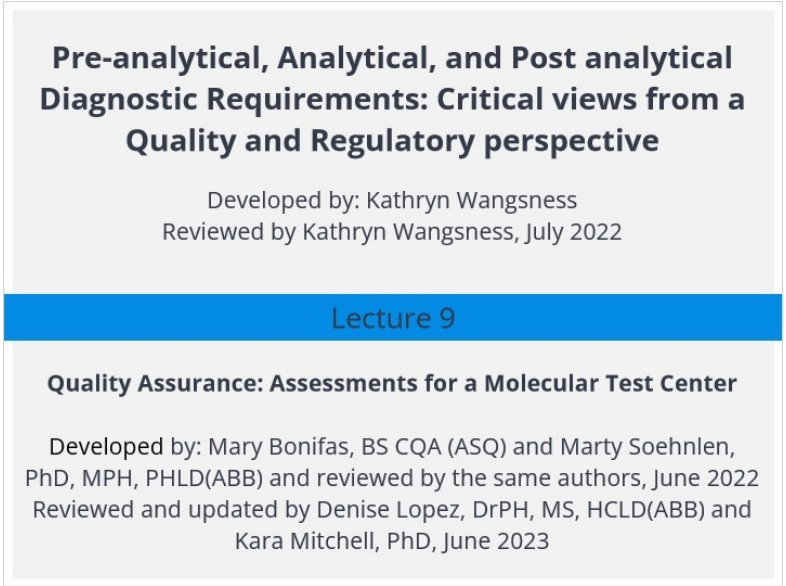
1. Lecture 9 - Pre-analytical Analytical and Post-analytical

1.1 Pre-analytical, Analytical, and Post-analytical diagnostic requirements: Critical views from a quality and regulatory perspective



Notes:

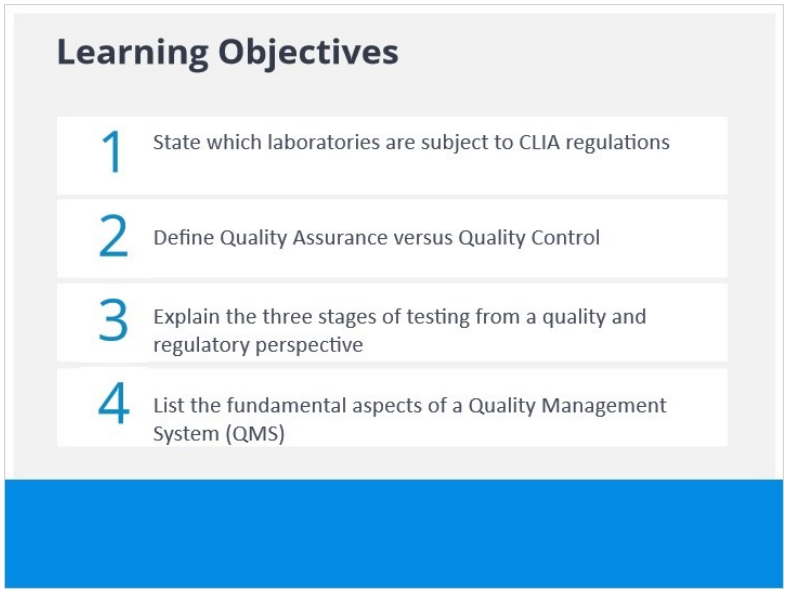
Welcome to Lecture 9 - Pre-analytical, Analytical, and Post-analytical diagnostic requirements: Critical views from a quality and regulatory perspective

This lecture was developed by: Kathryn Wangsness, the quality assurance manager at the Arizona State Public Health Laboratory and reviewed by Kathryn in July 2022

This lecture was then reviewed and updated by Denise Lopez, DrPH, MS, HCLD(ABB) and Kara Mitchell, PhD, June 2023 who added elements that were previously found in Lecture 13, Part 1 and entitled Quality Assurance: Assessments for a Molecular Test Center
That original lecture was developed by Mary Bonifas, BS, CQA (ASQ)
and Marty Soehnlen, PHD, MPH, PHLD(ABB)
Reviewed and updated by Mary Bonifas and Dr. Soehnlen, June 2022

We believe bringing these elements together creates a more cohesive topic.

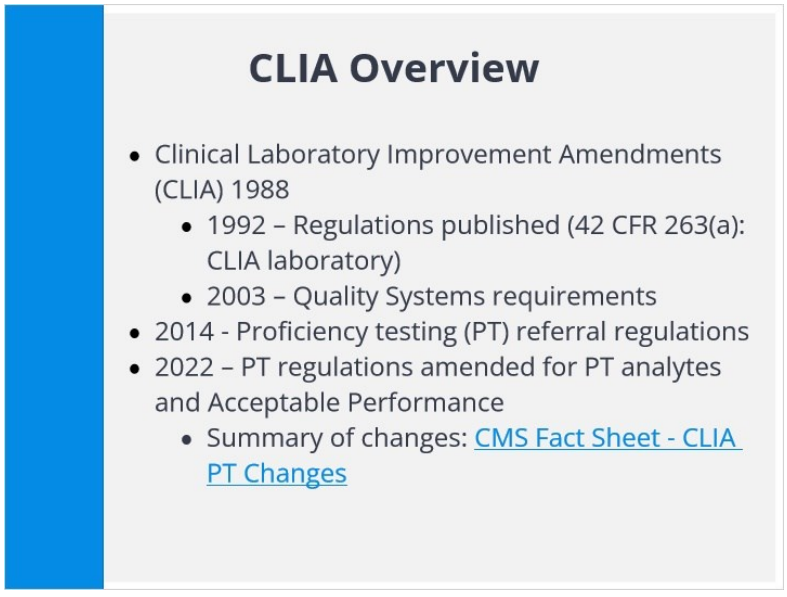
1.2 Learning Objectives



Notes:

By the completion of these slides you should be able to state which laboratories are subject to CLIA regulation, define common terminology related to Quality and Quality Control, explain the three stages of testing and the activities that happen in each stage, and list the fundamental aspects of a quality management system.

1.3 CLIA Laboratory



Notes:

CLIA Overview

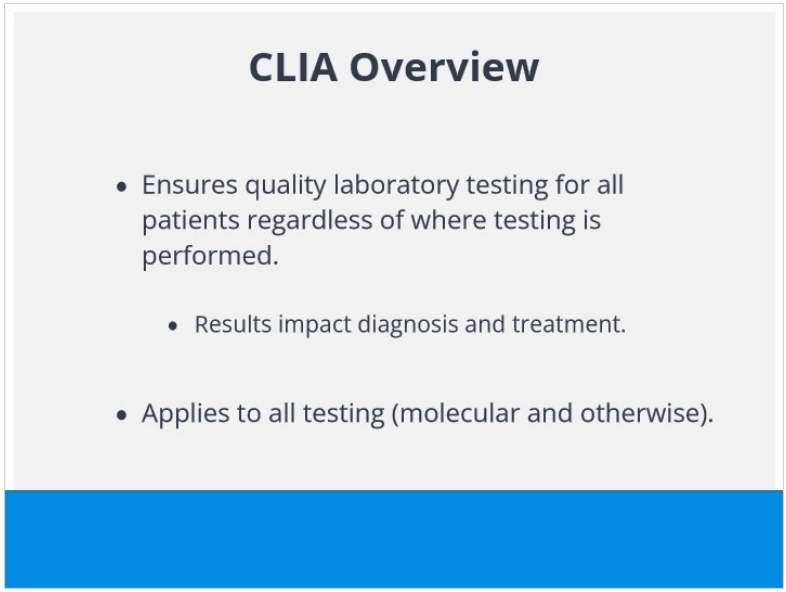
In 1988, Congress passed the Clinical Laboratory Improvement Amendments, or CLIA, which are applicable to all U.S. facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease. There are exceptions for certain forensic testing; research or surveillance; and some testing performed by Substance Abuse and Mental health Services Administration (SAMSHA) certified laboratories. The regulations for this are found in 42 CFR 263(a): CLIA laboratory.

The regulations were published in 1992 and revised Quality System requirements became effective in 2003.

Proficiency testing referral regulations became effective in 2014.

In 2022, new CLIA regulations went into affect for PT analytes, revised scoring criteria for acceptable performance for current and proposed analytes, clarification of PT requirements for the specific specialties or subspecialties, and the expansion of the proficiency testing referral prohibition. A summary of these changes can be found at the CMS Fact sheet linked here.

1.4 CLIA Laboratory



Notes:

CLIA Overview

CLIA ensures quality laboratory testing for all patients regardless of where testing is performed.

CLIA is vital for the US to ensure the appropriate accuracy, reliability, and timeliness of laboratory tests. The data obtained from regulated laboratories could directly impact diagnosis, prevention, or treatment of many diseases or impairments of human beings.

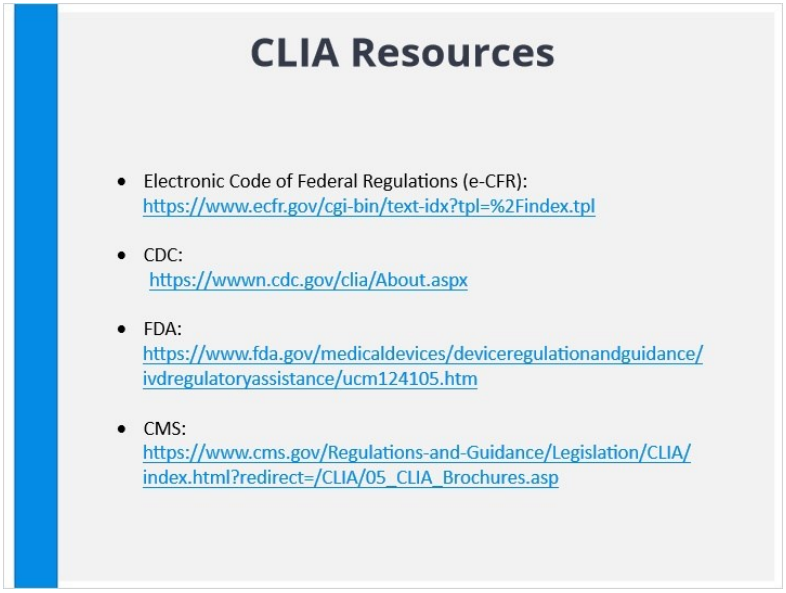
According to notes from the Federal register, as of January 2017, there were “246,143 CLIA-certified laboratories, of which 36,777 Certificate of Compliance and Certificate of Accreditation laboratories were required to enroll in a U.S. Department of Health and Human Services (HHS)-approved PT program and comply with the PT regulations*”.

While there are slight differences for the different CLIA-defined specialties and subspecialties, the CLIA regulations for assessments apply to all laboratories, not just those performing molecular testing. Molecular assays must follow the regulations like all other test specialties.

References:

* DEPARTMENT OF HEALTH AND HUMAN SERVICES Centers for Medicare & Medicaid Services 42 CFR Part 493 [CMS–3355–P] RIN 0938–AT55

1.5 ISO/IEC 17025 Standard



Notes:

CLIA Resources

The Electronic Code of Federal Regulations, or e-CFR, is available online at https://www.ecfr.gov/cgi-bin/text-idx?tpl=%2Findex.tpl

Regulations specific to laboratories are located within Title 42 (Public Health), Chapter IV (Centers for Medicare and Medicaid Services, Department of Health and Human Services), Subchapter G (Standards and Certification), Part 493 (Laboratory Requirements)

To learn more about CLIA, visit

the CDCs “About CLIA” webpage located at the url: https://wwwn.cdc.gov/clia/About.aspx,

the FDA CLIA webpage located at the url: https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm,

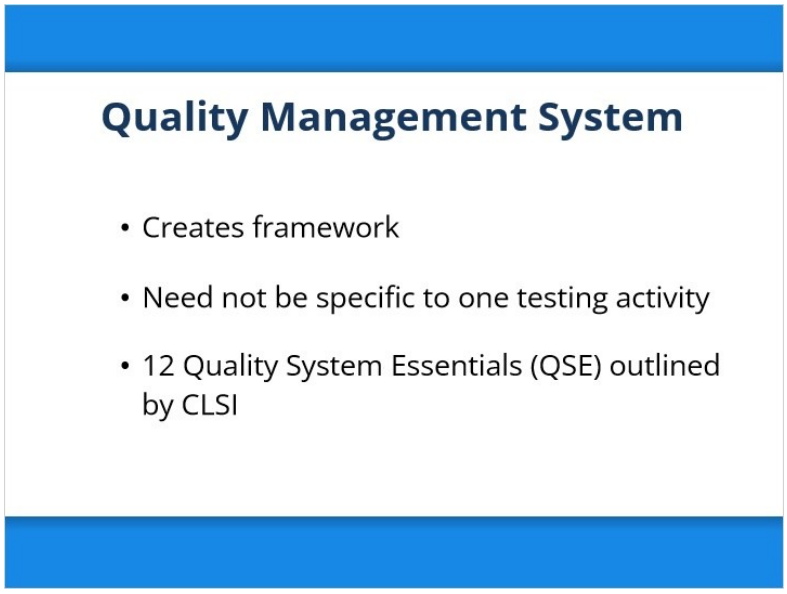
and the CMS CLIA webpage located at the url: https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/CLIA/05_CLIA_Brochures.asp

1.6 Good Laboratory Practice

Notes:

Good Laboratory Practice or GLP can be found from multiple sources that define what GLP means for laboratory work. A quick search will show that the World Health Organization (WHO), the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), the National Institute of Health (NIH) and others provide guidance for laboratorians on what should be considered in performing testing. These documents help fill a gap in laboratory regulations and guidance and provide a framework in support of quality data. The themes that run throughout include ensuring quality standards are in place such as documents, records, maintenance, personnel criteria, fundamental scientific practices such as ensuring equipment and instrumentation is calibrated, and creating accountability for the work produced.

1.7 Quality Management System



Notes:

Quality Management System (QMS)

Every laboratory needs to have a framework in place to support quality testing activities. The policies, processes, procedures, and responsibilities related to laboratory quality are housed within in the laboratory's Quality Management System, or QMS. A QMS provides the framework for all laboratory activities related to quality.

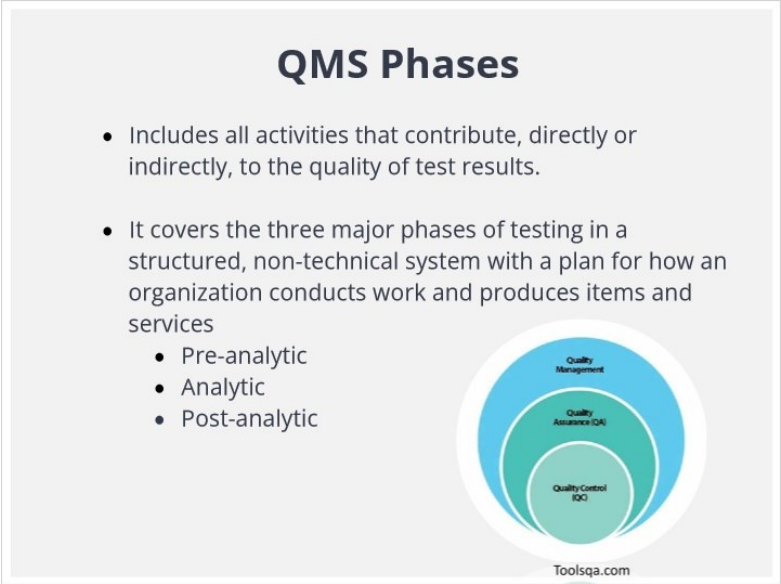
If a laboratory is developing a new molecular testing center, does that mean that an entirely new QMS must be developed? While there are specific molecular testing requirements that would need to be included, these can be built into the laboratory's existing QMS rather than starting from scratch. In fact, having a single, central, QMS can help ensure that quality requirements for all laboratory areas are clearly stated and that all testing areas are on the same page when it comes to quality.

The Clinical and Laboratory Standards Institute, or CLSI, outlines 12 quality system essentials, or QSEs*. These 12 QSEs are described by CLSI as the "building blocks" of the QMS. Each applicable block must be included to form a comprehensive QMS.

Reference

*https://clsi.org/about/blog/quality-management-in-the-laboratory/

1.8 QMS Phases

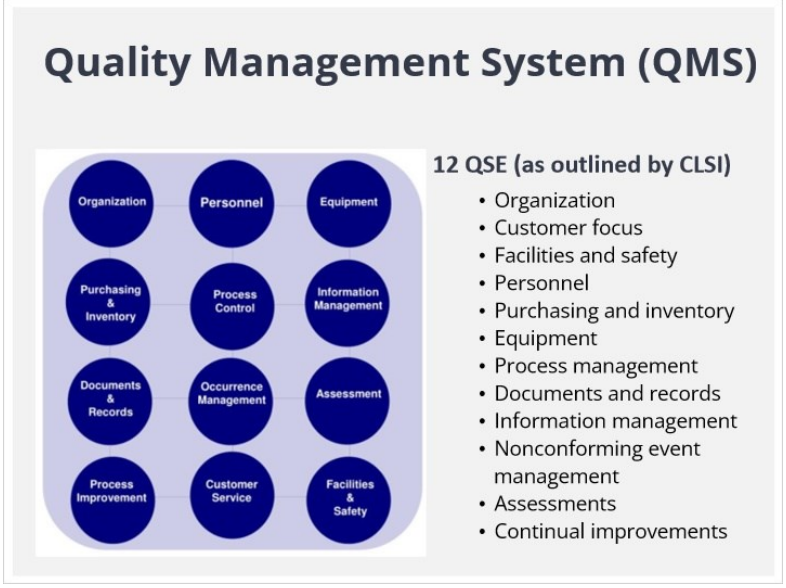


Notes:

Quality Management System (QMS) Includes all activities that contribute, directly or indirectly.

QMS is the overarching system that provides a structured, non-technical system covering the pre-analytical, analytical, and post-analytical phases including an implementation plan for how the organization, in this case a laboratory, conducts its work and produces its items and services.

1.9 Pre-analytical Phase



Notes:

Quality Management System (QMS) (continued)

The 12 quality system essentials as outlined by CLSI are, organization, customer focus, facilities and safety, personnel, purchasing and inventory, equipment, process management, documents and records, information management, nonconforming event management, assessments, and continual improvement*.

Documenting the laboratory's polices, process, and procedures for each of the 12 QSEs within the laboratory QMS will ensure that it is robust and all encompassing in it's approach to quality. While the CLIA requirements do not follow this same structure, there are overlapping similarities. It is important to remember that, regardless of where they are located, there are CLIA requirements associated with each of the QSEs .

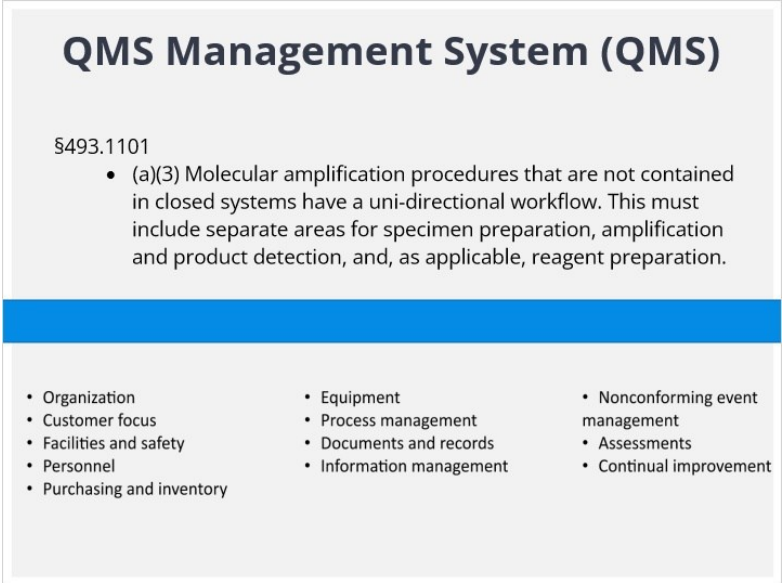
Laboratory CLIA requirements must also be incorporated in the QSEs of the QMS to ensure that all laboratory staff are aware what they must do to ensure quality in the laboratory.

Think of the QMS as the book, the QSEs as the chapters, and requirements as the basis for the text.

Reference

*https://clsi.org/about/blog/quality-management-in-the-laboratory/

1.10 QMS Management System (QMS)



Notes:

Quality Management System (QMS) (continued)

Let's take a look at a CLIA requirement and determine in which of the 12 QSEs it belongs.

CLIA §493.1101, a, 3, states that molecular amplification procedures that are not contained in closed systems have a uni-directional workflow. This must include separate areas for specimen preparation, amplification and product detection, and, as applicable, reagent preparation.

Which of the 12 QSEs would this fall under?

To incorporate a unidirectional workflow, there must be separate laboratory areas and a workflow path from pre-amplification to amplification and, finally, to post-amplification. This requires changes to the physical layout of the laboratory facility. This example would fall under the facilities QSE.

Requirement 493.1101 is the facilities standard in subpart J of the CLIA regulations. The text above is an excerpt of that requirement.

1.11 Quality Assurance vs Quality Control

Notes:

Quality Assurance vs Quality Control

Quality assurance and quality control are often used interchangeably in conversation. The two terms, however, point to two different quality activities.

Quality assurance is defined as all the actions taken to ensure that an organization delivers products that meet performance requirements and adhere to standards and procedures.*

Quality control is defined as the set of procedures designed to monitor the test measurement procedure and the results to ensure test system performance*

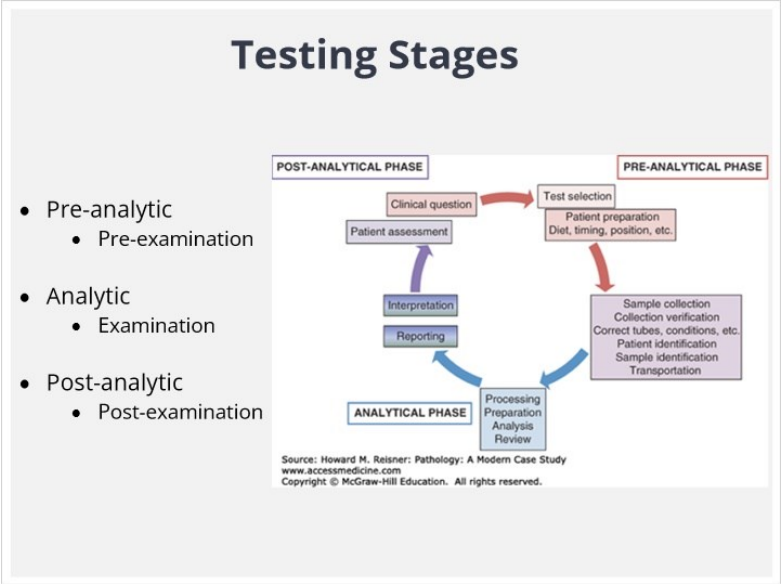
Quality control, then, is a smaller subset within quality assurance. These are the controls used to ensure a specific test is performing as expected while quality assurance would encompass those controls, document control used for the procedure, competency assessment of the individual performing the testing, an all the other components touched on by the QMS.

Think of quality assurance as the reason for your entire QMS. Your QMS is there to ensure that everything is in place and that the laboratory is being proactive about quality. Think of quality control as a single, reactive, activity within that QMS to ensure that one of the processes, or tests, is working as expected.

Reference

CLSI harmonized database (http://htd.clsi.org/)

1.12 Testing Stages



Notes:

Testing Stages

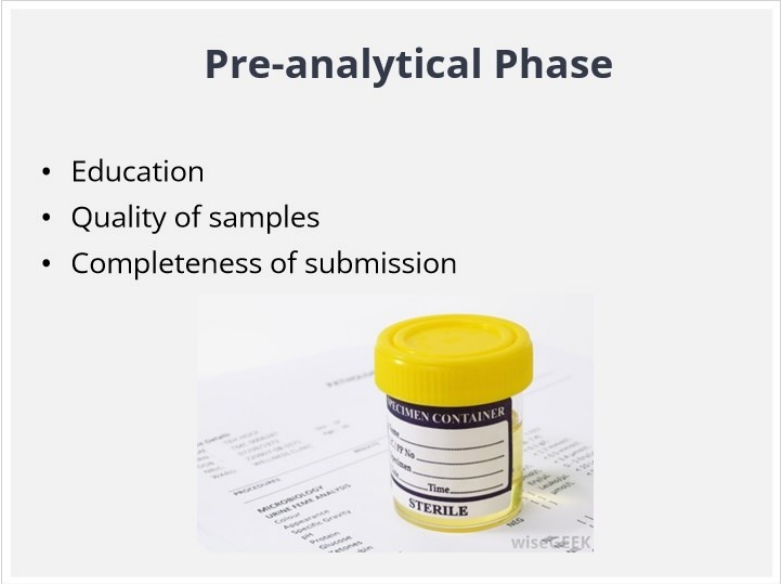
The three commonly referred to stages of laboratory testing are the pre-analytic, analytic, and post-analytic.

The pre-analytic (or pre-examination) stage includes the processes leading up to the analytic examination. This includes process such as patient preparation, filling out the requisition forms, sample transportation to the laboratory, and some sample accessioning activities.

The Analytic (or examination) stage includes the processes involved in the examination of a sample. Therefore, the analytic stage includes items such as sample acceptability, equipment calibration, internal quality control, and reagents.

And lastly, the post-analytic (or post examination) stage includes the processes following the examination of the sample. This includes items such as result interpretation and reporting.

1.13 Pre-analytical Phase



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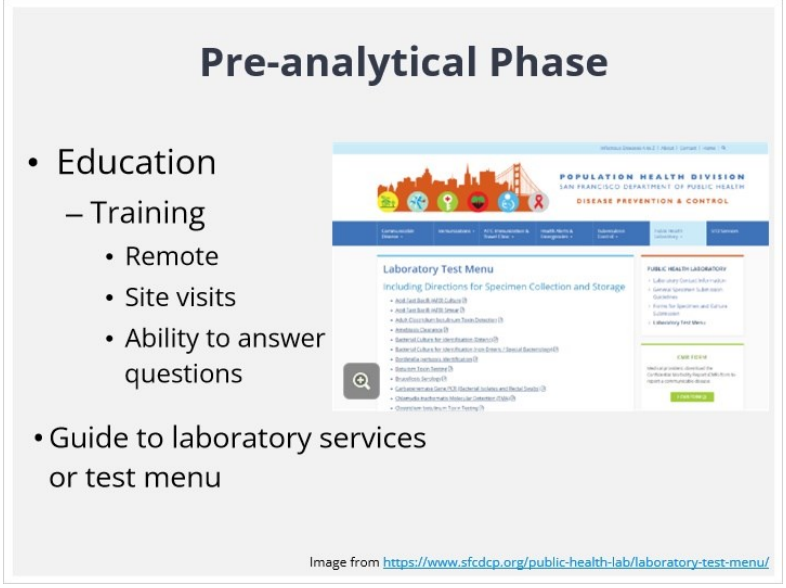
So, to start the pre-analytical phase has three main aspects that should be considered. These main aspects include education, quality of samples, and completeness of submission.

1.14 Pre-analytical Phase



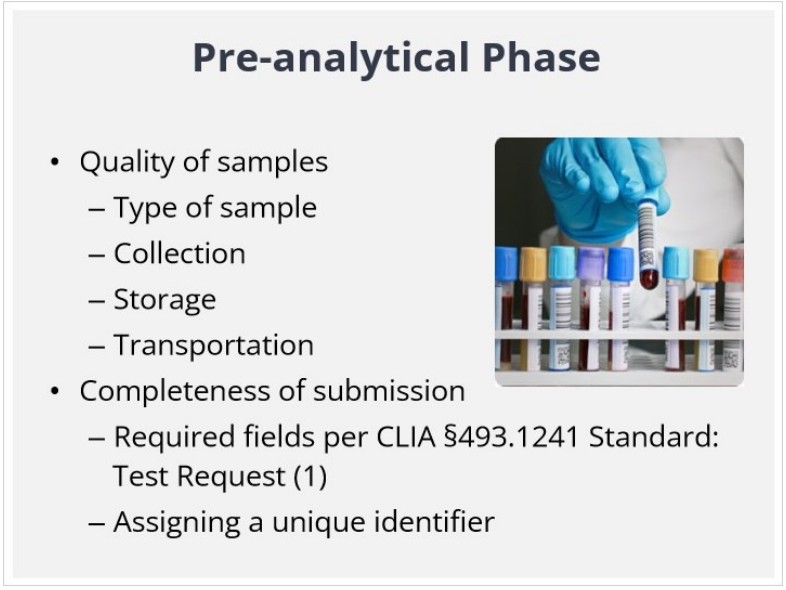
Notes:

Pre-analytic phase - Education

The majority of public health laboratories do not participate in the preparation and or collection of samples and are very rarely associated with a hospital. If the laboratory is a local, it may be associated with a clinic and have the ability to directly interface with the staff collecting samples. However, because the majority are separated from where the samples are being collected, it is important that a public health laboratory provide education to its sample/specimen collectors and submitters regarding the type and quantity of specimen needed to perform testing. It is also key to ensure that information regarding the quality of specimen is clearly explained as some tests require a high quality specimen where other tests can deal with a less than ideal specimen to achieve the needed results.

Education can be accomplished through a multitude of mechanisms and each public health laboratory will need to establish how their laboratory system best receives this information and the resources available to provide this information. A good way to discover this is to perform the Association of Public Health Laboratories (APHL) Laboratory System Improvement Program assessment. Having information readily available online via the laboratory's website or an accessible learning management system is one way to remotely provide needed information on specimen collection and handling. Another avenue is to provide this information through site visits such as a newborn screening outreach and education staff working with nurses or a trainer providing training to sentinel laboratories on collection and shipping. It is also key that staff members have the information, resources, and knowledge to answer questions from submitters. CLIA §493.1242 Standard: Specimen submission, handling, and referral discusses the need for written instructions for each client that sends specimens/test requests. These instructions may include details on specimen handling such as collection, preservation, storage, transport, and contact information. One way many laboratories ensure that this reaches clients is to post on websites a guide to the services, or test menu, offered by the laboratory.

1.15 Pre-analytical Phase



Notes:

Pre-analytic Phase – Quality of Samples and Completeness of Submission.

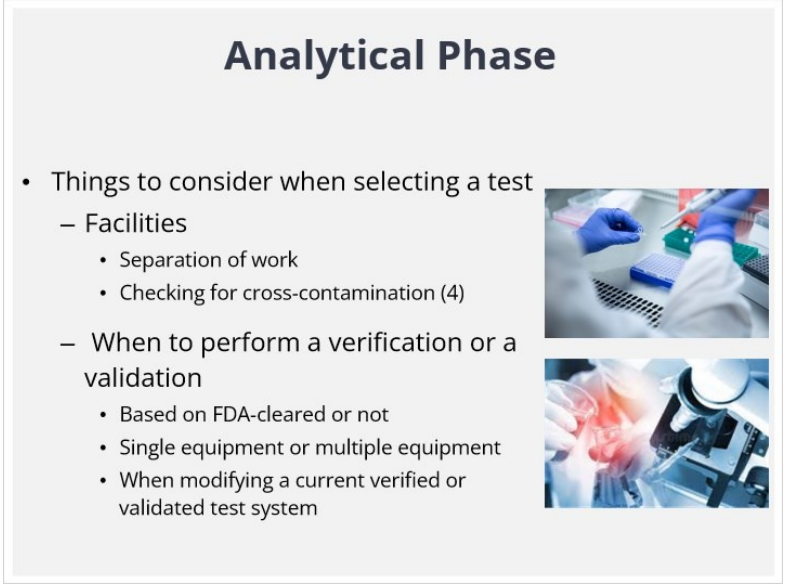
As we discuss outreach with the laboratory system community, the pre-analytical phase is not complete without discussion of the quality of specimens received. As a public health laboratory there are situations where samples may be less than ideal, such as dealing with a food outbreak or only having a few blood spots on a newborn card,

may be accepted to perform testing. Working with partners throughout the process and communicating the need for good quality specimens through education, outreach, and guides will assist in minimizing situations where less then ideal samples are received. Providing sampling kits and clear instructions will also assist in ensuring that the laboratory receives the best specimen. Ensuring that the appropriate specimen or sample type is obtained, the correction collection vessel or media is used, storage before sending, and transportation considerations are discussed with submitters will assist with providing the best quality result to the client.

Another aspect of the pre-analytical phase is completeness of submission to the laboratory. Key information is necessary in order to report out results to the submitter and to the public health agencies needing the information for population health. CLIA requires that the test request solicit information per the §493.1241 Standard: Test Request (1) regulation. This regulatory requirement looks for an authorized individual requesting the test, name and address of the entity submitting the sample, a contact person for questions and critical results, patient name or unique identifier, sex and age or date of birth, test requesting, source of specimen, and date and time, where applicable, of specimen collection, and any additional information necessary in order to ensure that results reported out contain accurate information and interpretations if needed. Labels on the specimen or sample should match information that is found on the accompanying submission or requisition form. As good laboratory practice, a quality management system regardless of regulatory oversight, will ensure that samples received by the laboratory collects key information such as submitter contact information for questions and results, key information about the sample, what test is being requested, source of sample, date and time of collection, and any additional information necessary for completing the requested test. Once received, the laboratory assigns a unique identifier using its laboratory information management system.

As you can see, while the pre-analytical phase for a public health laboratory may be the receipt of the sample, there are still a number of factors that need to be taken into account to ensure that the specimen received will assist in producing accurate and timely results to the submitters.

1.16 Analytical Phase



Notes:

Now we are ready for the fun part, the analytical phase or testing phase. As we receive samples and test requests we need to have determined what is the best method to use and there are a multitude of factors to consider. Specifically for molecular testing your facility needs to be a consideration in selecting the best test method. If you have a closed system with uni-directional workflow this may be less of an issue, but for those that are open systems a separate area for the different steps, which include but not limited to preparation, amplification, and reagent

preparation, is necessary. Routinely you will also need to ensure that you perform a check for any amplicon cross-contamination that may occur in the areas you perform molecular testing.

Another factor to consider as you select a test method is if the test must be verified or validated. If an **unmodified** FDA-cleared or approved test is chosen the laboratory performs a verification, but if the laboratory is choosing to use a **modified** FDA-cleared or approved test, a laboratory developed test (LDT), or a non FDA-cleared or approved method from either the Center for Disease Control and Prevention (CDC) or another public health laboratory they must perform a validation. An unmodified FDA-cleared test or assay under CLIA only requires a verification of the accuracy, precision, reportable range, and reference range. Modified FDA-cleared or approved test, a laboratory developed test (LDT), or a non FDA-cleared or approved method from either the Center for Disease Control and Prevention (CDC) or another public health laboratory require a validation which includes accuracy, precision, reportable range, analytical sensitivity, analytical specificity, and reference range. In addition, consideration should be taken regarding whether or not the laboratory will only have one piece of equipment for the test or multiple. If multiple equipment are available at the beginning of the verification or validation best practice recommends including them all in the verification or validation. If the laboratory adds equipment for the test at a later time then they will need to perform an equipment to equipment verification or validation. Any time the laboratory modifies the test either through changing the reagent volumes, specimen volumes, handling of specimens, incubation times or temperatures, changing a procedural step, changing the cutoff or method of calculating the cutoff and others per CLIA the laboratory must perform a new verification or validation of the test. As a note many other guidance and regulatory documents also indicate that changes such as the ones CLIA specifies would result in a new verification or validation.that changes such as the ones CLIA specifies would result in a new verification or validation.

1.17 Analytical Phase

Notes:

Analytic Phase (continued).

Supporting information

Documents

Standard operating procedures, forms

Records

Shows that quality management system has been followed

Quality control activities performed during analysis

Supporting quality components

1.18 Analytical Phase

Notes:

Analytic Phase (continued)

Personnel

Technical Supervisor

CLIA §493.1449 and 493.1451

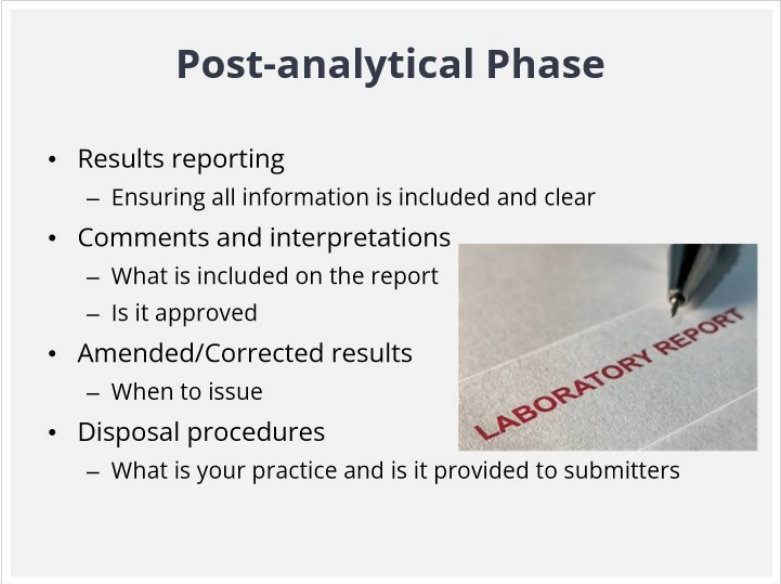
Qualified individual to oversee the particular specialty or subspecialty

Training and competency

Initial training

Competence assessment

1.19 Post-analytical Phase



Notes:

Post-analytic Phase

Results reporting

Ensuring all information is included and clear

Comments and interpretations

What is included on the report

Is it approved

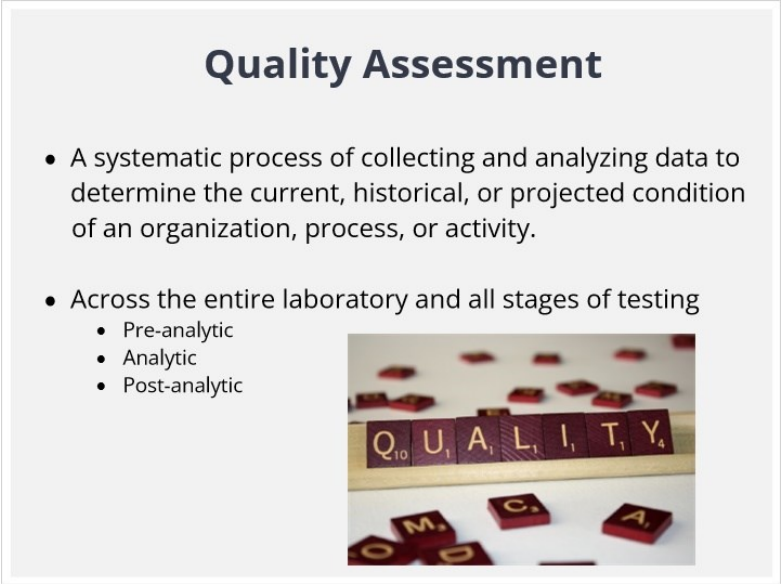
Amended/Corrected results

When to issue

Disposal procedures

What is your practice and is it provided to submitters

1.20 QMS and IT



Notes:

Assessment

An assessment is a systematic process for collecting and analyzing data to determine the current, historical, or projected condition of an organization, process, or activity.*.

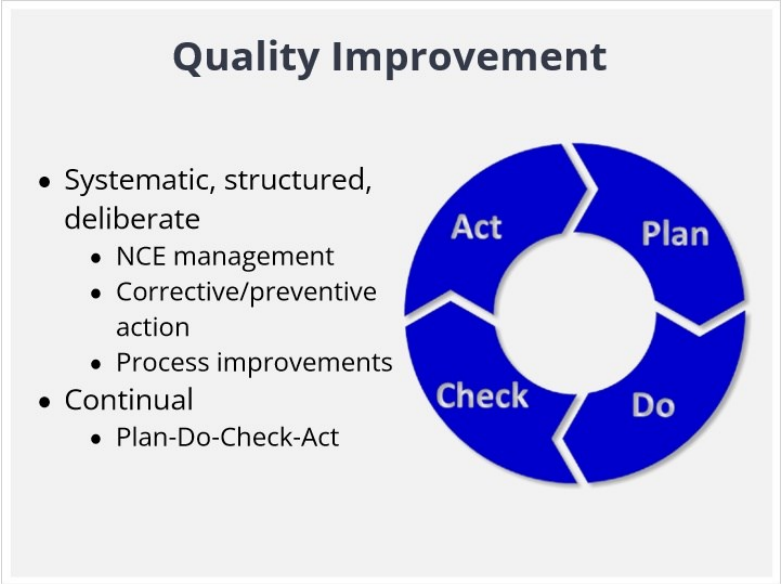
To simplify, an assessment collects objective evidence about a laboratory process or function. This evidence is compared against a standard to determine if the expectations are being met. Some common laboratory assessments include internal audits, proficiency testing, and competency assessments

Assessments are performed across an entire laboratory environment and across all stages of testing.

Reference

*CLSI harmonized database (http://htd.clsi.org/)

1.21 Conclusion



Notes:

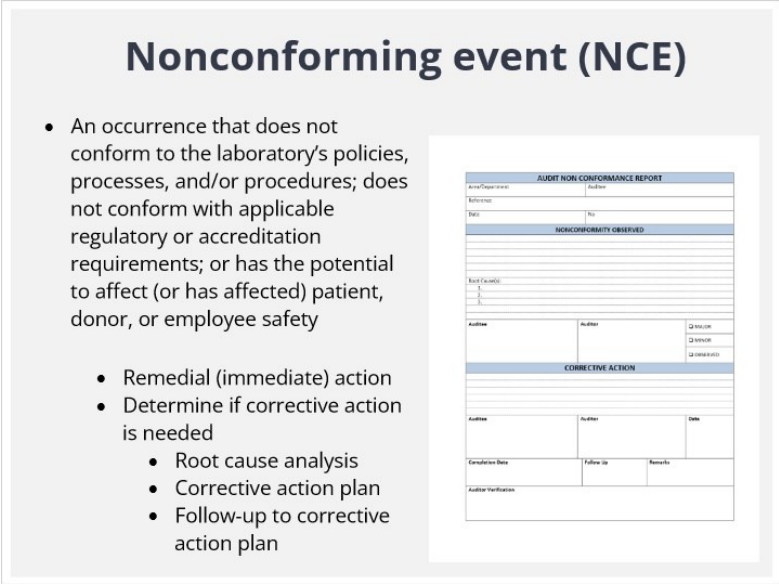
Quality Improvement

It is easy to think of quality improvement as something you do when you find something wrong. For instance, if you weren't meeting a requirement and made a change in your process so that you are now in compliance. Quality improvement, encompasses that activity and many more. It includes all systematic, structured, deliberate activities undertaken to improve quality control, quality assurance, or the QMS. Some examples of quality improvement are non-conforming event, or NCE, management, corrective and preventive action plans, and process improvement projects.

Quality improvement does not end. It is a continuous, circular, process. This is demonstrated with W. Edwards Deming's Plan-Do-Check-Act model. First the opportunity for improvement is noted and a change is planned (Plan). Next, the change is tested on a small scale (Do). Then, the outcome of the change is reviewed for effectiveness and lessons learned are identified (Check). Action is then taken based on the findings (Act). The results of the change then feed into another improvement cycle.

The more quality improvements built into the QMS, the more dynamic and able to withstand change the laboratory will be.

1.22 References



Notes:

Nonconforming event (NCE)

A nonconforming event as an occurrence that does not conform to the laboratory's policies, processes, and/or procedures; does not conform with applicable regulatory or accreditation requirements; or has the potential to affect (or has affected) patient, donor, or employee safety*.

In the laboratory, nonconforming events, or NCEs are, often, the start of the Quality Improvement cycle.

Nonconforming events require several different layers of follow-up. First, remedial or immediate action is completed. This is the immediate fix to the problem. The event should then be evaluated to determine if corrective action is needed. This is often done by classifying the event based on severity, frequency, and risk of recurrence. If it is determined that the issue is likely to reoccur, or has a high risk or severity factor, corrective action should be completed. Corrective action is not a single action. It is a process. First is determining the root cause of the issue. Then, a plan is created including what will be done to correct the root cause, who will do it, and a deadline for completion. Once the corrective action is implemented, the results of the corrective action plan should be reviewed at regular intervals to determine if it was effective at removing the root cause.

Reference

*CLSI harmonized database (http://htd.clsi.org/)

1.23 References

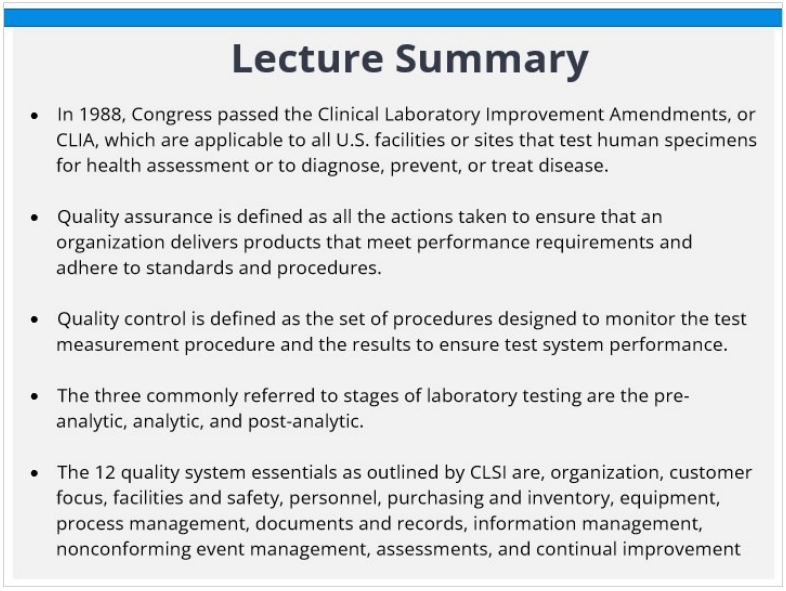
Notes:

QMS and IT

How does IT fit into the QMS

- Integrated into each phase of the process
- As we move forward with new testing methodologies we will need to have a strong relationship with IT
- CLIA requires verification that IT systems are working – how do you do this?

1.24 References



Notes:

Lecture Summary

In 1988, Congress passed the Clinical Laboratory Improvement Amendments, or CLIA, which are applicable to all U.S. facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease.

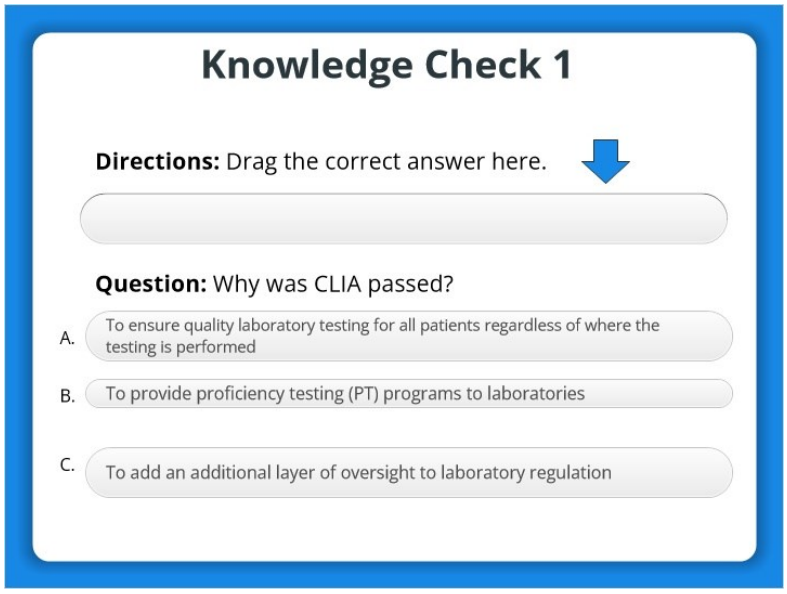
Quality assurance is defined as all the actions taken to ensure that an organization delivers products that meet performance requirements and adhere to standards and procedures.

Quality control is defined as the set of procedures designed to monitor the test measurement procedure and the results to ensure test system performance.

The three commonly referred to stages of laboratory testing are the pre-analytic, analytic, and post-analytic.

The 12 quality system essentials as outlined by CLSI are, organization, customer focus, facilities and safety, personnel, purchasing and inventory, equipment, process management, documents and records, information management, nonconforming event management, assessments, and continual improvement

1.25 Knowledge Check 1



Notes:

Knowledge Check 1

CLIA was passed to:

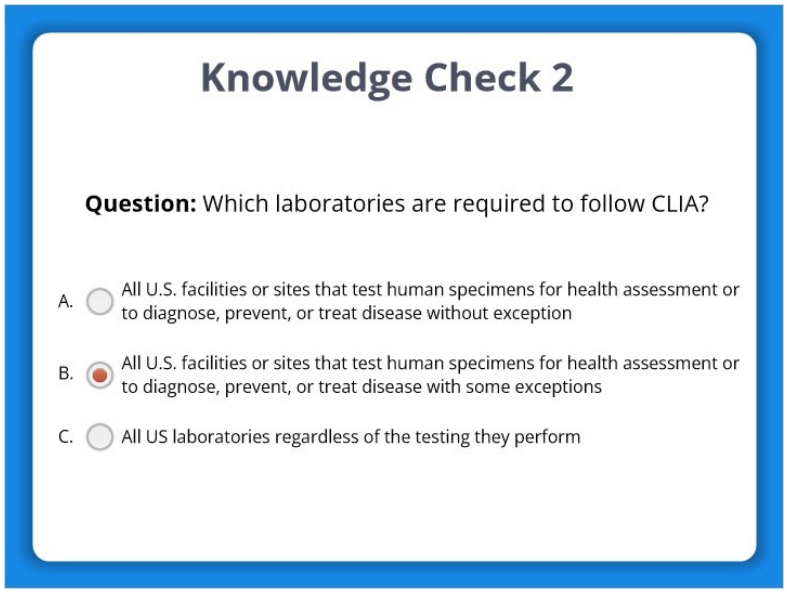
A - Ensure quality laboratory testing for all patients regardless of where the testing is performed.

B - Provide proficiency testing (PT) programs to laboratories

C - Add an additional layer of oversight to laboratory regulation

Answer: A

1.26 Knowledge Check 2



Notes:

Knowledge Check 2

Which laboratories are required to follow CLIA?

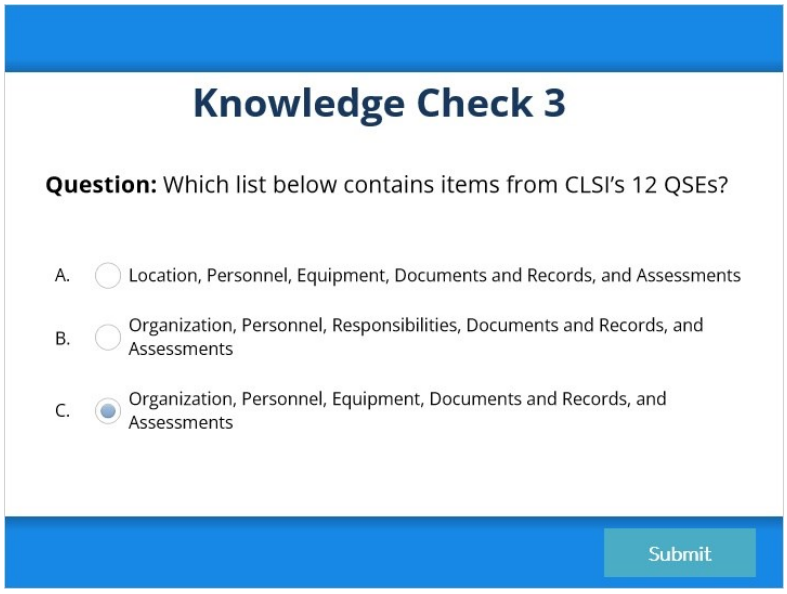
A - All U.S. facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease without exception.

B - All U.S. facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease with some exceptions.

C – All US laboratories regardless of the testing they perform

Answer: B There are exceptions for certain forensic testing; research or surveillance; and some testing performed by Substance Abuse and Mental health Services Administration (SAMSHA) certified laboratories.

1.27 MULTIPLE CHOICE QUESTION



Notes:

Knowledge Check 3

Which list below contains items from CLSI's 12 QSEs?

A – Location, Personnel, Equipment, Documents and Records, and Assessments

B – Organization, Personnel, Responsibilities, Documents and Records, and Assessments

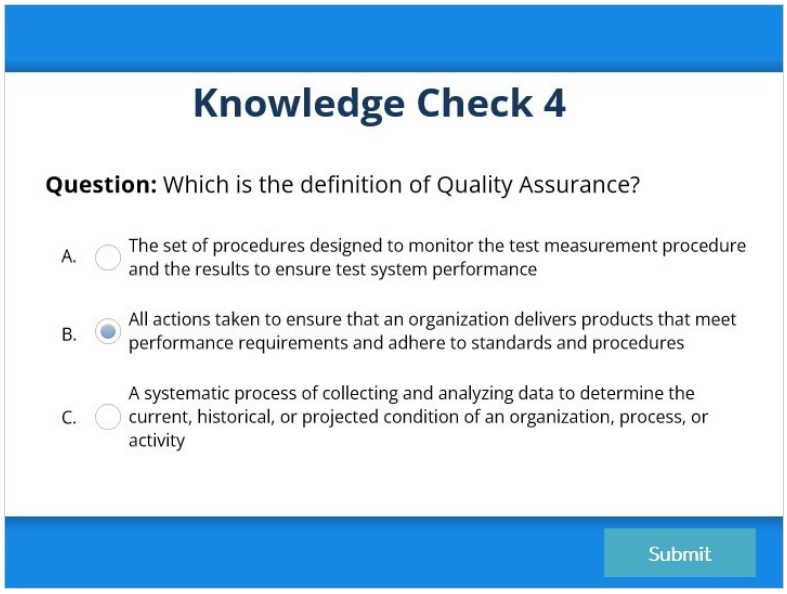
C – Organization, Personnel, Equipment, Documents and Records, and Assessments

Answer: C

A – Location is a subset of the QSE Organization

B – Responsibilities is a subset of the QSE Organization

1.28 MULTIPLE CHOICE QUESTION



Notes:

Knowledge Check 4

Which is the definition of Quality Assurance?

A – The set of procedures designed to monitor the test measurement procedure and the results to ensure test system performance

B – All actions taken to ensure that an organization delivers products that meet performance requirements and adhere to standards and procedures

C – A systematic process of collecting and analyzing data to determine the current, historical, or projected condition of an organization, process, or activity.

Answer: B

A – This is the definition of quality control

C – This is the definition of an assessment