at least three standards every six months or more frequently if the manufacture instruction so stat and this is especially important in those assays that utilize a single point standard or are calibrated using the extinction coefficient of product or substrate. There are numerous commercial sources for calibration verification materials and it is best to check availability with reagent or instrument vendors and the data are best presented in graphical form with expected values on the X-axis and recovered values on the Y-axis. The regulations state that values can only be reported that are no higher or no lower than the highest and lowest verification standard. The limits of acceptability of this data are not stated in the regulations it is the prerogative of the laboratory director to state the acceptable limits in the QC manual. An example might be to accept deviation of 5% of the observed value from the expected value [64].

ix. Control of precision

Precision it is agreement between replicate measurements and true value. It has no numerical value but this expressed by the term impression, to ensure the precision of reagents, one single vial or test strip of each lot may be analyzed. This also applies to taking 20 replicate tests for the first evaluation of each new instrument, and from a single lot for each specified analyzes. These measurements may be repeated at suitable time intervals, depending on technical requirements for the requested or locally produced. Remaining samples of serum or plasma can be collected each day, pooled and frozen. After a certain period of time (1-12 weeks, depending on the amount of

material and the stability of the analyze), all frozen samples are thawed, pooled, portioned in aliquot volumes (2 or ml depending on the daily volume needed) and frozen again and the concentration or activity of an analyze may be measured over 5-15 consecutive days to determine precision in the performance of analysis. It may be sufficient to plot the results of measurement on the quality control chart every day and calculate the data retrospectively after a suitable period of time (e.g. one week). The control materials must maintain sufficient stability of the analyses to be measured. Their composition should be similar to those in the patients' specimens. Control materials should not be used for calibration of a method and/or an instrument. The concentration or activity of a specified analyze may be chosen at borderline of the reference range [25].

For routing investigations, control of precision must be made in each series of measurements. The shortest series contains a single patient's small. In longer series of measurements, control samples should be inserted after each segment of 10 to 20 samples from patients and the precision measurement of specified analysis is acceptable if the relative standard deviation = (coefficient of variation) is smaller than the requirements in smaller than the requirements in clinical decision-making. Every new batch of control material should be compared with the control material in use prior to its introduction for the purpose of quality control [25].

The mean and standard deviation should be calculated from the results of the control materials at timed intervals (15 results every four months at the longest). In case of low precision the equipment, reagents and methodology as well as the calibration material need to be thoroughly reassessed [20].

Remaining samples of serum or plasma can be collected each day stored and frozen. After a certain period all frozen samples are thawed, pooled, divided into aliquot (2-ml) volume and frozen again. The concentration of an analyte may be measured over 5-10 consecutive days to determine

precision in the performance of analysis .The control materials must maintain sufficient stability of the analyte to be measured. Their composition should be similar to those in the patient specimens. Control material should not be used for calibration of a method and/or an instrument for routine investigations; Control of precision must be made in each series of measurements. The precision measurement of a specified analyte is acceptable if the relative standard deviation (SD) or coefficient of variation is smaller than the requirement in clinical -decision-making. Every new batch of control material should be compared with the control material in use prior to its introduction for the purpose of QC. The mean and SD should be calculated from the results of the control materials at timed intervals. In case of imprecision the equipment, reagents and methodology as well as the calibration material must be reassessed [65].

x. Errors of imprecision

Precision is a measure of reproducibility. Errors of imprecision are often referred to as errors of scatter because they are irregular, or random. Results, differ from the correct result by varying amounts and common causes of imprecision in laboratory practice, the following are the commonest causes of inconsistent random errors; incorrect and variable pipetting and dispensing caused when Pipetting and dispensing techniques are poor due to inadequate training, on supervision of trainees, or careless working; Pipettes with chipped ends or unclear markings are used; pipette fillers are difficult to use; automatic pipettes and dispensers are not used correctly or pipettes tips are not adequately cleaned and dried before reuse (where reuse is possible); inadequate mixing of sample with reagents; samples are not incubated consistently where incubation of tests is required; glassware or plastic ware is not clean or dried completely before reuse; equipment malfunction caused when laboratory staffs are not trained in the correct use and maintenance of equipment, instrument readings fluctuate due to unstable power supplies and the equipment is not

fitted with a voltage stabilizer; dirty or finger-marked curettes are used in colorimeters or the sample contains air bubbles; in hot humid climates, the glass surfaces of lenses and filters become damaged when not protected from fungal growth; battery operated equipment performs erratically because the battery is not sufficiently charged; incomplete removal of interfering substances such as red cells when performing serum assays [66].

xi. Control of accuracy

The materials for control of accuracy can also be produced locally but care has to be taken in evaluating the target values. Material for control of accuracy can be produced by manufactures with given assigned values, preferably reference method values made on each fourth or eight series of measurement every day, week or month depending on stability of the analytical system. Accuracy is checked when changing reagents instruments or control material or when changing the method. Accuracy must be assessed with control material containing the specified analyte in different concentrations: normal and abnormal values. Different concentration of a constituent in the control material should not be produced simply by diluting the control material with water or buffer solutions, unless it has been demonstrated that the dilution of all the constituents does not influence the analysis [65].

Accuracy its agreement between the best estimated of quantity and it is true value. It has no numerical value but this is expressed by the term of inaccuracy, the numerical difference between the mean of a set of replicate measurement, and the true value [66].

Accuracy control does not necessarily need to be assessed at every run. It may be made on each fourth or eighth series of measurements every day week or month, depending on the stability of the analytical system. Accuracy must be checked when changing reagent instruments or control

materials, and when changing the methodology for a specified analyzes. The time intervals for checking accuracy may depend on the technical requirements for the requested tests [66].

Accuracy must be assessed with control materials containing the specified analyze in different concentration at least one of them in a pathological range. The matrices of different control materials should show distinct differences in type and/or concentration of constituents in order to detect influences of the matrix. The type of control materials should be of the same nature as that of the patient's sample, e.g. control serum for serum constituents, control plasma for coagulation testing, whole blood for hematological tests, and urine for urinalysis, so that matrix effects of the control material and of the patient's specimen are identical, different concentrations of a constituent in the control material should not be produced simply silting the control material with waterier buffer solutions, unless it has been demon started that the dilution of all the constituents does not influence the analysis, it is good practice to have control materials that are made by different manufacturer than the test system, the use of quality control materials made by other companies to increase the assurance that these devices are performing successfully, laboratories should establish their own means and standard deviations when implementing statistical QC procedures, rather than use better values provided by manufacturer [66].

xii. Errors of inaccuracy

Accuracy is defined as the closeness of agreement between a test result and the accepted true value. Errors of inaccuracy are often referred to as errors of bias because they are consistent, or systematic. All the test results differ from their correct results by approximately the same amount and the following are the commonest causes of consistent systematic errors; incorrect or infrequent calibration of a test method or quantitative tests being read at an incorrect wavelength (incorrect filter used); using an automatic pipette set at an incorrect volume or one that has been calibrated

wrongly prepared, incorrectly stored, or used beyond its expiry date; consistent calculation error, incubating samples at an incorrect temperature due to the temperature of a water bath or heat block being wrongly set and checked and reliable test results depend on laboratory staff keeping errors of imprecision and inaccuracy to a minimum by good laboratory practice and quality control. Consistently reliable results depend on the early detection and correction of errors [22].

xiii. Systematic and Random Errors

Systematic errors are always of the same sign and magnitude and produce biases (which can be positive or negative), while random errors are unpredictable. Systematic errors may be constant or proportional. Several may exist at the same time, and only the net bias will be evident. Systematic errors shift the mean of the distribution, while random errors widen the distribution. Shifts or trends are types of systematic errors. A shift is defined as a change in QC results that happens abruptly and continues at the same level. This may be due to recent calibration, new shipment of control, or new lot number of calibrator. A trend is defined as a gradual change in one direction in QC recovery. This may be due to the aging of controls or reagents or to needed maintenance. Systematic error may be due to: aging reagents, aging calibrators, instrument components, optical changes, fluctuations in line voltage, wear and tear of instrument, reagent lot variability, calibration differences, technologist interactions and Random error may be due to: reagent dispensing, sample evaporation, temperature of analyzer, electro-optical mechanism, calibrator reconstitution, environmental conditions, instability of instrument, variation in handling techniques: pipetting, mixing, timing and variation in operators [67].

ivx. Commercial control samples

Commercially obtainable control samples for certain clinical chemical constituents have been available since 1953 and are now being given wide consideration and acceptance by laboratory

workers. Unfortunately, some of the manufacturers of control sera have lately gone so far as to claim their products to be standards as well as control sera. Such allegations could lead to serious consequences if left unchallenged. To forestall widespread uncritical acceptance and indiscriminate use of these materials as standards, the various aspects of such a practice should be thoroughly examined [68].

vx. Error of control samples

It is true that the values cited by the manufacturer for his product are, like those of the "standard samples" of the Bureau of Standards, the averaged results of their own analyses and those of the cooperating laboratories, and therefore are the truest values obtainable for the specified method of analysis. If such control sera are to be used as standards as suggested, the manufacturers should realize the tremendous responsibility that they are assuming voluntarily. It has already occurred that the values given for a few of the constituents of some control sera have been in error. Blind acceptance of erroneous values would tend to create even more problems for the clinical laboratory. Normal values as well as values in disease will be obscured, and discrepancies noted between laboratories and between methods that under normal circumstances might be nonexistent. An example of the dangers involved is illustrated by the longstanding discrepancy between the normal hemoglobin values of the United States and the United Kingdom. The disagreement was finally traced to the wide distribution and acceptance in Great Britain of an artificial standard whose (erroneous) hemoglobin equivalent had been established by fiat. Such problems are not apt to occur if the control sera are used simply as controls, since any discrepancy would result in an immediate investigation of one's own reference standard and/or reagents. If an error is traced to the control serum itself, a more reliable product by another manufacturer should then be sought. The important point is that, in the latter case, a fallacious report would not be sent out [68].

vix. Preparation of control materials

Control material can be prepared in the laboratory or obtained from external sources. Two categories can be distinguished according the matrix of the material [(69)]. Defined-matrix materials: Defined matrix materials are also known as non-biological or synthetic. It essentially refers to solutions of the component in a medium of known composition. The advantages of these types of material are that they are reproducible, that the quantity to be measured can be defined in the preparation (by weight, for instance), and that the present of interferences can be excluded since the composition of the matrix is known [(68)]. Biological-matrix materials: Refer to biological fluids, such as blood, plasma, serum, urine, etc., that have been appropriately stabilized. They are generally preferred for quality control, either internal or external, due to their similarity to patient samples [(70)]. Biological materials can be of human origin or derived from animals. Those of animal's origin have the advantage of being cheaper and presenting less risk of infection [(71)].

viix. Lyophilization of control materials

In aqueous control materials, water extraction by Lyophilization (sublimation under vacuum) allows a dry material to be obtained that normally remains stable at 4ºC for months or even years. Lyophilized control materials, although more stable than liquids, have the inconvenience of requiring reconstitution with water prior to use, thereby introducing a possible source of errors (water quality, accuracy of titration). Furthermore, the process of Lyophilization alters various properties of biological materials (viscosity, PH, turbidity, etc.) and affects proteins and lipoproteins [(22)].

viiix. Control charts

The control results obtained in successive series can be represented in charts that allow easy assessment of the behavior of a measurement procedure over a period of time. QC limits may be

set as a fixed difference from the target mean or as a multiple of the standard deviation of control material results over time. Most laboratories actually perform a combination of the two techniques, the standard deviation of a new control material is determined when the method is known to be performing well, typically, 20 control results from at least five different runs are used to establish the control materials standard deviation (SD). The standard deviation then is used to establish fixed control limits (such as ± 3 SD from the target mean). Few laboratories use a continually calculated "running" standard deviation to set their control limits (a procedure common in statistical process control in manufacturing). A control material may have more than one set of limits when multiple rules are used, when a single rule QC protocol is used, the upper and lower limits are based on the balance between error detection needs and desire to avoid false run rejection. A CAP Q-Probe study showed that laboratories typically choose limits of 2.2 to 3.2 times the standard deviation [72].

i***vxx. Levey – Jennings chart (LJ)***

Levey – Jennings (LJ) charts display quality control data over time (Levey, 1950). One axis is time or sequential run numbers. The other axis is the value of each quality control result. This axis typically is centered on the target mean with upper and lower control limits marked for easy viewing; LJ charts allow laboratories to visualize QC results over weeks or months. Trends and patterns can be identified. Saw tooth pattern can be recognized. The method has a tow-week interval between calibrations, but it is apparent that calibration begins to change after about nine days LJ charts also allow laboratories to apply multiple rules without the aid of a computer. The Levey-Jennings chart consists of a plot of the value obtained for the control material (y axis) in each series (x axis). Horizontal lines indicate the mean value of the control material and the established decision or tolerance limits. The value obtained for the control material in each series

can be shown as an absolute value or as the deviation obtained from the mean value (X_m) and expressed in multiples of the standard deviation, when the measurement procedure is stable, the results should oscillate randomly between one side of the mean value and the other, and the oscillations should occupy the width of the range Xm±2s [73].

xx. Cumulative sum control chart (Cusum chart)

Cumulative sum methods are used by only a small percentage of clinical laboratories, and the methods calculate the running difference between QC results and the target means. The commonest CUSUM method is called V-mask, because a plot of acceptable CUSUM results over time stays within a sideways. When an analytical method performs acceptably the CUSUM value will fluctuate around zero or will rise slowly over time. The magnitude of the fluctuation will be small. An analytical method with bias will exhibit CUSUM value that rise or fall rapidly over time. An analytical method with poor precision will exhibit large fluctuations in sequential CUSUM values. CUSUM methods readily identify consistent bias problems CUSUM methods, unless analyzed carefully for fluctuations, are relatively insensitive at identifying precision problem [71]. Cusum charts, although less widely used, show systematic errors more clearly than Levey-Jennings charts and can, there for, be used in parallel. It is necessary to calculate the difference between the value obtained for the control material and the mean value each day. This difference, which can be positive or negative, accumulates; in other words, the value is added to those obtained in earlier series [72].

xxi. Multiple Westgard rules

Westgard recognized that the use of simple upper and lower control limits lacked power to identify analytical problems [74]. To an acceptable rate of error detection, control limits had to be narrow and control testing frequency had to be high, Westgard realized that single rule QC protocols

ignored previous data and data obtained simultaneously on other control samples. He developed a set of rules that used this information. By using multiple rules, error detection rates can increase without increasing the false rejection rate. A nomenclature was developed to quickly describe multiple rules; each rule description has the form of Ab. A is either the number of control results needed to implement the rule (e.g. 1, 2, 10) or the letter R (for range). The subscript consists of one or two symbol that describe the statistic being applied to the control results (e.g. 2_s= 2 SD, T=trend, x=target mean). The symbolic description of the Westgard multirule set is: 1_{2s} (warning) 1_{3s}, 2_{2s}, R_{4s}, 4_{1s} and 10_s. This translates to a warning when a single control value is more than 2SD from the target mean and run rejection if any of the other rules is violated these rules are applied sequentially, and rejection criteria are described below:

1_{3s} – Any control result more than 3 SD from the target mean.

2_{2s} – The last two control results (or two results from the same run, even on different control materials) are more than 2SD from the target mean.

R_{4s} – The difference between successive results 4 SD 4_{1s} – The last four consecutive control results exceed x + 1_s or are below x - 1_s, 10_s – The last ten consecutive control results are on the same side of the target mean. Westgard multirule set can be modified by adding or subtracting rules, by changing the action limits for a rules (e.g. $1_{3.5s}$), or by changing the number of control results tested by the rules (e.g., 12). Each modification alters the error detection rate and the false rejection rate. These factors also can be adjusted by changing the number of controls per run (for batch analyses) or the frequency of control testing [75].

Good clinical laboratory practices (GCLP)

The Good Clinical Laboratory Practices (GCLP) concept possesses a unique quality, as it embraces both the research and the clinical aspects of GLP, the development of GCLP standards encompasses applicable portions of 21 CFR parts 58 (GLP) and 42 CFR part 493 (Clinical Laboratory Improvement Amendments -CLIA), due to the ambiguity of some parts of the CFR regulations, the GCLP standards are described by merging guidance from regulatory authorities as well as other organizations and accrediting bodies, such as the College of American Pathologists (CAP), and the International Organization for Standardization (ISO) 15189 . The British Association of Research Quality Assurance (BARQA) took a similar approach by combining Good Clinical Laboratory Practice GCLP [63]. The GCLP standards were developed with the objective of providing a single, unified document that encompasses sponsor requirements to guide the conduct of laboratory testing for human clinical trials. Examples of these types of tests include protocol-mandated safety assays such as diagnosis of HIV-1 infection, blood processing to obtain high quality specimens routinely, and cellular and serological immunogenicity assays (e.g., enumeration of antigen-specific cells by ELI Spot or flow cytometry, or enzyme-linked immunosorbent assays (ELISA) to support clinical trials on a product licensure pathway. The intent of GCLP guidance is that when laboratories adhere to this process, it ensures the quality and integrity of data, allows accurate reconstruction of experiments, monitors data quality and allows comparison of test results regardless of performance location [73].

In this paper, we expand the existing knowledge on GCLP standards based on GCP and GLP and included elements of CAP, CLIA, and ISO to enhance and provide implementation guidance for the GLP requirements [76]. To illustrate the need for a single unified GCLP standards document, Table 1 compares major elements of US, UK and other international guidance

documents, showing current gaps. The GCLP core elements described in this paper include: organization and personnel; laboratory equipment; testing facility operations; quality control program; verification of performance specifications; records and reports; physical facilities; specimen transport and management; personnel safety; laboratory information systems and quality management. By recognizing these standards as the minimum requirements for optimal laboratory operations, the expectation is that GCLP compliance will ensure that consistent, reproducible, auditable, and reliable laboratory results from clinical trials can be generated for clinical trials implemented at multiple sites. A corollary of this infrastructure is that the data will be produced in an environment conducive to study reconstruction, enable prioritization between candidate product regimens and guide rationale decision making for moving products forward into advanced clinical trials [77].

i*. *Organization and Personnel

Appropriately trained and well organized laboratory staff are key to the successful operation of a research facility. Systems are required to drive organizational structure, training and ongoing competency assessment to ensure appropriate accountability and communication during study conduct.

All personnel must receive direct and detailed training for the performance of all duties and tasks that they perform. Competency assessments must be conducted and recorded for all components of the employee's training and functional responsibilities upon completion of initial training. A clinical laboratory continuing education program that is adequate to meet the needs of all personnel must be documented, and evidence of ongoing adherence by all laboratory personnel must be readily available. A testing laboratory must have the following documents stored in the laboratory or readily available for authorized personnel: Organizational, departmental, and/or personnel

policies that address such topics as orientation, training, continuing education requirements, performance evaluations, benefits, discipline, dress codes, holidays, security, communication, termination, and attendance job descriptions that define qualifications and delegation of duties for all laboratory positions , personnel files that document each employee's qualifications, training, and competency assessments as they relate to job performance , and the organizational chart(s) that represent the formal reporting and communication relationships that exist among personnel management and between the main laboratory unit and satellite units [30].

ii. Job-description, education, and training

The laboratory director must designate staff who has overall responsibility for the study and serves as the single point-of-contact for document control, staff training and familiarity with GCLP. All laboratory personnel must receive direct and detailed job-specific training and continuing education to perform all duties so that they understand and competently carry out the necessary functions. Additionally, competency assessments must be conducted every six months during the first year of employment, and annually thereafter. Annual evaluations for the employee's overall performance of job responsibilities, duties, and tasks as outlined in the job description must be given to all laboratory personnel. The laboratory must employ an adequate number of qualified personnel to perform all of the functions associated with the volume and complexity of tasks and testing performed within the laboratory. All laboratory staff signatures, initials, or codes used as staff identifiers on any laboratory documentation must be linked to a printed name list. This laboratory's documented list should be a "controlled or traceable version" document that must be updated if changes occur in the laboratory. Signature logs should be archived so that those individuals who performed trial testing throughout the length of a trial are identifiable [30].

iii. Laboratory Equipment

A definition for laboratory equipment has been provided in NOTE under Clause 5.3 Laboratory Equipment to include instruments, reference materials, consumables, reagents and analytical systems. This definition broadens the calibration and maintenance program of equipment to cover demonstration of proper function of reagents and analytical systems. Preventive maintenance is in fact a term more appropriate than calibration to most medical equipment and analytical systems. Much of such equipment is maintained or calibrated, if required, by manufacturers which are not accredited laboratories. Nevertheless, proper maintenance and calibration, despite being carried out by manufacturers, has to be insisted upon, wherever necessary. Where calibration of standard laboratory equipment e.g. temperature monitoring device or volume measuring equipment, is involved and such equipment affects quality of results, calibrations should be conducted by accredited calibration laboratories [(78)].

Proper maintenance of all laboratory equipment is necessary for assays to function within manufacturer's specifications. Internal preventative maintenance activities as well as vendor provided maintenance/repair for laboratory equipment is paramount in providing accurate and reliable results. The standards below provide direction on how to accomplish this. Laboratory staff must conduct preventive maintenance and service per manufacturer specifications by following documented daily, weekly, and/or monthly routine maintenance plans for all equipment utilized to ensure that all equipment performs consistently and reproducibly during the conduct of the trial. Additionally, the laboratory must document all scheduled preventive maintenance, unscheduled maintenance, service records, and calibrations for all equipment utilized. This documentation should be readily accessible to operators. As a follow-up step, the laboratory director or designee must consistently review, sign, and date all documentation at least monthly to establish an audit

trail. The laboratory must establish tolerance limits for equipment temperatures and other monitored conditions (e.g., % CO_2, liquid nitrogen levels) that are consistent with manufacturers' guidelines and procedural activities because certain reagents and equipment perform optimally under specific conditions. The lab should also maintain daily (or "dates of use") record of temperatures and other monitored conditions (e.g. humidity). For observations that fall outside of designated tolerance ranges, the laboratory must maintain appropriate documentation of corrective action for these out-of-range temperatures and other conditions [30].

iv. Reagents and Materials

For quantitative tests, it is necessary to use control materials at known values that span the reportable range of the assay where clinical or patient management decisions are made. For example, in the ELI Spot assay, the use of Gag peptides or HIV-1 that traverses the assay dynamic range or negative sera that show a range of responses to Cytomegalovirus-derived peptides. For qualitative tests, include positive and negative controls with each run. For staining procedures, gram stains require both Gram positive and Gram negative control organisms to be used once per week and with each change of a lot number of any component in the stain procedure. Other stains require daily or day-of-use QC, using a positive reacting organism and a negative. The laboratory must establish and document site-specific tolerance limits for acceptance of control results because manufacturers tend to set wide ranges to accommodate a spectrum of laboratory settings. All QC samples must be tested in the same manner as study-participant specimens and by the personnel who routinely perform study-participant testing [79].

v. Quality of reagents and water

If specific water types are required per manufacturer for certain testing procedures, the laboratory must ensure that records of water quality testing are complete and/or indicate that the required

standards for water quality (e.g., pH, resistively) are consistently met the laboratory must document evidence of corrective action taken when water testing does not meet defined tolerance limits [80].

vi. Quality Control Materials and Reagents

All QC materials and reagents currently in use must be prepared and stored as required by the manufacturer. If ambient temperature is indicated for storage or use, there must be documentation that the defined ambient temperature is maintained and that corrective action is taken when tolerance limits are exceeded [81].

All QC materials and reagents must be properly labeled for content and include storage requirements, date opened, prepared, or reconstituted by the laboratory, and the initials of personnel who prepared/reconstituted the QC material and reagents, and expiration date [82]. An expiration date must be assigned to QC materials and reagents that do not have a manufacturer-provided expiration date or an expiration date that changes upon reconstitution or use. The manufacturer should be consulted should this situation arise. (Exception: Microbiological organisms—storage and sub-culturing techniques will determine time of use). Deteriorated or outdated (expired) QC materials and reagents must not be used because this may jeopardize the quality of collected data [83].

vii. Standard Operating Procedures (SOPs)

Standard operating procedures (SOPs) are critical for maintaining consistent test performance. The laboratory must write SOPs for all laboratory activities to ensure the consistency, quality, and integrity of the generated data. Current SOPs must be readily available in the work areas and accessible to testing personnel [30].

The laboratory must write these SOPs in a manner and language that is appropriate to the laboratory personnel conducting the procedures. SOPs should also be written in a standard format, such as the format recommended by the .Clinical and Laboratory Standards Institute (CLSI). All laboratory personnel must document and maintain verification that they have reviewed and understood all relevant SOPs so that there is evidence that all personnel are knowledgeable of appropriate laboratory SOPs [30].

viii. Quality Control Logs

Quality Control (QC) logs must document control results assayed with each test to determine the acceptability of the QC run and to aid in detection of shifts and trends in control data [84]. QC records must be readily available to the staff performing the test. Results of controls must be recorded or plotted in real time (e.g., Levy Jennings [LJ] charts or control charts) to readily detect a malfunction in the instrument or in the analytic system. Laboratory personnel who perform QC runs, record results, and plot data on graphs must record their initials, date, and time as testing is performed. QC records should contain detailed information to reconstruct establishment of ranges for each QC material used for monitoring analytic performance. Information should include, but is not limited to: Package insert (containing material name, manufacturer, concentration, lot numbers, etc.), opened dates, expiration dates, dates of testing, testing personnel, raw data, evaluation, approval, and other appropriate information. Laboratory supervisory personnel must regularly review, sign, and date QC records and corrective action logs at least monthly QC record retention time periods established by the laboratory must meet or exceed the requirements set forth by the product sponsor and/or any applicable regulatory bodies such as the FDA [85].

ivx. Document control plan

The laboratory must maintain a written current document control plan that addresses and ensures the following vital elements of SOPs: A master list of SOPs currently used in the laboratory; an authorization process that is standard and consistent, limiting SOP approvals to laboratory management ; assurance that all SOPs are procedurally accurate and relevant, as well as review of each SOP at appropriate time intervals ; removal of retired or obsolete SOPs from circulation and identification of them as retired or obsolete; and an archival system that allows for maintenance of retired or obsolete SOPs for a period defined by the laboratory that meets or exceeds the requirements of applicable regulatory bodies, such as the U.S. FDA [(30)].

x. Inventory control

The laboratory must have an established documented inventory system to maintain an appropriate amount of "working" supplies and reagents and to prevent delays in testing of specimens due to lack of required reagents , there must be evidence of a system which highlights the need to place supply orders, tracks orders (once placed), and defines alternate plans for delayed deliveries of supplies and recovery procedures for "out-of-stock" conditions (a system that details steps to ensure minimal lapse in ability to perform testing) [(86)].

xi. Testing of reference material

For each new lot, batch or kit of reagents, the laboratory must document that samples, manufacturer-provided reference materials or proficiency testing materials are tested in parallel with both the current lot and the new lot to assess test comparability before or concurrently with being placed into service. For quantitative tests, parallel testing should be performed by assaying the same samples or reference materials with both the old and new lot numbers to assess comparability. Quality control materials should also be tested when comparing old and new lots.

For qualitative tests, parallel testing must include re-testing at least one known positive (or abnormal) and one known negative (or normal) sample [87].

xii. Verification of specifications performance

Validation of manufacturer provided performance specifications, or the development of such specifications can be challenging. The assay development and approval status defines what parameters are required in a formal validation study. The standards below offer guidance on how to validate an assay [66].

The laboratory must verify and document optimal performance of non-waived CLIA tests used to acquire study-participant results following pre-defined specifications that are equivalent to the ones provided by the manufacturer. The definition of the normal range must include specifications for the Analytical Measurement Range (AMR) and the Clinically Reportable Range (CRR) of each test used. The laboratory must also include a correction factor for each test to account for systematic errors that occur between tests. The inclusion of correction factors ensures data comparability when multiple tests are conducted to measure the same analyte in support of study-participant results [12].

xiii. Verification of standards performance

Before reporting study-participant results, each laboratory that introduces a non-waived (a CLIA designation) test such as an ELISA test, must demonstrate performance specifications comparable to those established by the manufacturer (as found in manufacturer's Governmental such as user manuals or package inserts) to ensure the assay is performing optimally within the proposed testing environment. Documentation of experiment results and approval should be readily accessible. Methods that are defined as waived by CLIA do not require method validation, unless otherwise instructed by the sponsor. Laboratories are not required to verify or establish performance

specifications for any analytical test system used by the laboratory before April 24, 2003. Verification and documentation of normal responses for each test system including the Analytical Measurement Range (AMR) and the Clinically Reportable Range (CRR) and normal range(s) must be established to determine the usable and reliable range of results produced by that system [88]. For FDA-cleared/approved tests, analytical sensitivity documentation may consist of data from manufacturers or the published literature. If non-FDA approved methods are utilized, such as to monitor immunogenicity to a candidate vaccine, the laboratory must define, test and document the parameters described in the ICH Guidelines, Validation of Analytical Procedures: Text and Methodology, Q2 (R1) document that includes the original Q2A and Q2B documents [89]. The Bioanalytical Method Validation Guidelines provided for the Industry by the FDA to validate a Bioanalytical assay. Examples of Bioanalytical assays that have been validated for use in human clinical trials, using the ICH Guidelines are the ELI Spot and ICS assays. These include accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference intervals, and any other parameter required for test performance. If the test system to be validated is an unmodified, FDA-approved method, the manufacturer's reference range may be verified for the appropriate testing population. If the test is modified, or not FDA-approved, the reference range must be established [71]. The reference range must be established or verified for each analyte and specimen source/type (e.g., blood, urine, cerebrospinal fluid) when appropriate [66]. The laboratory may use the manufacturer's reference range when appropriate specimens are difficult to obtain (e.g., 24-hour urine specimens, 72-hour stool specimens, urine toxicology specimens) provided the range is appropriate for the laboratory's study participant population. In cases where the appropriate specimens are difficult to obtain and the manufacturer has not provided reference

ranges appropriate for the laboratory's study participant population, the laboratory may use published reference range [75].

An appropriate number of specimens must be evaluated to verify the manufacturer's claims for normal values or, as applicable, the published reference ranges. Typically, 20 specimens are required to verify the manufacturer's or published ranges. These specimens should be appropriately collected from patients that have been predetermined as "normal" by established inclusion/exclusion criteria (e.g., HIV-negative, HBs Ag -negative). The specimens should be representative of the population (age, gender, genetics, geographic area etc.) [90].

An appropriate number of specimens must be evaluated to establish reference ranges. Typically, the minimum number of specimens required to establish reference ranges is 120 specimens per demographic group (e.g., if the laboratory wishes to establish gender-specific reference ranges, then the minimum number of specimens would be 240: 120 normal male and 120 normal female) .Reference intervals must be evaluated at the following times: Upon introduction of a new analyte to the test offerings by a laboratory, with a change of analytic methodology, or with a change in study-participant population [15].

ivx. Correction factors

Correction factors represent adjustments made to compensate for constant and proportional errors when more than one assay format is being used to report study participant data. To ensure interchange ability of the data from any assay used, a correction factor must be incorporated into the relevant test procedure and reflected in the appropriate SOPs if the laboratory has determined the need for correction factors based on the validation exercises [91].

Postanalytical variables

Postanalytical variables are those that affect the patient results in the reporting stage. These include reporting the patient results in a timely manner and in an accepted format that can be understood and correctly interpreted by health-care providers. Maintaining and monitoring records of patient results also sustains QA practices. Postanalytical factors, including setting up and using reference ranges, medical decision limits, and critical values, will be discussed in the latter portion of this chapter.

i. Records and reports

The laboratory must define and maintain a system to provide and retain all clinical trial data records and reports for a period of time to troubleshoot potential problems, or if it is necessary to reconstruct the study for auditing purposes. These records may include specimen tracking forms, laboratory requisitions, chain-of-custody documents, laboratory reports, equipment service and maintenance records, and instrument printouts [(92)].

The laboratory director must define alert or critical values in consultation with study-related clinicians' complete procedures must be in place for immediate notification of key study personnel/responsible clinic staff when assay results fall within established alert or critical ranges. the laboratory must, upon request, make available a list of test assays employed by the laboratory and, as applicable, the performance specifications established or verified [(93)]. When the laboratory cannot report study-participant test results within the time frames established by the laboratory, the laboratory must notify the appropriate individual(s) of the delays. The laboratory referring study participant specimens for testing to another laboratory must not revise results or information directly related to the interpretation of results provided by the testing laboratory and must retain the testing laboratory's report for the period of time defined by the laboratory [(92)].

ii. Review of quality control results

Quality Control must be performed and acceptable results obtained (as defined in the written QC program) before test results are reported to ensure quality and accuracy of all aspects of the work performed and reported. Quality Control must also be run and reviewed after a change of analytically critical reagents, major preventive maintenance service, or change of a critical instrument component [(94)]. The laboratory personnel performing the testing must use the laboratory's QC program as a guide for selecting the appropriate corrective action to take for QC data that falls outside of established tolerance limits. Records should include detailed information of actions taken leading to resolution and include staff initials and dates. The laboratory must ensure a corrective action log is present to facilitate documentation and resolution of QC failures In the event the QC data is determined to be unacceptable, the laboratory must re-evaluate all study-participant test results since the last acceptable test run to determine if a significant clinical difference has occurred, in which case, the instrument QC should be re-established and the affected testing repeated (ISO/IEC 17025. 2005)[(22)].

iii. Critical values of the results

Critical values, otherwise referred to as panic or alert values, are medical decision level concentrations that would indicate a potentially or imminently life-threatening' situation. Medical decision levels are the concentrations at which the test results' are critically interpreted for purposes of diagnosis, monitoring, and therapeutic decisions. There may be several medical decision levels for a given analyte. When a critical value is obtained, it is necessary to quickly notify the clinical team for immediate patient evaluation and treatment. Laboratories are mandated by CLIA '88 to establish a list of critical values as well as a written policy for notification and documentation. Critical values can be determined through the joint efforts of the medical staff,

administration, risk managers, pathologists, and laboratory personnel. Medical and laboratory literature and information provided by the College of American Pathologists, such as the "Critical Value Q-Probes" [95].

The list should only include tests that are essential for the acute treatment of patients. Glucose, potassium, magnesium, sodium, total CO_2, inorganic phosphorus, calcium, and blood gases are examples of tests requiring critical value limits. There may he defined subsets of critical ranges, such as elevated total bilirubin for neonates or ammonia and iron in pediatric patients. The outpatient clinic may require a different critical cut-off than that established for the hospitalized patient. The overall goal of critical value selection is to enhance patient outcome while balancing resource and time constraints.

Laboratory personnel are responsible for screening results in a timely manner and evaluating' a result before releasing' it. Critical values warrant immediate notification of patient care personnel. CLIA regulations state to "alert the individual or entity requesting the test or the individual responsible for utilizing the test results". This may include the physician, nurse, or other health-care giver. A reasonable attempt must be made to deliver results, exhausting all avenues of communication (e.g., telephone, paper, answering service). It is not advisable to leave critical results on an answering machine, or send results through a fax machine or by e-mail. There is no guarantee of result retrieval in a suitable time frame. The joint Commission on Accreditation of Healthcare Organizations (JCAHO) has instituted a "read back" policy for critical values. This means that the individual receiving the critical results must write down the information and read back the patient's name, the analyte, and the critical results. Documentation of the individual's name and item of notification should be recorded [96].

iv. Report format

Reports generated by the Laboratory Information System (LIS), and those created by other means, must be concise, readable, standardized in format, and chronological. The laboratory's test report must indicate the following items: Either the study participant's name and/or a unique identifier; the name and address of the laboratory location where the assay was performed; the date and time of specimen receipt into the laboratory; the assay report date; the name of the test performed; specimen source (e.g., blood, cerebrospinal fluid, urine); the assay result and, if applicable, the units of measurement or interpretation or both; reference ranges along with age and gender of study-participants, if these affect the reference range; any information regarding the condition and disposition of specimens that do not meet the laboratory's criteria for acceptability; and the records and dates of all assays performed [(97)].

v. Archiving of reports and records

All clinical trial data records and reports must be safely and securely (e.g., fire-proof storage with limited access) retained by the laboratory for a period of time that has been defined by the laboratory to be able to fully reconstruct the study, if necessary. Retention time periods established by the laboratory must meet or exceed the requirements set forth by the product sponsor and/or any applicable regulatory bodies such as the FDA. The laboratory may archive test reports or records either on- or off-site. Stored study-participant result data and archival information must be easily and readily retrievable within a time frame consistent with study/trial needs, e.g. within 24 hours [(98)].

Environmental conditions and physical facilities

The environment in which laboratory testing is performed must be conducive to efficient operations that do not compromise the safety of the staff or the quality of the pre-analytical, analytical and post-analytical processes. The laboratory design must account for equipment placement, proper ventilation, and have a designated area for reagent storage as well as archiving of data in a secure fire-proof (preferred), fire-resistant, or fire-protected environment with access to only authorized personnel [(99)].

i. Laboratory Space and design

The laboratory room 4×7 meter at least with bench's height 90 cm from the floor, bench width 65-75 cm, offices should be separated from laboratories, the laboratory shall be completely separated from outside area (i.e., shall be bound by four walls and a roof or ceiling), all work surfaces as bench tops shall be impervious to the chemicals and materials used in the laboratory, the laboratory shall be designed so that it can be easily cleaned, laboratory flooring in chemical use areas and other high hazard areas such as biological contamination facilities shall be chemically resistant, the walls shall be painted easily to decontamination and cleaning, designer qualifications , the designer shall have the appropriate professional license in his/her area of expertise and have prior experience designing laboratories, the laboratory shall have self-closing doors, the space between adjacent workstations and laboratory benches should be five feet or greater to provide ease of access and spaces between benches , cabinets and equipment shall be accessible for cleaning and servicing of equipment, (ISO, 15189). Laboratory work areas must have sufficient space so that there is no hindrance to the work or employee safety. Laboratory room (ambient) temperature and humidity must be controlled so that equipment and testing is maintained within the tolerance limits set forth by the manufacturer , ambient temperature logs should be utilized to document the

acceptable ambient temperature range, record daily actual temperatures, and allow for documentation of corrective action taken should the acceptable temperature ranges be exceeded ,all floors, walls, ceilings, and bench tops of the laboratory must be clean and well maintained . (ISO 15189, version 2007).

ii. Laboratory Information Systems (LIS)

A LIS is a powerful tool to manage complex processes, ensure regulatory compliance and promote collaborations between multiple laboratories. Usually a LIS is capable of consolidating disparate scientific processes into a single, compliant platform with comprehensive reporting, surveillance and networking capabilities. The result is vastly enhanced data management and data sharing-within the laboratory and across laboratories [(100)].

The purpose of a LIS, the way it functions, and its interaction with other devices or programs must be documented with validation data and results including data entry, data transmission, calculations, storage and retrieval Since patient management decisions and product advancement decisions are based on laboratory data, appropriate steps must exist to ensure data quality and integrity through documentation. Both abnormal and normal data must be used to test the system. Any changes or modifications to the system must be documented, and the laboratory director or designee must approve all changes before they are released for use. Computer time-stamped audit trails must be used by the LIS [(26)]. The laboratory's LIS policies must ensure that LIS access is limited to authorized individuals. The laboratory must maintain a written SOP for the operation of the LIS and should be appropriate and specific to the day-to-day activities of the laboratory staff as well as the daily operations of the Information Technology staff. Documentation must be maintained indicating that all users of the computer system receive adequate training both initially and after system modification, documented procedures and a disaster-preparedness plan must exist

for the preservation of data and equipment in case of an unexpected destructive event (e.g., fire, flood) or software failure and/or hardware failure, allowing for the timely restoration of service [26].

Internal audits for the laboratory

The laboratory's monitoring of the QM Program must include an internal auditing program. Internal audits involve an individual or a group of laboratory personnel performing a self-assessment comprised of a comparison of the actual practices within the laboratory against the laboratory's policies and procedures (e.g., personnel files, training documentation, QC performance, review of SOPs). These audits may also compare the laboratory's practices against a standard set of guidelines or standards. All findings (compliance, non-compliance, or deficiencies) that result from the internal audit should be documented in an organized format to allow for appropriate corrective actions and follow-up through resolutions. The laboratory must have a list of assay turnaround times readily available to all laboratory staff as well laboratory customers. The laboratory must also have a non-retaliatory policy for employees to communicate concerns regarding testing quality or laboratory safety to laboratory management (ISO, 15189).

Certification for clinical laboratories

The organization accrediting or certifying medical laboratories are governmental or authoritative organizations, the development in laboratory accreditation as the college of American pathologists (CAP), LAP, Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and CLIA 88, accreditation is a producer by which an authority body gives formal recognition that a body is competent to carry out specific tasks, certification is a procedure by which a third party gives written assurance that a product, process or service confirms to a specific requirements [101]. Certification is a process in which conformity with the EN ISO 9000 series of standards is confirmed certification certifies the use of general system for quality management in medical laboratory regardless of its overriding function as a testing laboratory, expected value assignment laboratory, or reference laboratory certification is awarded by an impartial third part than certifies conformance with ISO 9000 series of standard for a manufacturing process, a method, or a service (conformity testing). Certification according to ISO 9000 if is the only internationally recognized for of external certification available to date. It is a point of differentiation in the marketplace for individual laboratory and a manufacturer of in vitro diagnostics products (Medical Products Certification, when manufacturers are active in the world market, the focus on global or international standards such as: ISO 9001:2000 Quality management systems; ISO 13485:2003; CE Mark; In Vitro Diagnostic medical devices (IVD); TÜV Mark (102). Formal certification of your quality management system, specifically for medical devices, to ISO 13485:2003 proves advantageous, and in many cases essential, for medical companies which export their products to the global market, ISO 9001/ISO 13485- Who is certified to these standards? Companies who design, manufacture, distribute, install and service medical devices for the European and World Markets [103].

ISO 9001:2000 for Quality management systems

ISO 9001:2000 Quality management systems- Requirements is intended for use in any organization which designs, develops, manufactures, installs and/or services any product or provides any form of service. It provides a number of requirements which an organization needs to fulfill if it is to achieve customer satisfaction through consistent products and services which meet customer expectations ISO 9001. The EC Mark is a mandatory European marking for certain product groups to indicate conformity with the essential health and safety requirements set out in European Directives. The Letters 'CE' are an abbreviation of Conformité Européenne, French for European conformity [40].

i. ISO 15189 Standards for clinical laboratory quality and competence

In January 2003, the International Organization for Standardization (ISO) published the world's first harmonized clinical laboratory practice standard. Laboratories have used ISO 17025 for years, while this standard provided a generic framework relative to clinical laboratories were missing. Consequently, the laboratory community approached the ISO Secretariat about creating a standard specifically for the unique requirements of clinical laboratory practice. The standard that was published is known as ISO 15189 [104]. ISO 15189 (Medical laboratories- Particular requirements for quality and competence) outlines the controls required to manage risks that may have an impact on the validity of examination results, and tools to help the laboratory to improve its operations and customer satisfaction. ISO 15189's requirements are designed to apply to all types of Human pathology testing [105]. Adoption of ISO 15189 will help countries employ a uniform approach to determine medical laboratory competence in their technical capacity and the effective quality management of a professional service and its staff with or without the aim of accreditation. ISO 15189 by itself is not a generic (certification) standard, but a specific one, which means that it is a

guideline for orientation, which is presents more technical requirements related to quality management than to operational procedures [106]. The potential problems with the quality of these new services should be a major concern. One way of identifying some of these problems is to examine what is in place or lacking in the diagnostic labs to guarantee good performance [107].

ii. Adoption of ISO (15189) requirements

The adoption of an integrated quality management system (IQMS) based on ISO 15189:2003 (accreditation) and ISO 9001:2000 (certification) will be a very good opportunity to improve the quality of internal processes and achieve the best results in clinical laboratories. This IQMS can be considered one of the best ways to assure continual improvement and, as a bonus; it also makes it easier to evaluate the management and performance of the entire system [106]. It suits perfectly the real world of our clinical laboratories, helping us to make the difficult liaison between the quality-driven nature of our services and the current performance- driven reality in the Health Care. Adoption of ISO 15189 requirements in the total testing process will help laboratories hire a uniform approach to determine medical laboratory competence. It will also encourage laboratories to adopt internationally accepted practices, where possible. The availability of a new international standard, ISO 15189:2003; specifically designed for medical laboratories, which contains requirements for both quality systems and competence, should stimulate the adoption of this standard and promote harmonization of accreditation programs at an international level. The increasing demand for accountability, accessibility, professional excellence, customer satisfaction, and better cost management has underpinned the development of systems for quality assurance and improvement in healthcare, with an increasing focus on certification, accreditation, and several other forms of external review mechanisms. Moreover, many countries have introduced regulations for quality assessment in laboratory services [108].

iii. ISO 15189 standards and clinical laboratory accreditation

Accreditation processes are widely known in clinical laboratories and medical services. In United States of America (USA); collages of American pathologist (CAP), Commission Office of laboratory accreditation (COLA) and Joint Commission Accreditation of Health Organization (JCAHO) have an established know-how in the field. However, The ISO 15189 standard, since its Governmentalation in 2003, is gaining more and more acceptance by accreditation bodies worldwide as the standard for medical laboratories and has been adopted as the accreditation criteria used by many countries, including New Zealand, Canada, Hong Kong, Thailand, while others, including Malaysia, China, Japan, are also planning to start accreditation of medical laboratories using this new standard [(109)]. For accreditation, the rules require that the accreditation process be carried out by 'third party' organizations: that means not by peers, not by 'first parties' (suppliers) and not by 'second parties' (customers). "Third party' is defined as a person or body that is recognized as the laboratory or the laboratory's parent organization. Although very well known in the majority of the other industries, ISO standards are relatively new in the context of health services. The ISO 15189 standard is finally catching the attention of American laboratories and accreditation agencies in the last few years. Also, Under the International Laboratory Accreditation Cooperation (ILAC) Multilateral Mutual Recognition Arrangement (MLA), Accreditation of medical laboratories against ISO 15189 is acceptable. As more labs embrace accreditation based on ISO 15189, this will eventually make clear the strong synergy that exists between the accreditation with ISO 15189: 2003 and the certification with ISO 9001: 2000, and more labs will also seek the ISO certification [(110)].

Laboratory accreditation

In the past, a laboratory quality has been concentrated on the analytical process. But laboratory professionals accept that quality control of pre-analytical and post–procedures analytical reflect both a high level of service and exceptional laboratory quality [111]. Although accreditation has only become a familiar word for the scientific community and the society community and the society I recent years its beginning go back to the 1970s and before that in world [18]. Laboratory accreditation can be defined as a formal recognition by an authoritative body of the technical competence of a laboratory to perform tests or calibrations. This recognition is given by an accreditation body, which acts as a third party between the laboratory and its clients, an aim to establish confidence between them. One of main objectives and reasons for the existence of accreditation system is need to remove technical barriers to international trade, i.e., that product once tested in an accredited laboratory should not need to be retested by clients systems, since another accredited laboratory in another country would find a similar result. Nevertheless, accreditation is normally granted for limited scope of activities or tests, which generally do not include all the tests or analysis that the laboratory offers to its clients. It is up to the laboratory to propose to the accreditation body which tests or types of tests they wish to include in the scope of accreditation [112].

Accreditation has been from a number of perspectives since it started: originally it was a voluntary activity, required sometimes for specific tasks. Then it became a competitive factor, seen as a commercial strategy and nowadays it is a survival requirement in many sectors, since it has become mandatory (by government) or preferred for the Governmental [113].

i. Accreditations and international agencies

Globally, the organizations accrediting or certifying medical laboratories are of different types, i.e. governmental or authoritative organizations. The development in laboratory accreditation started, as it became clear to the United Stated Congress the unsatisfactory testing was performed within health care sector. Consequently, the College of American Pathologists (CAP) initiated the first accreditation scheme in 1961 specially designed for medical laboratories: the Laboratory Accreditation Program (LAP). Today, the CAP program, is recognized by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and has a decision authority under the Clinical Laboratory Improvement Amendments of 1988, (CLIA'88). The International Laboratory Accreditation Cooperation (ILAC) to be used as the international standard for the accreditation of medical laboratories worldwide. In Japan, the Japanese Committee for Clinical Laboratory Standards (JCCLS) and the Japan Accreditation Board for Conformity Assessment (JAB) conjointly started the accreditation program in August, 2005, and a total of 46 medical laboratories had been accredited edition). In Australia the National Association of Testing Authorities (NATA) as a principal inspection agency, has experience with accreditation for over 50 years mainly for the benefit of Australian industry, government, and the community [(114)].

The Canadian Council on Health Services Accreditation (CCHSA) introduced a Client Centered Accreditation Program in 1995, focusing on the implementation of Total Quality Management in medical laboratories, but no federal approach has yet been developed, in addition to patient care the scope of medical laboratory analyses are also included in medical trails. In this context, medical laboratories have to follow good laboratory practice (GLP) standards as tests are performed in the pre-clinical phase [(30)].

In European countries the GLP directive is based on the principles based on the Organization for Economic Co-operation and Development, the OECD guideline, while the laboratories involved with medical trails are controlled by the U.S. Food and Drug Administration (FDA). The National Committee for Clinical Laboratory Standards (NCCLS) in the US contributes to guidelines for health care professionals and manufacturers in terms of GLP and medical laboratory testing [115].

To demonstrate the required quality procedures European medical laboratories started to take actions during the 1990s in developing their quality systems according to EN 45001based on the ISO/IEC Guide 25, or ISO 9000 standard series. The first medical were accredited in Sweden in 1992 by SWEDAC, the Swedish accreditation body .Since then, the number of accredited laboratories, representing disciplines of clinical chemistry, clinical microbiology, blood banking, and pathology has been growing exponentially in the Nordic countries. Today, more than twenty medical laboratories in have fulfilled the accreditation requirements assessed by FINAS. The Finnish Accreditation Service that together with other accreditation bodies is a member for European co-operation for Accreditation. In the United Kingdom, medical laboratories follow the national standards set by the Clinical Pathology Accreditation (CPA), which serves also as the national accreditation body. Guides and recommendations were established in many countries by international, national, organizational, and professional groups to facilitate this demanding work [7].

In addition to analytical issues, guidance for documenting and implementing some special actions has been taken in account. These actions include e.g. internal audits, an important management tool which medical laboratories might not have been so familiar with before [68]. The results of these different EQAs still show the need for improved quality in the lab services. Too many laboratories make significant errors – in some cases 1–5%– even in a particular EQA scheme [116].

The new international standard ISO/IEF 17025, General requirements for testing and calibration laboratories 84, replaced the criteria of the EN 45001 and ISO/IEC Guide 25 standards for laboratory accreditation by the end of 2002. 24 In co-operation between ISO, the US standardization body, American Standards Institute (ANSI), and the NCCLS, the ISO Technical Committee 212, ISO/TC212 has worked out the first International Standard for Quality management in the medical laboratories EN/ISO 15189 [117]. A large series of training session all over Europe on quality assurance for labs substantially increased the awareness for quality. The French government, as a result, made it compulsory for all labs to become accredited under ISO 15189 [118].

Laboratory safety

The safety of all laboratory staff is paramount to avoid laboratory accidents that may jeopardize acquisition of infectious agents through handling of blood materials, as an example. Although exposure cannot always be avoided, every precaution must be taken to provide a safe work environment [119]. Safety policies defined according to regulatory organizations such as the Occupational Safety and Health Administration (OSHA) or the International Organization for Standardization (ISO) must be present in the laboratory. The following safety policies must be in place to ensure the safety of laboratory staff and any authorized individuals: Standard Precautions/Universal Precautions Policy, Chemical Hygiene/Hazard Communication Plan, Waste Management Policy, Safety Equipment, and general safety policies (these policies address less specific topics as they relate to laboratory safety, such as fire and back safety) [120].

i. Safety training

All laboratory staff must receive safety training. At a minimum, the safety training must include, Blood borne pathogens, PPE, Chemical Hygiene/Hazard Communications, use of safety equipment in the laboratory, use of cryogenic chemicals (e.g., dry ice and liquid nitrogen), transportation of potentially infectious material, waste management/biohazard containment, and general safety/local laws related to safety. Safety training must be documented and maintained. Safety training must be completed before any employee begins working in the laboratory and on a regular basis thereafter. Ongoing safety training must take place each calendar year. Documentation of this training must be signed and dated by the employee [41].

ii. Safety for records and reporting

Safety-related incidents must be documented, submitted, reviewed, and signed by the Laboratory Manager or designee on a regular basis, not to exceed one month from time of submission. Safety

reports must be incorporated into the Quality Management (QM) program allowing the laboratory to note trends and correct problems to prevent recurrence [100].

iii. Safety of equipments and materials

Fire extinguishers, emergency shower, eye wash, and sharps containers must be present in each laboratory, in compliance with general safety/local laws. Periodic inspection and/or function checks of applicable safety equipment must be documented , the employer must assess the workplace to determine if hazards are likely to be present which necessitate the use of Personal Protective Equipment (PPE) and provide access to PPE to all laboratory staff at risk , all laboratory employees must use PPE if there is a potential for exposure to blood or other potentially infectious material through any route (e.g., skin, eyes, other mucous membranes) ,the laboratory must have Material Safety Data Sheets (MSDS) or equivalent in the workplace for each hazardous chemical that they use [41].

In Africa, few developing countries such as Cameron, Rwanda Uganda and Senegal have established laboratory quality standards that are affordable and easy to implement and monitor. For all laboratories providing clinical testing services. The results were showed in different way according to the evaluation by quality measures between Sudanese States and the similar laboratory results in other countries Syria and Egypt, but in the recent years, laboratory performance of these countries were improved when they were established a national External Quality Assessment Program. In others country such as Malaysia they establish the National Accreditation Standard for medical testing laboratories based on ISO 15189, and the passing of the Pathology Laboratory Act in Parliament in mid-2007 [121].

References

(1) Samuel KM. Is the ISO 9000 series for total quality managment? International Journal of Physical Distribution & Logistics Management 1995.

(2) Katz JM. Compenents of performance management, managing quality. Ch 3 1997;24-9.

(3) Giedt WR. Quality assurence plan, public health laboratories. shoreline, Washington 2000.

(4) Raab SS. Improving patient safety through quality assurance. Arch Pathol Lab Med 2006 May;130(5):633-7.

(5) Hollensead SC, Lockwood WB, Elin RJ. Errors in pathology and laboratory medicine: consequences and prevention. J Surg Oncol 2004 Dec 1;88(3):161-81.

(6) Chiozza ML, Plebani M. Clinical Governance: from clinical risk management to continuous quality improvement. Clin Chem Lab Med 2006;44(6):694-8.

(7) WHO. **Basics** of **quality assurance** for **intermediate** and **peripheral laboratories**. 1992.

(8) Kenneth O, Klich I, Mann A, Revzen M. Repulsive Casimir forces. Phys Rev Lett 2002 Jul 15;89(3):033001.

(9) Hardwick D. Directing the clinical laboratory. 1990.

(10) Stander HF. [Medical emergencies in daily dermatological practice]. Hautarzt 2012 Apr;63(4):329-38.

(11) Plebani M. Appropriateness in programs for continuous quality improvement in clinical laboratories. Clin Chim Acta 2003 Jul 15;333(2):131-9.

(12) Round D. Quality control for tests of moderate or high complexity, or both in the clinical laboratory improvement act (CLIA) and the physician's office laboratory: interpretive guidelines: laboratories, health care, university of Lowa, DEC. 2000.

(13) Burnett D, Blair C, Haeney MR, Jeffcoate SL, Scott KW, Williams DL. Clinical pathology accreditation: standards for the medical laboratory. J Clin Pathol 2002 Oct;55(10):729-33.

(14) Larry H. PrFont34Bin0BinSub0Frac0Def1Margin0Margin0Jc1Indent1440Lim0Lim1What constitutes a Laboratory Quality Monitoring Program?. American Journal of Medical Quality 1990.

(15) El-Nageh MM. Basic of quality assurance for intermeidate and preipheral laboratories. 1992.

(16) Hill P, Froning M, Schlager M, Zoriy MV, Lennartz R. Accreditation of testing laboratories in dosimetry: the use of a flexible scope at the Competent Incorporation Measuring Body Julich. Radiat Prot Dosimetry 2011 Mar;144(1-4):47-51.

(17) Cooper WG. Quality control practices and preferences in today's clinical laboratory. A report for government regulators, decision makers, and advisors. MLO Med Lab Obs 1997 Jun;29(6):56-5.

(18) Newble D. Handbook for clinical teacher. Ch 4 1986;1st:4-61.

(19) Kazmicrczak SC. Laboratory quality control using patient data to assess analytical performance. Clin Chem Lab Med ; 2003;(41):617-27.

(20) Riebling N. Six Sigma project reduces analytical errors in an automated lab. MLO Med Lab Obs 2005;6(37):22-3.

(21) Solveig L. Measurement tools for quality assurance in medical laboratory. 2003.

(22) Jean C. External quality assurance programmes in medical laboratories, accreditation and Quality Assurance. Journal for Quality, 2001;6:152-3.

(23) Hinckley CM. Defining the best quality. Control system by design and inspection. clin chem 1997;(43):873-9.

(24) David. Carbohydrates, in Tietz fundamentals of clinical chemistry. 14 ed. 1996.

(25) Monica C. Total quality management of districts laboratory services, District Laboratory Practice in tropical countries. 1 ed. 2002. p. 1-21.

(26) Ladenson J. Use of a major medical center clinical laboratory as a reference laboratory for a developing country: ordering patterns help set laboratory priorities. Clin Chem 2003;(49):162-6.

(27) Bonini P, Plebani M, Ceriotti F, Rubboli F. Errors in laboratory medicine. Clin Chem 2002 May;48(5):691-8.

(28) Lombardi G, Farina C, Andreoni S, Fazii P, Faggi E, Pini G, et al. Comparative evaluation of Sensititre YeastOne vs. the NCCLS M27A protocol and E-test for antifungal susceptibility testing of yeasts. Mycoses 2004 Oct;47(9-10):397-401.

(29) WHO. **Basics** of **quality assurance** for **intermediate** and **peripheral laboratories**. 1992.

(30) Bull M. quality manual for the clinical laboratory. J Immunol 2007;(322):57-69.

(31) Kenneth D. Clinical laboratory medicine. second edition ed. 2002.

(32) Burnett D, Blair C. Standards for the medical laboratory--harmonization and subsidiarity. Clin Chim Acta 2001 Jul 20;309(2):137-45.

(33) Mallapaty G. Situtation analysis helath laboratory services in Nepal, Health services management. 2000.

(34) Patton SJ. Benchmark for evaluating the quality of DNA sequencing: proposal from an international external quality assessment scheme. Clin Chem 2006;(52):728-36.

(35) Uldall A. Quality Assurance in Clinical Laboratories. An updated supplement to a bibliography. Eur J Haemtology 2009;45(53):22-37.

(36) Willis R. Challenges for clinical diagnostic devices. Analytical chemistry and developing nations. Challenges for clinical diagnostic devices. Lack of healthcare personnel, few reagents, no follow-up visits. Can technology find a way around these problems?. Anal Bioanal chem 2006;(78):61-5.

(37) Kayaly N. Quality of Clinical Laboratory Results. Journal of clinical laboratory 2007;7(4):91-5.

(38) Montoya ID. Patient safety and quality improvement: a policy assessment. Clin Lab Sci 2010;23(4):212-8.

(39) Henry B. The clinical laboratory: Organization, purposes and practice. J Clin Pathol 2001;2.

(40) Ritter C. More on the measurement of ionized magnesium in whole blood. MLO Med Lab Obs 2004;(36):26-7.

(41) Robert R. Performance in Proficiency testing: An indicator of laboratory Quality, Wadsworth Center for Laboratories and research, State University of New York at Albany Albany. 1995.

(42) Seamark D. Transport and temperature effects on measurement of serum and plasma potassium. Scand J Clin Lab Invest Suppl 1996;(224):275-80.

(43) Stankovic AK. The laboratory is a key partner in assuring patient safety. Clin Lab Med 2004 Dec;24(4):1023-35.

(44) Barrueto F, Jr., Jortani SA, Valdes R, Jr., Hoffman RS, Nelson LS. Cardioactive steroid poisoning from an herbal cleansing preparation. Ann Emerg Med 2003 Mar;41(3):396-9.

(45) Cooper K. Errors and error rates in surgical pathology: an Association of Directors of Anatomic and Surgical Pathology survey. Arch Pathol Lab Med 2006 May;130(5):607-9.

(46) ISO/IEC Guide 99. International vocabulary of basic and general terms in metrology. 2007.

(47) CITAC. Cooperation on International Traceability in Analytical Chemistry. 2008.

(48) L331. Directive 98/79/EC of the European Parliaments and of the Council of 27 October 1998 on in vitro diagnostic medical devices. J Eur Communities 1998;(41):1-37.

(49) International Organization for Standardization. In vitro diagnostic medical devices—measurement of quantities in biological samples—metrological traceability of values assigned to calibrators and control materials. 2003.

(50) World Health Organ Tech Rep Ser. World Health Organization. Standardization of procedures for the study of glucose-6-phosphate dehydrogenase. 5: 25; 1967. Report No.: 366.

(51) Cali JP. Standardization of diagnostic materials; 2: problems of standardization in clinical chemistry. 1973. Report No.: 48.

(52) Cali JP. Worldwide reference methods [Letter]. Clin Chem 1975;(21):1344.

(53) Bu¨ ttner J. Reference methods as a basis for accurate measuring systems. Eur J Clin Chem Clin Biochem 1991;29(223):235.

(54) Tietz NW. A model for a comprehensive measurement system in clinical chemistry. PrFont34Bin0BinSub0Frac0Def1Margin0Margin0Jc1Indent1440Lim0Lim1Clin Chem 1979;(25):833-9.

(55) Rifai N CGBWV. Clinical Chemistry journal has contributed to progress in lipid and lipoprotein testing for fifty years. Clin Chem 2004;(50):1861-70.

(56) Little RR. Glycated hemoglobin standardization: National Glycohemoglobin Standardization Program (NGSP) perspective. Clin Chem Lab Med 2003;(41):1191-8.

(57) Pontius CA. JCAHO and COLA collaboration and CLIA 1997 heading for committees. MLO Med Lab Obs 1997 Oct;29(10):28, 59.

(58) Westgard JO. Charts of operational process specifications ("OPSpecs charts") for assessing the precision, accuracy, and quality control needed to satisfy proficiency testing performance criteria. Clin Chem 1992 Jul;38(7):1226-33.

(59) Westgard JO, Wiebe DA. Cholesterol operational process specifications for assuring the quality required by CLIA proficiency testing. Clin Chem 1991 Nov;37(11):1938-44.

(60) Westgard JO, Wiebe DA. Cholesterol operational process specifications for assuring the quality required by CLIA proficiency testing. Clin Chem 1991 Nov;37(11):1938-44.

(61) WHO. Establishment of Quality Systems and Accreditation in Health Laboratories Report of an intercountry Workshop Thailand. 2007.

(62) Bonini P, Plebani M, Ceriotti F, Rubboli F. Errors in laboratory medicine. Clin Chem 2002 May;48(5):691-8.

(63) Still K. Calibration of Materials for clinical laboratory. 2003.

(64) Mayura K. Quality standards in Health Laboratories Implementation in Thailand. 2005.

(65) Khattab A. Total Quality Management, Essential Chemical Pathology. 1st edition ed. 2007.

(66) Libeer JC. Total quality management for clinical laboratories: a need or a new fashion? Acta Clin Belg 1997;52(4):226-32.

(67) Seehafer J. Corrective actions, what to do when control results are out of control. MLO Med Lab Obs 1997;3(29):34-40.

(68) Buttner J. International Federation of clinical chemistry approval recommendation on quality control in clinical chemistry**.** 1983.

(69) Kallner A. Accreditation of medical laboratories. Some reflections from the Nordic Horizon. Clin Chim Acta 2001 Jul 20;309(2):163-5.

(70) Kallner A. Accreditation of medical laboratories. Some reflections from the Nordic Horizon. Clin Chim Acta 2001 Jul 20;309(2):163-5.

(71) Kociba P. laboratorioiden akkreditointi *Suomessa.* Klin Lab Diag 1997;(14):10-2.

(72) Stephenson S. Control chart for clinical laboratory. 2009.

(73) WHO. Guidelines on Good Practice in Clinical Laboratories. Part I *Clinical chemistry* ed. 1991.

(74) Westgard JO, Westgard SA. The quality of laboratory testing today: an assessment of sigma metrics for analytic quality using performance data from proficiency testing surveys and the CLIA criteria for acceptable performance. Am J Clin Pathol 2006 Mar;125(3):343-54.

(75) Westgard JO. Basic Method Validation.second ed. AACC Press; Washington. 2003.

(76) Plebani M. Appropriateness in programs for continuous quality improvement in clinical laboratories. Clin Chim Acta 2003 Jul 15;333(2):131-9.

(77) Nutt L, Zemlin AE, Erasmus RT. Incomplete laboratory request forms: the extent and impact on critical results at a tertiary hospital in South Africa. Ann Clin Biochem 2008 Sep;45(Pt 5):463-6.

(78) Bella H. Practical Application of ISO 15189 by Accreditation Bodies. Available at *http://www.ifcc.org/ejifcc/vol15no4*. 2004.

(79) Bonini P, Plebani M, Ceriotti F, Rubboli F. Errors in laboratory medicine. Clin Chem 2002 May;48(5):691-8.

(80) Dubey S, Clair J, Fu TM, Guan L, Long R, Mogg R, et al. Detection of HIV vaccine-induced cell-mediated immunity in HIV-seronegative clinical trial participants using an optimized and validated enzyme-linked immunospot assay. J Acquir Immune Defic Syndr 2007 May 1;45(1):20-7.

(81) Hallak G. The Lebanese External Quality Assessment Scheme for laboratories: was it worth establishing? J Med Liban 2005 Jan;53(1):9-15.

(82) Bremond J, Plebani M. IVD industry role for quality and accreditation in medical laboratories. Clin Chim Acta 2001 Jul 20;309(2):167-71.

(83) Kenny D. ISO and CEN documents on quality in medical laboratories. Clin Chim Acta 2001 Jul 20;309(2):121-5.

(84) Westgard JO. Westgard QC. c2000]. Available from P://westgard.com/biodatabase1.htm. 2007.

(85) Kayamori Y, Toyofuku M, Hotta T, Fujise M, Egashira S, Kang D. [ISO 15189 accreditation acquisition and the procedure]. Rinsho Byori 2009 Feb;57(2):146-55.

(86) Uji Y, Kawashima T, Kuwabara T, Yoshida C, Niimi H, Kitajima I. [Effect of ISO15189 accreditation in Clinical Laboratory Center of Toyama University Hospital]. Rinsho Byori 2009 Aug;57(8):752-60.

(87) Kallner A. Accreditation of medical laboratories. Some reflections from the Nordic Horizon. Clin Chim Acta 2001 Jul 20;309(2):163-5.

(88) Dubey S, Clair J, Fu TM, Guan L, Long R, Mogg R, et al. Detection of HIV vaccine-induced cell-mediated immunity in HIV-seronegative clinical trial participants using an optimized and validated enzyme-linked immunospot assay. J Acquir Immune Defic Syndr 2007 May 1;45(1):20-7.

(89) Powers M. Development and use of analytical Quality specifications in the invitro diagnostic medical device industry. J Clin lab Invest: 1999;(59):34-44.

(90) Locke J. Development of laboratory accreditation in the United States. Review. Accred Qual Assur; 1998;:356--361.

(91) John B. Clinical diagnosis and management by laboratory methods0th. Ed. USA. 2001.

(92) Carla B. Total quality management- Tietz Text Book of Clinical Chemistry. second ed. 1994.

(93) Kubono K. [Quality management system in the medical laboratory--ISO15189 and laboratory accreditation]. Rinsho Byori 2004 Mar;52(3):274-8.

(94) Westgard JO, Westgard SA. The quality of laboratory testing today: an assessment of sigma metrics for analytic quality using performance data from proficiency testing surveys and the CLIA criteria for acceptable performance. Am J Clin Pathol 2006 Mar;125(3):343-54.

(95) Howanitz PJ. Errors in laboratory medicine: practical lessons to improve patient safety. Arch Pathol Lab Med 2005 Oct;129(10):1252-61.

(96) Joint C. National Patient Safety Goal 2 Laboratory Program at http:// www.jcaho.org/accreditcd+orgaizations/patient+safety/06_npsg/06_npsg_lab.htm. 2006.

(97) Doug C. Using, shewhart P control charts of external quality-assurance program data to monitor analytical performance of clinical chemistry laboratory. Clin Chem 1990;9(42):78-82.

(98) WHO. Quality standards in health laboratory implementation in Thailand: A Novel Approach WHO Regional Office for South-East Asia New Delhi. 2005.

(99) Plebaine M. Errors in clinical laboratories or errors in laboratory medicine? Department of Laboratory Medicine. Clin Chem 2006;6(44):50-9.

(100) Mitchell G. Establishing a Simple and Sustainable Quality Assurance Program. Clin Chem 2007;(53):45-53.

(101) Carrell M. Employee induction. R.(1)Resource Management in South Africa. Ch 7 2000;20-3.

(102) Kallner A. Accreditation of medical laboratories. Some reflections from the Nordic Horizon. Clin Chim Acta 2001 Jul 20;309(2):163-5.

(103) Kallner A. Accreditation of medical laboratories. Some reflections from the Nordic Horizon. Clin Chim Acta 2001 Jul 20;309(2):163-5.

(104) Uganda NAoS. Establishing and Promoting Good Laboratory Practice and Standard for Running Safe, Secure and Sustainable Laboratories in Sub-Saharan Africa. Kampala, Uganda, September . 2009.

(105) nata UI1. Accreditation Requirements for Medical Laboratories, available at, http://www.nata.com.au. 2007.

(106) Hong K. Workshop on Joint EQAS Program in **Clinical** Chemistry - by Bio-Rad and HKMTA - for participants of Joint EQAS in **Clinical** Chemistry only 3.Links - Consultation - **Laboratory** Accreditation provided by **Hong Kong** Accreditation Service - Introduction,... 2003.

(107) Berwouts.S. Quality assurance practices in Europe: a survey of molecular genetic testing laboratories. Eur J Hum Genet 2012.

(108) Stephenon P. The Evidence for Continuous Quality Improvement: A Literature Review. 2009.

(109) Davies P. **ILAC news, issue.** 2005.

(110) pierre D. **ILAC news, issue 33, April (2008).** 2008.

(111) Moraba MM. Quality of laboratory service provided by state (Governmental) laboratories-Northern Province. Ch 5 2002;(80).

(112) Hoeltge GA, Phillips MG, Styer PE, Mockridge P. Detection and correction of systematic laboratory problems by analysis of clustered proficiency testing failures. Arch Pathol Lab Med 2005 Feb;129(2):186-9.

(113) Locke JW. Laboratory accreditation. Environ Sci Technol 1987 Apr 1;21(4):332-3.

(114) Kallner A. Accreditation of medical laboratories. Some reflections from the Nordic Horizon. Clin Chim Acta 2001 Jul 20;309(2):163-5.

(115) Dybkaer R, Jordal R, Jorgensen PJ, Hansson P, Hjelm M, Kaihola HL, et al. A quality manual for the clinical laboratory including the elements of a quality system. Proposed guidelines. Scand J Clin Lab Invest Suppl 1993;212:60-84.

(116) Touitou I. An international external quality assessment for molecular diagnosis of hereditary recurrent fevers. Eur J Hum Genet 2009;(17):890-6.

(117) Sergi C, Mikuz G. External quality assurance as a revalidation method for pathologists in pediatric histopathology: Comparison of four international programs. BMC Clin Pathol 2008;8:11.

(118) La loi. http://www.sante.gouv.fr/la-loi-hopital-patients-sante-et-territoires.html. 2011.

(119) Fred D. Achieving and assessing Acceptable analytical performance: the challenge of matrix effects, Johnson & Johnson Clinical Diagnostic Inc. 1995.

(120) Da RG. Pre-analytical workstation: A tool for reducing laboratory errors. Laboratory Medicine. ASL 3 2009.

(121) Kubono K. [Quality management system in the medical laboratory--ISO15189 and laboratory accreditation]. Rinsho Byori 2004 Mar;52(3):274-8.