Disclaimer

• "The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry (CDC/ATSDR)"
Learning Objectives

• Recognize the purposes and process of regulations
• Identify key regulatory roles (CMS, FDA, CDC, and professional organizations)
• Recognize penalties for noncompliance
• Describe responsibilities of laboratory personnel
Regulations

- Provide rules
- Establish consistency
- Provide basis for evaluation
- Identify the problem to be addressed
- Incorporate expertise, guidance, recommendations, good laboratory practices
Regulatory Process

• Identify problem
• Develop policy alternatives
• Select policy
• Implement
• Evaluate
• Regulations translate general laws into specific rules that make a policy a reality.
Federal regulatory oversight of clinical laboratories = CLIA

- Centers for Medicaid and Medicare Services (CMS)
- Centers for Disease Control and Prevention (CDC)
- Food and Drug Administration (FDA)

CLIA 88

1990-95 proposed rules developed and implemented

http://wwwn.cdc.gov/clia/Regulatory/Chronology.aspx = CLIA History
NOTE: Over 50 FR Notices/regulations published related to CLIA
Local regulations

• State Laboratory Licensure
  – New York State Dept. of Health
  – Washington State
  – California
  – Florida

• Local
  – IRB
  – Informed consent
  – Environmental protection
CLIA:

- Issues laboratory certificates
- Collects user fees
- Conducts inspections and enforces regulatory compliance
- Approves private accreditation organizations and approves state exemptions (NY & WA)
- Monitors laboratory performance on Proficiency Testing (PT) and approves PT programs
- Publishes CLIA rules and regulations
CLIA:

- Provides analysis, research, and technical assistance
- Develops technical standards and laboratory practice guidelines
- Conducts laboratory quality improvement studies
- Monitors proficiency testing practices
- Develops and distributes professional information and educational resources
- Manages the Clinical Laboratory Improvement Advisory Committee (CLIAC)
CLIA:

- Categorizes tests based on complexity
- Reviews requests for Waiver by Application
- Develops rules/guidance for CLIA complexity categorization
CLIA certification

- All laboratory testing performed (in the US) on human clinical specimens intended for diagnostic or therapeutic purposes (not research, not forensics, not breathalyzer)
- CLIA program regulates laboratories that perform testing on patient specimens to ensure accurate and reliable test results
CLIA certification

- Medicare approved billing requires a CLIA certificate
- Failure to comply may incur penalties or sanctions*
- Violations result in barring from participation in Medicare business (one lab may affect others in institution)

*regarding billing practices (Anti-Kickback Statute, Stark Self-Referral Prohibitions, Beneficiary Inducement Statute)
CLIA Certification

• All laboratories (that meet the definition) must be certified
• Certification structured by test characteristics
  – “Waived Testing” or “Non-Waived Testing”
  – Provider Performed Microscopy
  – “Moderate Complexity” or “High Complexity”
• Medicare billing requires CLIA number for approval
Certification Process

• Current certificate requires
  – Application, description of services (type, volume)
  – Payment of a biennial fee – by # tests/year
  – On-site inspection*, verifying compliance with regulations
    • Certificate type testing
    • Personnel qualifications
    • Successful proficiency testing performance
    • Quality control, maintenance, testing records

*for certificate of compliance or certificate of accreditation labs, not waived labs or PPM
CLIA ’88: 42 CFR Part 493 – Laboratory Requirements

- Subpart E – Accreditation by a Private Non Profit
  - Accreditation organization or exemption under an approved State laboratory program
- Subpart H & I – Proficiency Testing
- Subpart K – Quality Systems for Nonwaived Testing
- Subpart M – Personnel for Nonwaived Testing
- Subpart Q – Inspection
- Subpart R – Enforcement Procedures
Molecular testing – what’s different?

• No specialty under CLIA 88 – general requirements
  – Clinical cytogenetics – 2003; karyotyping
  – No molecular genetics specialty
• Nonwaived, High complexity testing, LDTs
• Trained personnel - performance and interpretation
• Results interpretation and reporting
• Quality control and specific reference materials
• Proficiency testing – interlaboratory comparison or alternative performance assessment
• So how does a lab bridge the gap from general CLIA requirements to the specific quality practices necessary for accurate molecular testing?
Quality requirements

- Total testing process
- Personnel - qualifications & responsibilities
- Proficiency testing
- Analytical validation
- Quality controls
- Consent and confidentiality
- Test results reporting
- Records management
Example: Assay Verification and Validation

• FDA-cleared, -approved and CE-IVD labeled
  – Per manufacturer’s instructions
  – Lab must verify and document demonstration of performance specifications
  – Same sample matrix
  – Same acceptable sample types
  – Does it work in your lab the way the manufacturer claims it should?
Example: Assay Validation

• LDTs, *modified* FDA-cleared, -approved and *modified* CE-IVD labeled
  – Lab must perform a full assay validation
  – Performance specifications (precision, accuracy, reportable range, analytical sensitivity, analytical specificity, reference intervals, limit of detection, and linearity for quantitative assays)
  – Comparison to a reference method to assess trueness
  – Interfering substances, environmental conditions
Assay Verification and Validation

• Verification and validation must assess the total testing process
  – Reagents
  – Instruments
  – Software
  – For all types of samples that will be tested
Assay Verification and Validation

• Quantitative testing
  – Precision requires range of concentrations of positive samples
  – within-run repeatability
  – between-run reproducibility between operators, between labs
  – Negative controls

Linearity

• Measuring ranges – test system’s ability to measure results in direct proportion to concentration of measurand in the sample

• Limit of detection – lowest amount of analyte that can be distinguished from background signal of a negative control

• Limits of quantification - lower and upper limits of measurement linearity
FAQ

• How many samples must be used for verification and validation?
  – Type of assay
  – Complexity of the assay
  – Prevalence of the target in the population
  – Data analysis required
  – Established accuracy of the reference method


Clinical validation

- What is the diagnostic question?
- Do the assay results correlate to disease or condition?
- Does the assay support or surpass other diagnostic methods?
- Clinical utility – Intended use; beyond CLIA
  - What is the significance of the assay results for medical decision-making?
  - How will the care of the patient or public be affected by this test result?
Factors affecting Clinical utility

- Population dynamics – eg, Microbial seasonal prevalence
- Genetic variation
- Replication rates/status
- Host factors – disease stage, concurrent conditions
- Specimen type
- Status of nucleic acid – cell-free, encapsulated, modified, plasmid, etc.
Resources

• Guidelines, recommendations or practice standards
  – Consensus formulated by expert workgroups
  – Professional organizations or societies
  – Evidence-based practices

Recommendations and Reports

- MMWR
- CDC
- CAP

American College of Medical Genetics

Standards and Guidelines for Clinical Genetics Laboratories

Clinical and Laboratory Standards Institute

Evidence to Practice: Evaluation of Genomic Applications in Practice and Prevention
Recommendations and Reports

Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
Good Laboratory Practices
for Molecular Genetics Testing

Start the course

QUALITY LABORATORIES, HEALTHIER PEOPLE
CLSI. *Quantitative Molecular Methods for Infectious Diseases; Approved guideline*. CLSI document **MM06-A2** (ISBN 1-56238-736-7). 2010


SUMMARY OF CHANGES
INTRODUCTION
APPLICABILITY
QUALITY MANAGEMENT AND QUALITY CONTROL
    GENERAL ISSUES
    PROCEDURE MANUAL
    ASSAY VALIDATION
    COLLECTION, TRANSPORT, PREPARATION, AND STORAGE OF SPECIMENS
    QUANTITATIVE ASSAYS, CALIBRATION AND STANDARDS
    REAGENTS
    CONTROLS
METHODS AND INSTRUMENT SYSTEMS
    Restriction Endonucleases
    Sanger Sequencing and Pyrosequencing
    Next Generation Sequencing
    Next Generation Sequencing of Maternal Plasma to Identify Fetal Aneuploidy
    Analytical Wet Bench Process for NGS
    Bioinformatics Pipeline for NGS
    Electrophoresis
    Target Amplification/Polymerase Chain Reaction (PCR)
    Arrays
    Parentage and Forensic Identity Testing
    Fluorescence and Non-Fluorescence In Situ Hybridization (FISH, ISH)
    Brightfield In Situ Hybridization
    Spectrophotometers
    Signal Detection Instruments
    Film Processing/Photographic Equipment
    Instruments and Equipment
POST ANALYSIS
    Results Reporting
    Records
PERSONNEL
LABORATORY SAFETY
RADIATION SAFETY
Regulatory compliance

- Certificate of accreditation - Deemed authority organizations
  - CAP
  - AABB
  - TJC (formerly JCAHO)
  - ASHI
  - COLA
  - AOA
  - States – NY, WA
  - Veteran’s Administration – has its own CLIA-like program
FDA Oversight

- FDA regulates manufacturers and devices under the Federal Food, Drug, and Cosmetic Act (FFDCA) to ensure that devices, including those intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, are reasonably safe and effective.
In vitro devices

• IVD are a subset of medical devices which are “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae”
Laboratory assay regulations

• FDA/CDRH/OIVD reviews laboratory testing devices and components based on
  – Complexity, safety, and efficacy
  – Intended use
  – Quality of design and manufacturing process

• Defines 3 classes of devices based on risk to patient
  – Class I - Low
  – Class II - Moderate
  – Class III - High
CLIA Test Categories

• Waived tests
  – “tests so simple and accurate that error is unlikely, or pose no reasonable risk of harm”
  – no pre-treatment of the specimen, no calculations, no interpretation necessary
  – untrained staff may perform by following manufacturer’s instructions
  – Proficiency testing is not required (but may improve performance)

• Non-waived
  – Moderate complexity
  – High complexity
CLIA Categorization

• FDA categorizes complexity of diagnostic tests by reviewing package insert instructions during premarket approval

• Seven criteria are evaluated & score 1-3 is assigned to each

• Score of 1 is lowest level of complexity, 3 is highest level

• Summarize scores; 12 or less are moderate complexity, >12 are high-complexity
Categorization Criteria for Test Complexity

1. Knowledge
2. Training and experience
3. Reagents and materials preparation
4. Characteristics of operational steps
5. Calibration, QC, and Proficiency testing
6. Test system troubleshooting and equipment maintenance
7. Interpretation and judgment

http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm393229.htm
Scoring criteria for complexity

• Are minimal (1) or specialized (3)
  – Knowledge & training required to perform testing?
  – Interpretation and judgment of results required?

• Are general (1) or specialized (3) Reagents required?

• Premeasured (1) or manual (3) handling?

• Automated (1) or closely monitored (3) operational steps?

• QC & External PT materials available and Stable (1) or Labile (3)?

• Automated troubleshooting (1) or decisions and interventions required (3)?
FDA’s CLIA Database of Test Categorization

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/Search.cfm?sAN=0
IVD Risk-based classification

- **Class I = 50% of IVDs; lactic acid, sed. rate**
  - Lower risk, exempt from pre-market submission, general assay controls; labeling requirements; report ADEs and recalls

- **Class II = 42% of IVDs; AST, TSH**
  - Moderate risk, 510(k) premarket clearance, general and special controls, safety effectiveness, labeling, post-market reporting

- **Class III = 8% of IVDs; HPV, total PSA, HBV**
  - Higher risk of serious injury, Premarket approval (PMA) req’d; FDA inspects production facility, clinical data, biomarker must correlate with specific clinical indications (existing or prospective); post-market reporting, monitoring AEs, recalls
IVD review and approval

- Registration and listing
- GMP and QSR
- Labelling & use as directed
- Records and reports to FDA
- Recall notification
- Other = Pre-IDE, IDE*, EUA*

*IDE=Investigational device exemption;
EUA= Emergency use authorization
FDA Device Classification

- FDA has purview to regulate but has exercised enforcement discretion
- While clinical labs do not consider themselves to be device manufacturers, this term has relevance to Laboratory Developed Tests (LDTs)
LDT

• Laboratory developed test – traditionally designed in a single lab to test patients at the same facility

• Most of the focus for LDT regulation has been on molecular pathology testing for genetic disorders or cancer

• Also includes mass spectrometry, flow cytometry, biochemical testing, and many other assays

• Lab director has responsibility for performance characteristics of LDT
LDT changes

- LDTs have become more complex in design and data interpretation
- Some assays use proprietary data analysis algorithms to report risk factors
- Difficult to evaluate LDT validation documents during lab inspection
- Commercial biotech CLIA labs – not at clinical care site
- Direct-to-Consumer testing, high risk clinical claims
LDT regulation

• Congress wants increased oversight of
  – Diagnostic testing
  – Personalized medicine tests/claims; companion diagnostics for drug response markers
  – Direct-to-Consumer testing (DTC)
• FDA has issued
  – Guidances
    • ASR, IVDMIA, RUO, IUO, companion diagnostics
  – Warning letters
    • DTC genetic testing
• FDA drafted LDT oversight policy
  – guidance to provide general oversight of LDTs
  – standards for FDA notification and medical device reporting
  – quality system requirements
• Publication for public comment - date unknown
CLIA and LDTs

• CLIA ‘88 – Focuses on quality of labs not test manufacture; compliments FDA IVD process
• LDTs are high-complexity tests
• CLIA does not require clinical validation but FDA does, including software design controls
• CLIA does not provide for
  – premarket review of data and testing claims
  – post-market reporting or recalls
• HR 3207 in 2011 by Rep. Michael Burgess
How to Influence a Regulation

• Provide comments to regulators during proposed rule comment period
• Contact legislators
• Petition government
• Provide input to government advisory panels
• File lawsuit
• Contact media
• Stories that raise issues/interest (eg, human interest, studies, etc)
• Interest group involvement
• AMA and other physician societies
• Medical Device Manufacturers
• Clinical Laboratories
• Consumer groups
Conclusions

• Regulations are subject to influence
• Government agencies serve as ‘honest broker’ among competing interests and objectives
• Failure to comply with regulations can result in penalties