

The Do's And Don'ts of Validating Laboratory Developed Tests

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What is an LDT?

Laboratory developed tests (LDTs) are *in vitro* diagnostic tests that are developed, validated and used for in-house clinical diagnostic purposes only by the laboratory that developed them.

...AKA homebrew tests, laboratory developed assays (LDA's), proprietary tests

LDT's-Opportunities

- Market and demand exists
- LDTs can be developed without FDA review and clearance
- Faster path to market-responsive to emerging diseases and conditions
- Most genetic tests are LDT's-not enough prevalence for large-scale studies

LDT's-Disadvantages

- Requires bridging the gap between R&D and clinical application
- Can require substantial investment
- Uncertainty in regulatory and accreditation requirements
- Laboratory assumes responsibility and risk for assay performance

FDA-Then and Now

FDA's historically exercised "enforcement discretion" for LDT's because they:

- Were relatively simple, well-understood tests with low test volumes
- Were for rare diseases or unmet needs,
- Were intended to be used by physicians and pathologists in a single institution where they were actively involved in patient care

FDA-Then and Now

"Enforcement discretion" reconsidered:

- Expanding LDT marketplace, increased distance from test developer to patient
- Government and media scrutiny
- High-risk, high complexity tests, complex interpretation
- Tests aggressively advertised, developed by laboratories set up specifically for LDTs, marketed directly to consumers (DTC)

Types of LDT's-FDA Actions

Homebrew assays: 2003 guidance: assays that incorporate "general purpose reagents and general purpose instruments"

IVDMIA's: 2006 and 2007 guidance: multiple values, non-transparent result (score, index), require FDA clearance

ASRs: 2007 guidance: single target reagents; exempt from PMA if used with specific labeling and report disclaimer requirements; certain uses (combining, promoting) not allowed

Types of LDT's-FDA Actions

RUO/IUO: draft guidance April 2011: manufacturer cannot market for diagnostic use or assist in validation; must halt sales if it discovers assays are being used for diagnostic purposes, or submit assay for FDA review

DTC Genomics: from "watchful vigilance" in 2009 to enforcement letters in 2010, GAO reports "Misleading Test Results, Deceptive Marketing and Questionable Practices". Public hearings in March 2011, FDA forming a personalized medicine program

Types of LDT's-FDA Actions

Companion Diagnostics: Draft guidance July 2011: tests used to direct or monitor therapies should be cleared contemporaneously with the target drug or IVD

The FDA held two days of public meetings in July of 2010 to get feedback from regulators, industry and clinical practitioners on models for LDT oversight.....

Possibilities for LDT's

- Full FDA review of LDT's as IVD's (by OIVD or a new branch)
- Central registration or listing of LDT's
- CLIA approval of LDT's , through evaluation of developing laboratory
- Hybrid FDA/CLIA approach, based on risk stratification model

Other Oversight Models

- CLIA: Surveyors look for documentation of validation for LDT's, LDT's =high complexity
- CAP: Proposes stratified requirements for validation based on risk, RUO's allowed only after laboratory documents no comparable ASR or FDA cleared assay exists
- Joint Commission: Follows CLIA model, supports FDA review and approval for high-risk assays
- NYS: Must review and approve any LDT, RUO, IUO or modified FDA-cleared assay

Validating LDT's-Do's and Don'ts

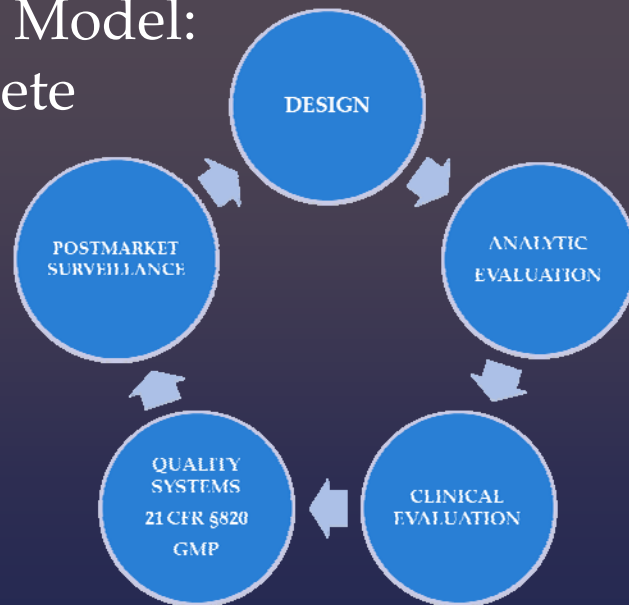
Think...what makes an LDT different from an FDA-cleared IVD assay?

Examine the FDA's IVD clearance process

Avoid the land mines.....

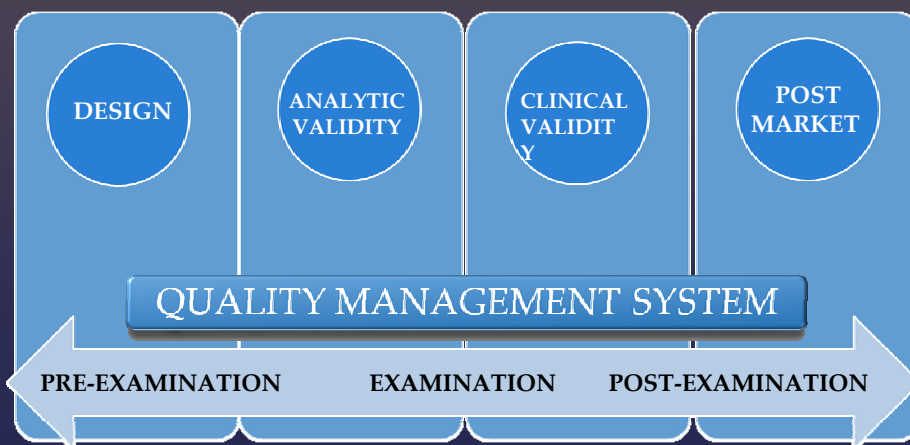


The FDA Model: A Complete Product Lifecycle



LDT Development

Apply Quality Management Systems
(QMS) Principles to FDA Validation Model



LDT Development

FDA requires assays to be developed in a quality systems environment

- Quality Systems Regulations (QSR) at 21 CFR §820 (Good Manufacturing Practices or GMP)
- FDA Guidance Document: Medical Device Quality Systems Manual; A Small Entity Compliance Guide-First Edition

Clinical laboratories are already subject to Quality Management....

FDA QSR (GMP) Model

The FDA Medical Device Quality Systems Manual:

Design Controls	Labeling
Process Validation	Product Evaluation
Personnel	Packaging
Buildings and Environment	Storage, Distribution, and Installation
Equipment and Calibration	Complaints
Device Master Record	Servicing
Document and Change Control	Quality Systems Audits
Purchasing and Acceptance Activities	Factory Inspections

LDT Development Lifecycle

PHASE ONE: DESIGN: DO establish master policies and procedures for method validation- a *validation protocol*:

- Assay development-who, what, where and how
- Pre-defined expectations for assay performance
- Algorithms and statistics for assay validation
- Use of reference assays and/or clinical findings
- Subject and IRB compliance, if applicable
- On-going validation, including QC, external assessments, and quality assurance

LDT Development Lifecycle

PHASE ONE: DESIGN. DO consider the following :

- Intended Use: Define the analyte or target, purpose (diagnosis, screening) and population
- Qualitative or quantitative assay
- Sample Types: Serum, CSF, urine , other (validation must include all sample types)
- Variables to be considered (temperature, analyte and specimen stability, interfering substances)
- Limitations, safety and effectiveness

LDT Development Lifecycle

PHASE ONE: DESIGN: DO develop a customized validation plan for each LDT, to include

- Authorities, roles ,responsibilities for personnel
- Necessary equipment, supplies and budget
- Define what will be measured
- Design how will it be measured
- Determine how many will be measured (statistical significance)
- Define acceptance/rejection criteria and how discrepant results will be handled
- Define required documentation and a system of document control

LDT Development Lifecycle

PHASE ONE: DESIGN

DO use tried-and-true methods to evaluate performance characteristics: two options:

- Comparison of results between new method and “reference” or gold-standard method
- Evaluate results using new method on certified reference materials (recovery)

Guidance on validation available from the FDA; user-friendly guides being developed by CLSI, with review by the FDA, expected in 2012

LDT Development Lifecycle

PHASE TWO: ANALYTIC EVALUATION

Does the assay detect what it is designed to detect in an accurate and reproducible manner?

Performance characteristics include:

- Accuracy aka "Trueness"
- Precision (reproducibility)
- Sensitivity (limits of detection/quantitation)
- Specificity (cross-reactivity or interferences)
- Linearity or analytic measurement range

LDT Development Lifecycle

PHASE TWO: ANALYTIC EVALUATION

DO use FDA recognized standards for analytic validation e.g., CLSI (also accepted by CAP and JC)

EP05 – Evaluation of Precision

EP06 – Evaluation of Linearity

EP09 – Evaluation of Bias and Comparability Using Pt. Samples

EP10 – Preliminary Evaluation (Bias, Carryover, Drift, Linearity)

EP12 – Evaluation of Qualitative Tests

EP17 – Limits of Detection and Limits of Quantitation

C28 – Defining, Establishing and Verifying Reference Intervals

GP10 – Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots.

DO
organize
your
method
validation
data



LDT Development Lifecycle

PHASE TWO: ANALYTIC EVALUATION: DO
conduct statistical analysis using established methods:

- StatisPro: a Windows software based on CLSI EP validation guidelines –assists in study design , data gathering, aggregation, and review for all required parameters
- FDA: FDA Laboratory Procedure Manual:
<http://www.fda.gov/ScienceResearch/FieldScience/LaboratoryManual/default.htm>
- NIH, National Genome Research Institute

LDT Development Lifecycle

PHASE TWO: (POST) ANALYTIC EVALUATION

DO design a customized quality control strategy that takes into account performance, risks and limitations of your assay.

- EP23-A, Laboratory Quality Control Based on Risk Management: New protocol from CLSI that addresses factors to be considered in QC design
- Discipline –specific guidance: NIH, ASM, AACC

DO establish clinical validity and clinical utility



"What's the opposite of 'Eureka!'?"

LDT Development Lifecycle

PHASE THREE: CLINICAL EVALUATION.

Clinical Validity: Does the result correlate with clinical condition or patient outcomes?

- Clinical sensitivity: Pos. result = condition
- Clinical specificity: Neg. result = no condition
- Positive and negative predictive values (sensitivity and specificity vs. prevalence)
- Clinical reference range
- Panic or alert values

LDT Development Lifecycle

PHASE THREE: CLINICAL EVALUATION

Clinical Validity: DO's

- DO use characterized specimens for assay validation (known clinical condition)
- DO document and adhere to clinical indications for testing (for LDT's, the lab defines intended use)
- DO provide robust test descriptions and interpretive information on patient reports
- DO reference reputable and current peer-reviewed literature

LDT Development Lifecycle

PHASE THREE: CLINICAL EVALUATION

Clinical Utility: FDA requirements at 21CFR 860

- Clinical effectiveness : reasonable assurance that the use of the device will provide clinically significant results
- Test association with improved clinical outcomes or quality of life and its usefulness to patient and clinician decision-making
- Safety: reasonable assurance that the probable benefits outweigh any risks

LDT Development Lifecycle

PHASE THREE: CLINICAL EVALUATION.

Clinical Utility

- Most difficult parameter to measure/predict; requires analysis of multiple variables and correlation with clinical outcomes
- Developing laboratory not required to establish clinical utility (per CLIA) but due diligence should be demonstrated
- DO research literature, survey end-users, track clinical outcomes, design and participate in long-range studies including economic utility

LDT Development Lifecycle

PHASE FOUR: POST-MARKET SURVEILLANCE

Does the assay continue to behave as expected?

- FDA conducts post-market surveillance of cleared IVD's through its Medwatch system
- Tracks adverse events and ensures manufacturer responds
- Actions can include relabeling, recalls

LDT Development Lifecycle

PHASE FOUR: POST-MARKET SURVEILLANCE

Does the assay continue to behave as expected?

Laboratories have options to track LDT performance "post-market:

- Quality Control
- External Assessment
- Non-Conforming Events
- Complaints
- Clinical Correlation

LDT Development Lifecycle

PHASE FOUR: POST-MARKET SURVEILLANCE

Does the assay continue to behave as expected?

- DO document non-conforming events and complaints; take corrective action and redesign as appropriate (reactive)
- DO use quality control, external assessments and quality assurance monitors (proactive)
- DO collect data to demonstrate clinical validity and clinical and economic utility (forward-thinking)

Other LDT DO's

DO subject validation records to document control

- Prepare summary report of validation (use assay validation plan as a template, retain and reference original data, e.g., worksheets, instrument printouts)
- Have protocol for review and approval of report by designated laboratory leadership
- Document any revalidation and verification to support modification of the assay

Other LDT DO's

DO retain samples used for validation, if possible

DO document any algorithms , statistical or automated calculations to validation

DO comply with regulatory and accreditation requirement as for any other laboratory test: SOPs; training and competence , external assessments or other measures of accuracy (internal blinded specimens, duplicate analysis by different systems/staff)

LDT DON'Ts

DON'T develop an LDT if a generally accepted FDA assay already exists, unless you can document why your test is better. Think twice about RUOs/IUOS

DON'T allow validation by the developing entity e.g., R&D department-maintain objective validation protocols by a separate team and standardize them across all sections of the lab

DON'T be driven by market forces-use good science, transparency and realistic claims

Don't get your LDT in the news

The New York Times

The Dark Report



LDT's in the News

GENOME WEB DAILY NEWS
Responding to FDA, LabCorp Discontinues Offering OvaSure Test

Concerns from clinicians and professional organizations that specificity and sensitivity claims were not supported by validation data; assay predictive value overstated, intended use not clear

FDA issues a warning letter; takes the position that the assay was developed by Yale, not LabCorp, so it is not an LDT, it is an IVDMA and subject to FDA oversight

LDT's in the News

What happened?

“Immense need” for test to detect ovarian cancer; competitive market pressure

Test released to market based on preliminary validation studies



Nature; March 2011

LDT's in the News

Do's

DO make sure the assay is developed and fully validated in your own laboratory (NYS considers an off-site R&D subsidiary acceptable if it is under common ownership and assay performance is verified at the site where the assay will be performed)

DO scrutinize data to ensure it supports the assay intended use and performance claims

LDT's in the News

DARK DAILY" <DARK_DAILY@mail.vresp.com>
01/08/2009 12:10 AM

News Flash! New York Times Hits Quest Diagnostics for Erroneous Vitamin D Results!

January 2008-Quest sends out thousands of letters noticing clinicians that Vitamin D results may be inaccurate, retesting advised.

LDT's in the News

What happened?

Vitamin D assay is a home-brew tandem mass – spec assay; it measures both D2 and D3 components of Vitamin D, results did not always correlate against the the more widely used, FDA approved RIA assay

There were inconsistencies in preparation of calibrators and problems with the manual integration of peaks

LDT's in the News

Do's

DO correlate any LDT's using a new (especially more sensitive and specific) methodology against existing assays, recalculate reference ranges and re-educate end-users

DO incorporate peer-graded external assessment specimens to ensure the initial and ongoing validation of any LDT assay

DO monitor assay calibration and performance

Questions?

Thank you!

More Questions?

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www.wadsworth.org/clep/methodapproval.htm