Navigating the Regulatory and Compliance Environment in Clinical Laboratory Testing

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Objectives

- Understand the difference between regulatory and non(sub)-regulatory
- Differentiate between the various HHS areas of oversight
- Define deemed status entities
- Differentiate between various test kits and laboratory developed assays
- Understand analytical validation

Regulatory versus Non-regulatory

- Regulatory = law

  If you don't follow the law, you can go to "jail" (pay huge fines)

  In Federal Register

    - Subject to Notice of Proposed Rulemaking (NPRM)
      - Allows comment prior to becoming law

- Non-Regulatory

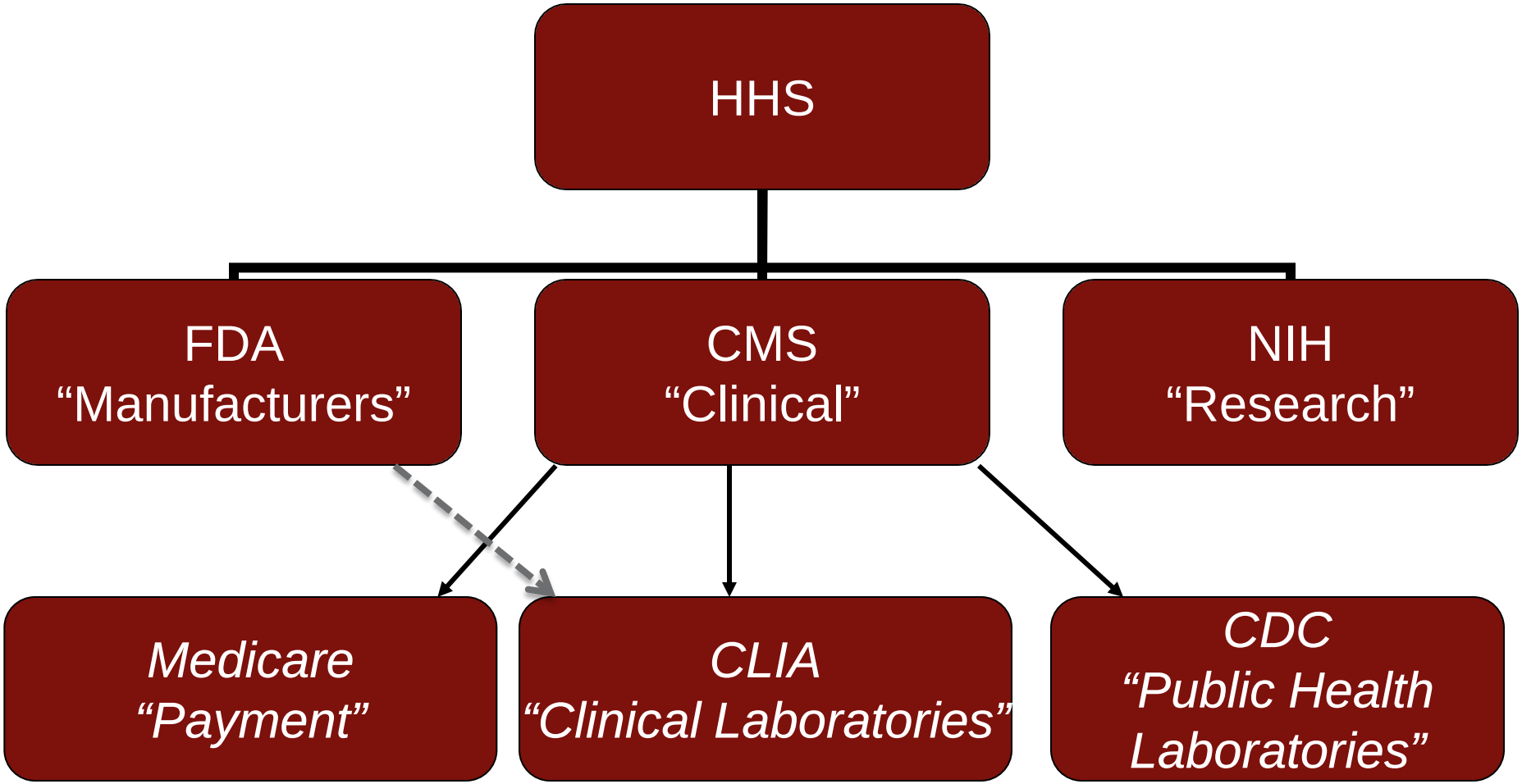
  AMP (Association for Molecular Pathology) guidelines

  ACMG (American College of Medical Genetics) guidelines

  CAP (College of American Pathologists) guidelines

  NCCN (National Comprehensive Cancer Network) guidelines

Oversight


HHS
FDA
“Manufacturers”
CMS
“Clinical”
NIH
“Research”
Medicare
“Payment”
CLIA
“Clinical Laboratories”
CDC
“Public Health
Laboratories”

CLIA

CMS

- CLIA'88 – responsible for clinical laboratory testing
  - Quality assurance standards
  - Proficiency standards
  - Record maintenance
  - Personnel qualifications
  - Quality control
- Medicare reimbursement
- If not doing medical testing, don't need CLIA license
  - Ancestry
  - Paternity
  - Recreational genetics

CLIA'88

- The Clinical Laboratory Improvement Amendments of 1988 statute is an amendment to the Public Health Services Act in which Congress revised the federal program for certification and oversight of clinical laboratory testing (42 CFR 493)

CLIA deemed status

- Has higher standards than CLIA
- Includes

  NYSDOH (http:// www.wadsworth.org)

  CAP (http://www.cap.org)

CLIA – CAP - NYSDOH

- CLIA: Any medical test and bill CMS
- CAP: Most labs obtain

  Suggests higher quality than CLIA

  Administers PT program
- NYSDOH: required if testing patients from NY

  Suggests higher quality than CLIA

  Administers PT program

CMS/CLIA "Speak"

- Laboratory director = CLIA license holder
  - Only 1 per CLIA license
- Technical supervisor = often referred to as a director
- General supervisor = supervisor
- Technical consultant = MD, PhD, or DO; cannot be GC
- Technologist

CLIA "Speak" #2

- Laboratory classifications
  - Physician office labs – POC (Point of care)
    - pregnancy tests
    - Strep test
  - Low complexity
  - Medium complexity
  - High complexity
    - Almost all genetic tests fall into this category, especially NGS

Proficiency Testing (PT) /Alternative Assessment (AA)

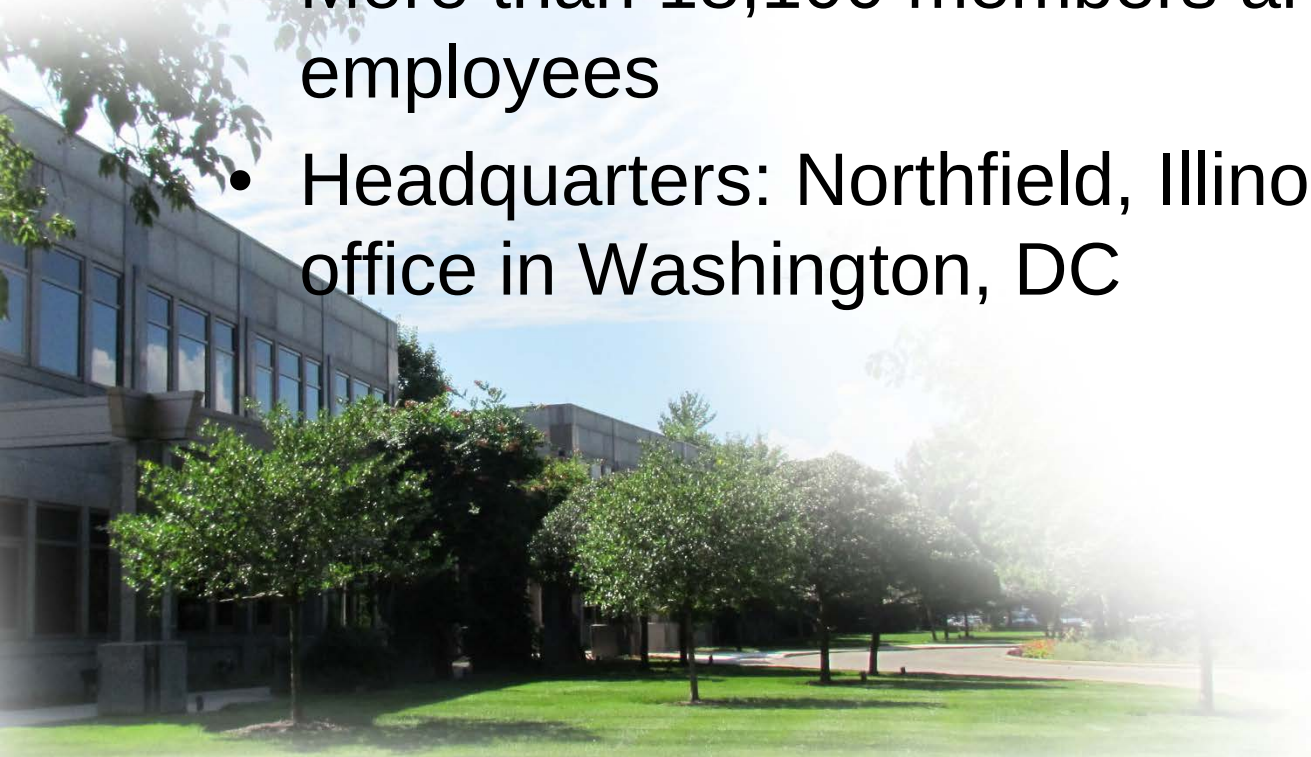
- Required 2X per year for every analyte
- CAP and NYSDOH have PT programs
- Other programs
  EMQN (Europe)
  INSTAND (Germany)
- If no formal program, must do AA
  Exchange samples with another lab
  Re-test samples in blinded manner in own lab

Regulated vs. Non-regulated analytes

- PT is required for only the limited number of tests found in Subpart I, Proficiency Testing Programs for Nonwaived Testing, of the CLIA regulations.
- CLIA requires laboratories to take steps to assure the accuracy of testing in lieu of testing PT samples. CLIA requires that, at least twice annually, you verify the accuracy of any test or procedure that you perform that is not listed in Subpart I.

CAP Overview

- Established in 1946
- Leading organization for board-certified pathologists
- More than 18,100 members and 600 employees
- Headquarters: Northfield, Illinois; Advocacy office in Washington, DC



Headquarters: Northfield, Illinois, a suburb of Chicago

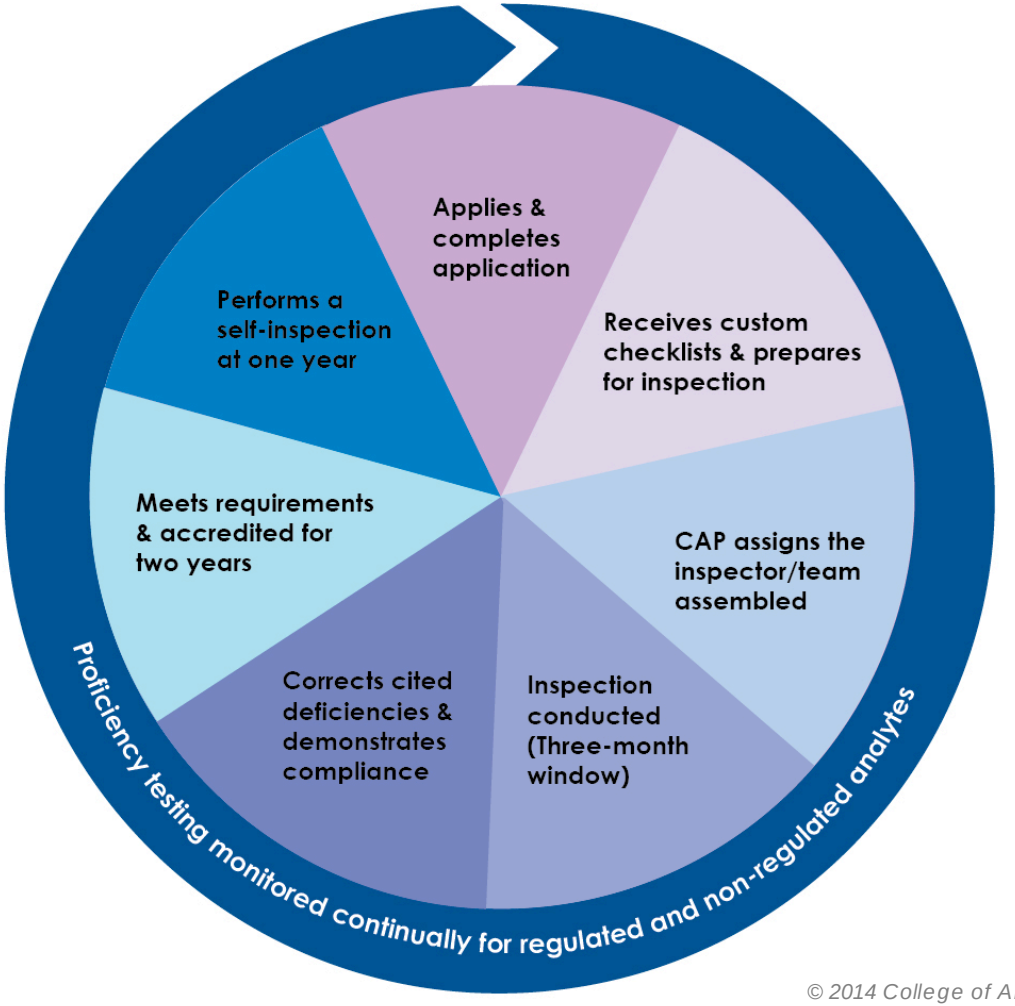
CAP Accreditation Overview

- Offering laboratory accreditation since 1963
- Helps laboratories achieve the highest standards of excellence
- More than 7,600 CAP-accredited laboratories in 50 countries
- Estimated 22,000 laboratories in 100 countries enrolled in the CAP's proficiency testing (PT) programs

CAP Accreditation

- Sets high standards for clinical, anatomic, and specialty laboratories that address quality, efficiency, and safety:
- Extends beyond CLIA regulatory requirements
  - focuses on improving quality
  - encourages quality culture
- CAP performs biennial inspections
- Uses trained peer inspectors
- Self inspections required
- Laboratories need to adhere to checklist requirements
- CLIA only requires formal PT for 83 analytes, but CAP includes many more
- CAP helps facilitate interlaboratory proficiency exchanges
- Explicitly requires clinical validity, which can be documented by literature
- CAP programs help labs attain excellence in testing
- Leads in developing requirements for molecular oncology, cytogenetics, and reproductive medicine

CAP Laboratory Accreditation Program: Two-Year Cycle



CAP Standards for Laboratory Accreditation

- Standard I – **Director and Personnel**
  - qualified, responsible for meeting standards, given authority
- Standard II – **Physical Resources**
  - nature, adequacy, safety, disabilities
- Standard III – **Quality Management**
  - extensive list of policies and procedures to ensure quality testing and patient safety
- Standard IV – **Administrative Requirements**
  - checklists, inspections, self assessment, records and documentation, terms of accreditation

Accreditation Checklists

- Laboratory General
- All Common
- Anatomic Pathology
- Team Leader Assessment of Director and Quality
- Chemistry and Toxicology
- Clinical Biochemical Genetics
- Cytogenetics
- Cytopathology
- Flow Cytometry
- Hematology and Coagulation
- Histocompatibility
- Immunology
- Limited Service Laboratory
- Microbiology
- Molecular Pathology
- Point-of-Care Testing
- Transfusion Medicine
- Urinalysis

CAP Laboratory Accreditation Program: Value of Peer-Based Inspections

- Laboratory professional (pathologist, technologist, etc.)
  - Gains insight through interacting with peer professionals
  - First-hand knowledge to offer constructive feedback
- Promotes continuous education & improvement
- Inspectors with Specialty Expertise
- Working professionals exposed to new technologies
- Domestic and international inspections
- Staff Inspectors
  - Ancillary sites and large groups of limited service labs
  - Participate in all for-cause inspections

FDA

FDA

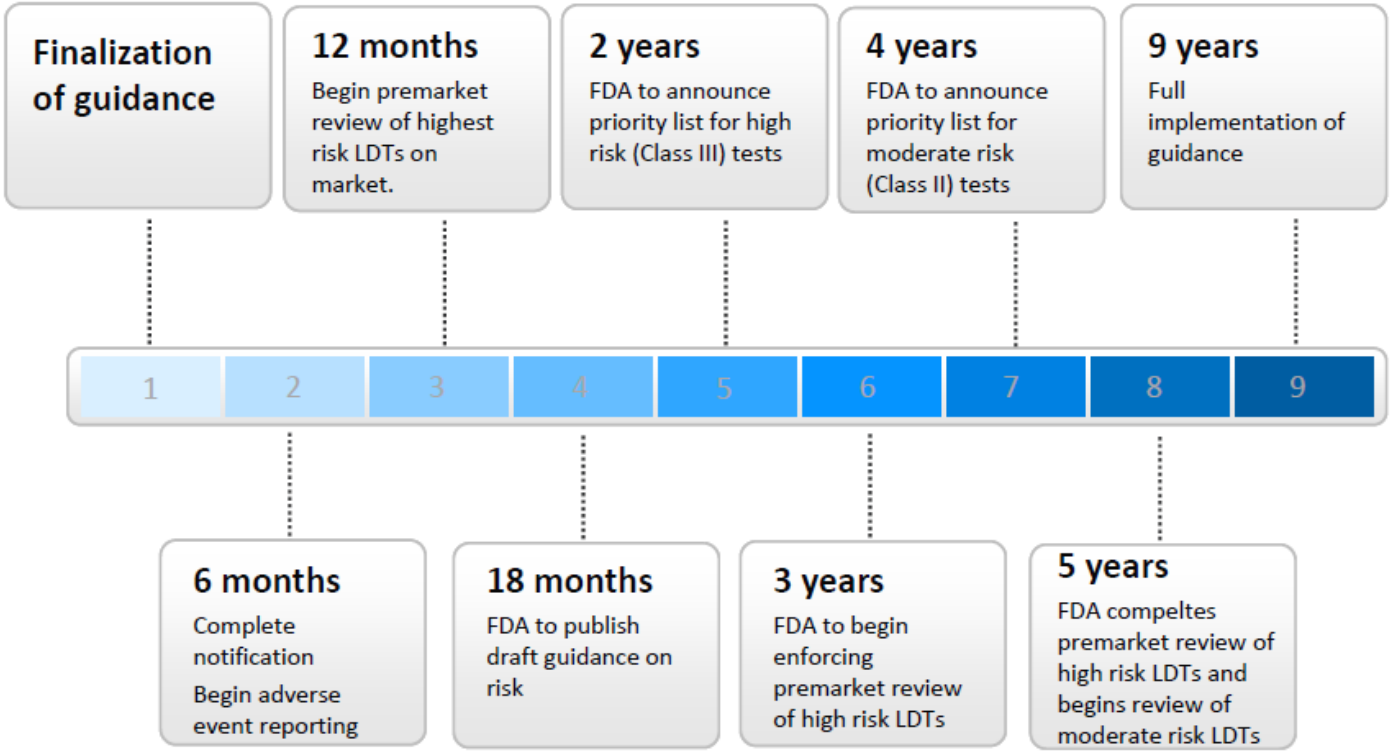
- Mandate that device is “safe” and “effective”
  - PMA = new device (FDA-approved)
  - 510K = equivalent to predicate device (FDA-cleared)
  - De novo 510K = lower risk new device (FDA-cleared)
    - May also be new assay on approved platform
  - HDE = Humanitarian device exemption

- Requires QSR = Quality system regulation (similar to ISO = International Organization for Standardization)
- Approval/Clearance does not determine reimbursement

Draft Guidance for Oversight of LDTs

- 60-day to Congress on 31 July 2014
- Notice by the Food and Drug Administration on 10/03/2014 in federal register
- Goal to ensure analytical and clinical validity
- 2016 – to finalize

FDA Oversight of LDTs: Phased and Risk-based



Operational issues

- Conflicts between CLIA and FDA regulations
  - FDA restriction of off-label promotion versus CLIA allows clinical consultation
  - CLIA regulation versus FDA's quality system regulation (QSR)
  - Laboratory service directory versus package insert
  - Malpractice versus product liability insurance

Professional Societies/Organizations

- Have no regulatory oversight
- Can determine standards of care

  ACMG guidelines

  AMP guidelines

Rehm et al. ***ACMG clinical laboratory standards for next-generation sequencing.*** *Genet Med (2013) 15, 733–747 doi:10.1038/gim.2013.92*

Green et al. ***ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing.*** *Genet Med (2013) 15, 565-574. doi: 10.1038/gim.2013.73.*

AMP/ACMG/CAP interpretation of sequence variants (in draft)

TEST KITS

FDA-cleared/approved

- A kit that includes all or most of the test components and a written procedure

- Affymetrix CytoScan® Dx Assay
  FDA-cleared (de novo 510K)

FDA-cleared/approved (modified)

- A kit that includes all or most of the test components and a written procedure

  Modifications/changes that validated and are not in package insert

- Illumina's FDA-cleared MiSeq instrument and reagents (MiSeq Universal Kit) may be used as FDA-modified for gene(s) in clinical testing

Investigational use only (IUO)

- Includes all or most of the test components and a written procedure
- Undergoing initial development and evaluation concurrent with clinical studies
- Not to be used as a diagnostic procedure without confirmation of the diagnosis by a second, medically established diagnostic device or procedure

http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253307.htm

IUO (modified)

- A kit that includes all or most of the test components and a written procedure

  Modifications/changes that validated and are not in package insert

- Still considered IUO

Research use only (RUO)

- Includes all or most of the test components and a written procedure
- Intended for performing basic scientific or animal research in the search for a diagnostic hypothesis or intended use for a new diagnostic device.
- Good manufacturing practices (GMP) are not required
- Not intended for use as building blocks for laboratory-developed assays and not intended to be used to facilitate the reporting of results to patients or health care professionals for clinical purposes

http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253307.htm

RUO (modified)

- A kit that includes all or most of the test components and a written procedure

  Modifications/changes that validated and are not in package insert

- Still considered RUO

Always consult with your institution's legal team

CE (Conformité Européenne)-marked

- A kit that includes all or most of the test components and a written procedure

- OK for Europe
- May be considered RUO in USA

Forensic use only

- A kit that includes all or most of the test components and a written procedure

- OK for forensics
- May be considered RUO in clinical testing

Laboratory developed procedures/tests

- Components of assay are determined by laboratory

  May use kits for part of assay

NON-KITS / REAGENTS

Analyte-Specific Reagents (ASRs)

- Generally a single reagent, such as an antibody or nucleic acid probe, that can be used by laboratories in developing a functional clinical assay

ASRs

Vendors

- Must register their establishments and list their reagent(s) with the FDA.
- Must manufacture per the Quality Systems Regulation (QSR).
- Can provide information about the reagent to the user, such as identity and purity, but should not provide information on specific performance characteristics (eg, sensitivity or specificity), estimate of a systematic measurement error

Research Use Only

- Includes a component of a test with a written procedure (eg, DNA extraction), but NOT specific to an analyte

http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253307.htm

General Purpose Reagents

Reagents with general laboratory application and are not labeled or intended for specific diagnostic applications

- Buffers (eg, saline, TE, TBE, TAE)
- Restriction enzymes
- Alcohols (eg, ethanol, methanol)

Laboratory equipment, software and automated or powered systems are not considered to be GPRs.

Laboratory-developed tests (LDTs)

- Completely developed in the laboratory
- May include the following reagents/kits

  Kits without a specified analyte
  - DNA extraction kits

  RUO reagents

  ASRs

  GPRs

ANALYTICAL VALIDATION

Validation/Verification

- Proving that you can detect what you say that you can detect

Verification

- Confirmation that specified requirements have been fulfilled (ISO 9000:2005).
- One-time process to determine/confirm test performance characteristics
- In USA, used for a FDA-cleared assay
- In Europe, used for existing test or technology

Performance Specifications

- **CLIA Section 493.1253(b)(1) states**

  Each laboratory that introduces an unmodified FDA cleared or approved test system must verify the following performance characteristics before reporting patient tests results:

  Accuracy

  Precision

  Reference Interval

  Reportable Range

Validation

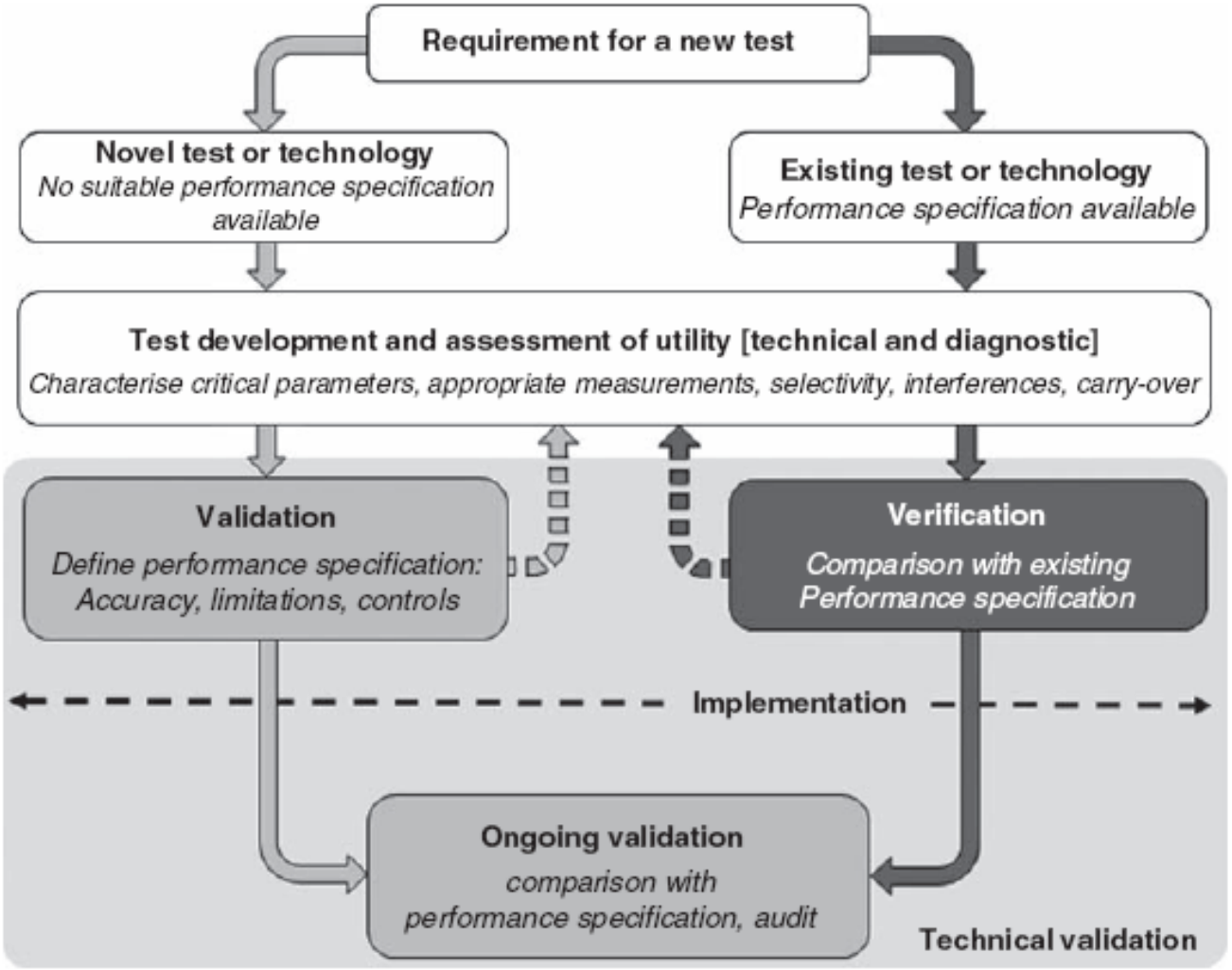
- Confirmation though the provision of objective evidence that requirements for a specific intended use or application have been fulfilled (ISO 9000:2005)
- Action (or process) of proving that a procedure, process, system, equipment, or method used works as expected and achieves the intended results (WHO-BS/95.1793)
- In USA, used for LDTs or modifications to FDA-cleared assay
- In Europe, used for novel test or technology

Performance Specifications

- **CLIA Section 493.1253(b)(2) states**

  Each laboratory that modifies an FDA-cleared or approved test system, or that introduces a test system not subject to FDA clearance or approval (including methods developed in-house … or standard methods such as textbook procedures or Gram stains or KOH Preps) must establish (validate) the following performance characteristics before reporting patient tests results:

  - Accuracy
  - Precision
  - Reportable Range
  - Reference Interval
  - Analytical Sensitivity
  - Analytical Specificity
  - Any other characteristic necessary to perform the test (Carryover, Dilutions, Calculation or QC frequency)

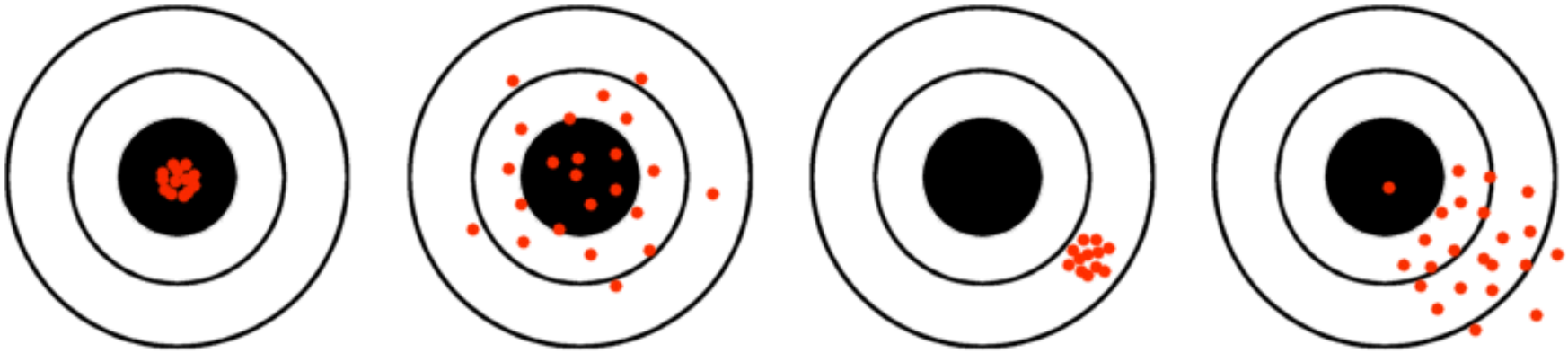


Mattocks et al. 2010. Eur J Hum Genet 18:1276-1288.

The words can be confusing

Accuracy

- Trueness of measurement
- Accuracy = true result / (true result + false result)



Accurate Precise

Accurate Not Precise

Not Accurate Precise

Not Accurate Not Precise

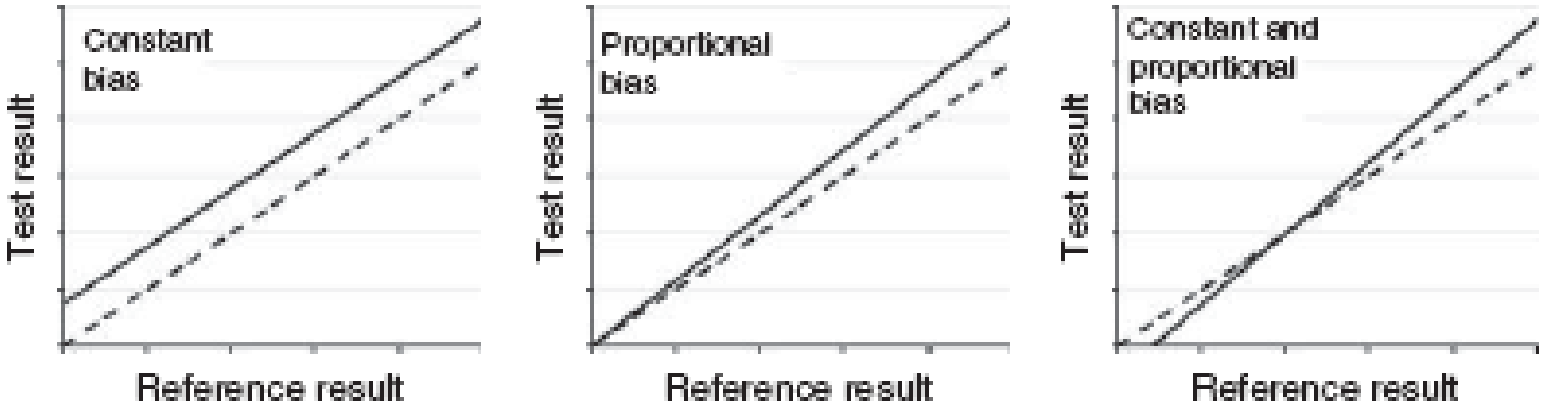
http://www.med4you.at/laborbefunde/allgemeines/

Precision

- Repeatability and reproducibility of a test result
  - within-technologist
  - between-technologist
  - within-run
  - and between-run

Bias

- (of measurement) estimate of a systematic measurement error



Mattocks et al. 2010. Eur J Hum Genet 18:1276-1288.

Analytic sensitivity

- The ability of a test to detect a mutation when that mutation is present

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive + false negative}}$$

It is important to document confidence intervals

- Also, some refer to the lower limit of detection (LoD) for the analyte of interest (i.e., the lowest concentration of analyte that the assay can detect). It is preferable to specify LoD, if important for assay.

Analytic specificity

- The ability of a test to give a normal (negative) result in specimens without the mutation being tested

$$\text{Specificity} = \frac{\text{True negative}}{\text{True negative} + \text{false positive}}$$

It is important to document confidence intervals

- Also, some refer to the ability of a test to detect the analyte without cross-reacting with other substances. It is preferable to specify cross-reactivity, if important for assay.

Example 1

TO ESTIMATE CONFIDENCE INTERVALS FOR SENSITIVITY, SPECIFICITY AND TWO-LEVEL LIKELIHOOD RATIOS:

Enter the data into this table:

	Reference standard is positive	Reference standard is negative
Test is positive	25	0
Test is negative	0	75

Enter the required confidence interval (eg, 95%) here: 95

RESULT:

Sensitivity: 100% CI: 0.8668 to 1

Specificity: 100% CI: 0.9513 to 1

*www.pedro.org.au/wp-content/uploads/CI**calculator**.xls*

Example 2

TO ESTIMATE CONFIDENCE INTERVALS FOR SENSITIVITY, SPECIFICITY AND TWO-LEVEL LIKELIHOOD RATIOS:

Enter the data into this table:

	Reference standard is positive	Reference standard is negative
Test is positive	5	0
Test is negative	0	10

Enter the required confidence interval (eg, 95%) here: 95

RESULT:

Sensitivity: 100% CI: 0.5655 to 1

Specificity: 100% CI: 0.7225 to 1

*www.pedro.org.au/wp-content/uploads/CI**calculator**.xls*

How to *verify* an Unmodified IVD

- Perform the assay according to the manufacturer's specifications
- Using positive and negative samples, verify that the assay can detect the analytes (mutations) as claimed (analytic specificity and analytical sensitivity)
- Perform inter- and intra-assay runs (precision)
- Run blinded panel from reference method, if available (accuracy)

How to *validate* a LDT

- Develop a procedure that is fit for purpose
- Using positive and negative samples, verify that the assay can detect the analytes (mutations) as claimed (analytic specificity and analytical sensitivity)
- Perform inter- and intra-assay runs (precision)
- Run blinded panel from reference method (accuracy)

Conclusions

- It is important to understand the regulations of clinical testing when performing clinical laboratory services