Current Topics in NYS Clinical Laboratory Oversight

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NEW YORK STATE OF OPPORTUNITY. Department of Health | Wadsworth Center

Clinical Laboratory Reference System (CLRS)

(i) to monitor, improve, and broaden the clinical capabilities of participating laboratories and blood banks

(ii) to provide guidelines, quality control standards and procedures to be used by permit-holding clinical facilities, and

(iii) to provide continuing education opportunities for technical personnel involved in the operation of clinical laboratories through training and remediation programs.

CLRS granted exempt status by the federal Centers for Medicare and Medicaid Services (CMS) – at least as stringent as CLIA

https://www.wadsworth.org/regulatory/clep

Clinical Laboratory Evaluation Program (CLEP)

Administrative arm of CLRS

- On-site survey
- Proficiency testing (PT)
- Certificate of Qualification (CQ)
- Laboratory test review

Laboratory Tests

1 – A laboratory must hold a NYS permit and the appropriate category to perform clinical testing on NYS specimens, including but not limited to:

- Diagnosis
- Prognosis
- Screening
- Treatment or therapy
- Clinical trials, if the results are reported and used for clinical decision making
- Research testing, if the result is used in patient management OR if the laboratory is “ethically compelled to report” the result

2 – A laboratory must verify or establish performance specifications for any test system before testing patients.

Laboratory Tests

- Waived test
  - waived by FDA using CLIA criteria
  - may use in comprehensive clinical lab, under control of comprehensive lab, or point-of-care
- IVD approved, cleared, or exempted by FDA
  - use only in or under control of comprehensive clinical lab
- Standard method
  - established record of reliability and clinical validity
  - standardized protocol that is universally applied
  - use only in or under control of comprehensive clinical lab

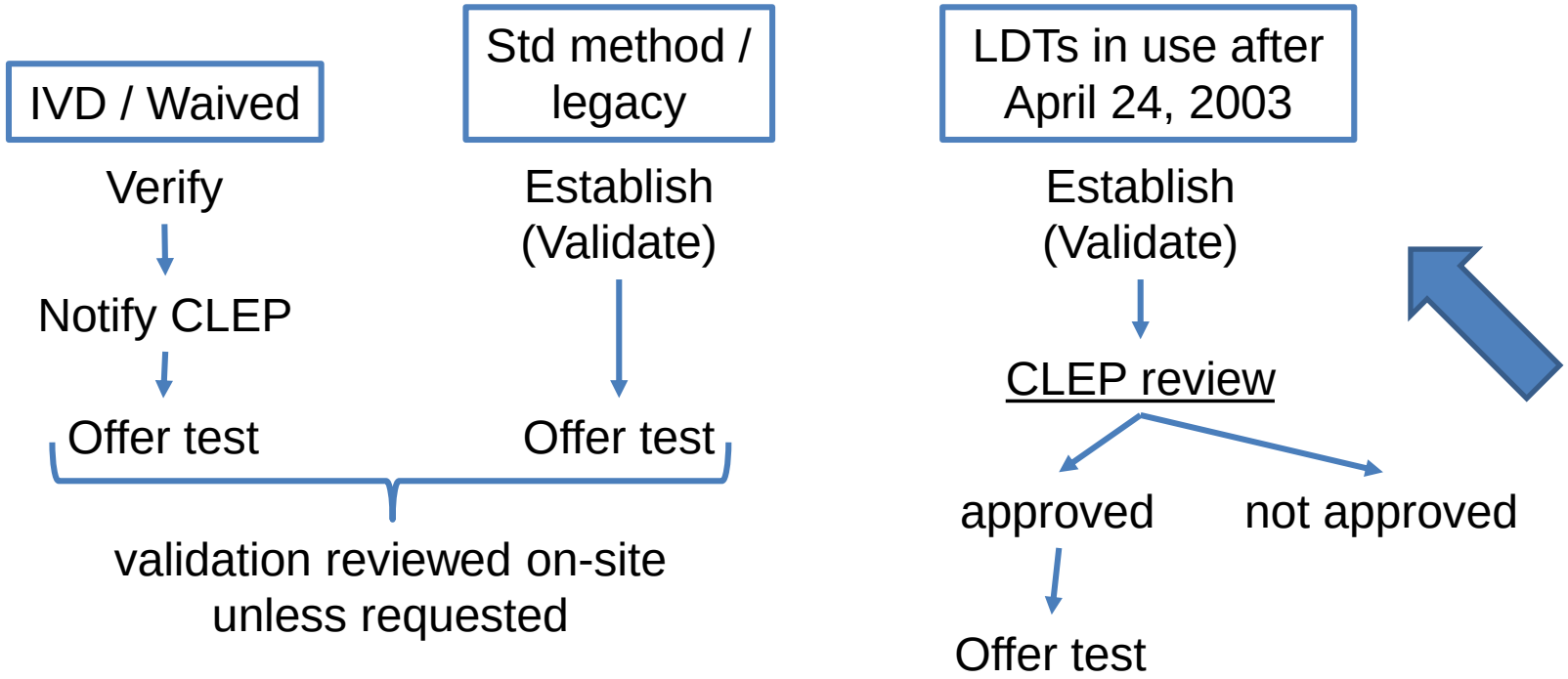
Laboratory Tests

- Laboratory developed tests (LDTs)
  - NOT FDA approved/cleared/waived – including RUO/IUO
  - offered ONLY by lab that developed the test
  - use only in or under control of comprehensive clinical lab

- Legacy assay – documented use by laboratory before April 24, 2003

https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval

Laboratory Tests – Adding a Test



Adding a Non-Legacy LDT

Validation

- NYS expectations - how to “establish performance specifications”

Validation package – what to submit

- Risk Assessment
- Validation checklist
- Documents on validation checklist

Review process and criteria

NYS expectations - how to “establish performance specifications”

Analytical Validity

- Analyte and specimen matrix stability
- Specimen transport conditions
- Storage time and temperature
- Accuracy
- Precision (reproducibility, both within (intra-) and between (inter-)runs)
- Reportable range, where applicable (calibration of quantitative tests).
- Analytical sensitivity (limit of detection and/or quantitation)
- Analytical specificity, address potential cross-reactivity (for infectious disease testing) and any interferences (endogenous and exogenous)

NYS expectations - how to “establish performance specifications”

Clinical validity (sensitivity and specificity)

- Describe the protocols used to determine the clinical status of test subjects
- Describe the procedure used to blind the clinical status of specimens during testing
- Describe the procedures used to resolve discrepant or equivocal test results

What to submit - Risk Assessment

Summary (not more than 500 words) :

- Methodology and technology
- Intended use, including target population if applicable
- Specimen type(s)

What to submit - Risk Assessment

1 - Is test a modification of a previously approved test (NYS or FDA)?

2 – Describe modification(s) – specimen type, reagents, algorithm, intended use, instrumentation, etc

3a – Does the lab have previously-approved tests using same method?

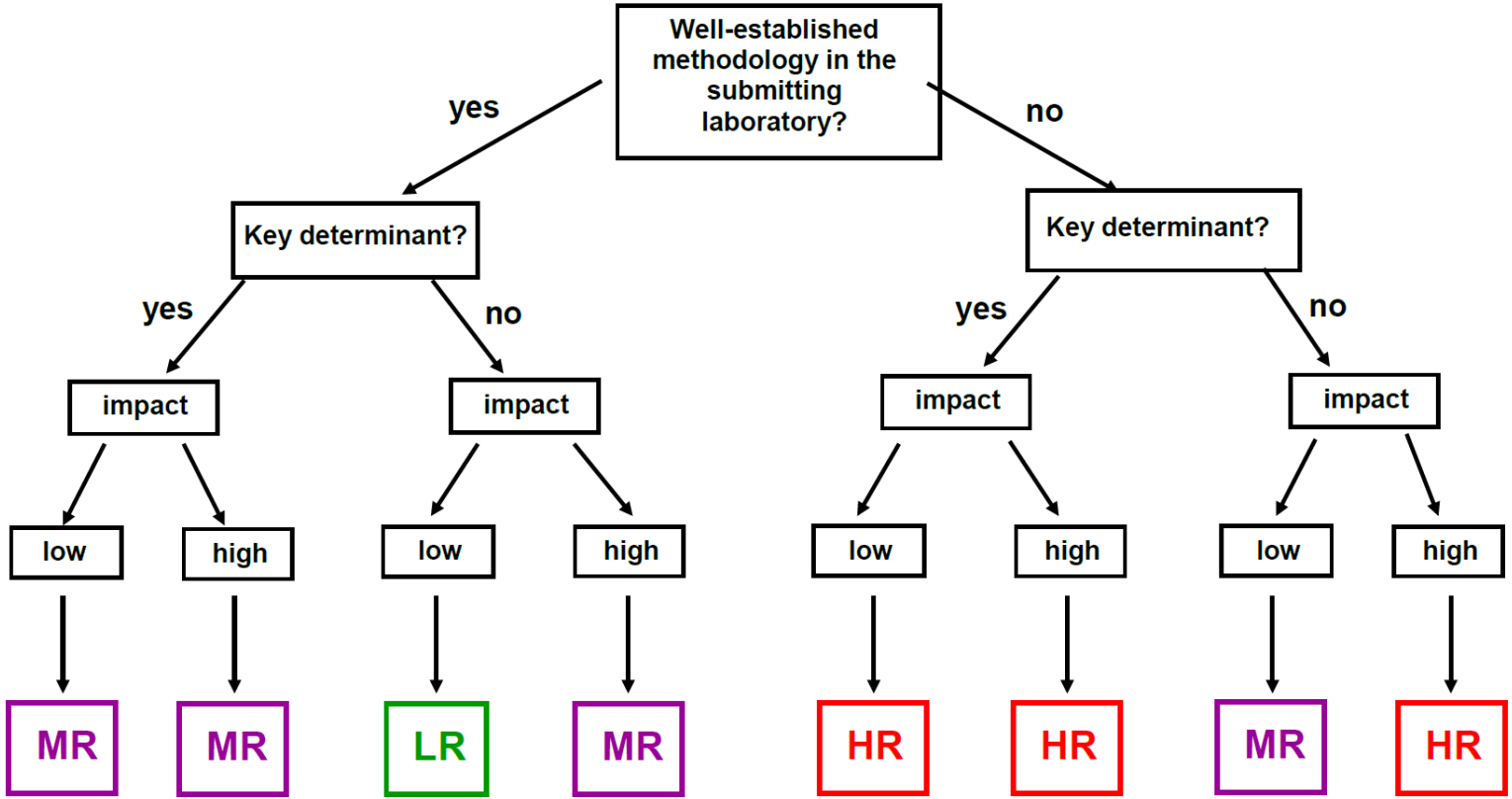
3b – Is the method well-established in your lab and generally accepted in the field?

4 – Evidence for intended use?

5 – Key determinant for diagnosis, pre-disposition or likelihood, treatment options, or prognosis?

6 – Impact of incorrect result?

NYSDOH Policy for Risk-based Evaluation of Laboratory Developed Tests (LDT)



What to submit - Validation Package

Standard

Validation checklist

Test description:
Method
Clinical purpose
Analytes
Specimen type(s)

Procedures
Validation data
Requisition
Reports
Informed consent
References

Under Exemption from Comprehensive Submission

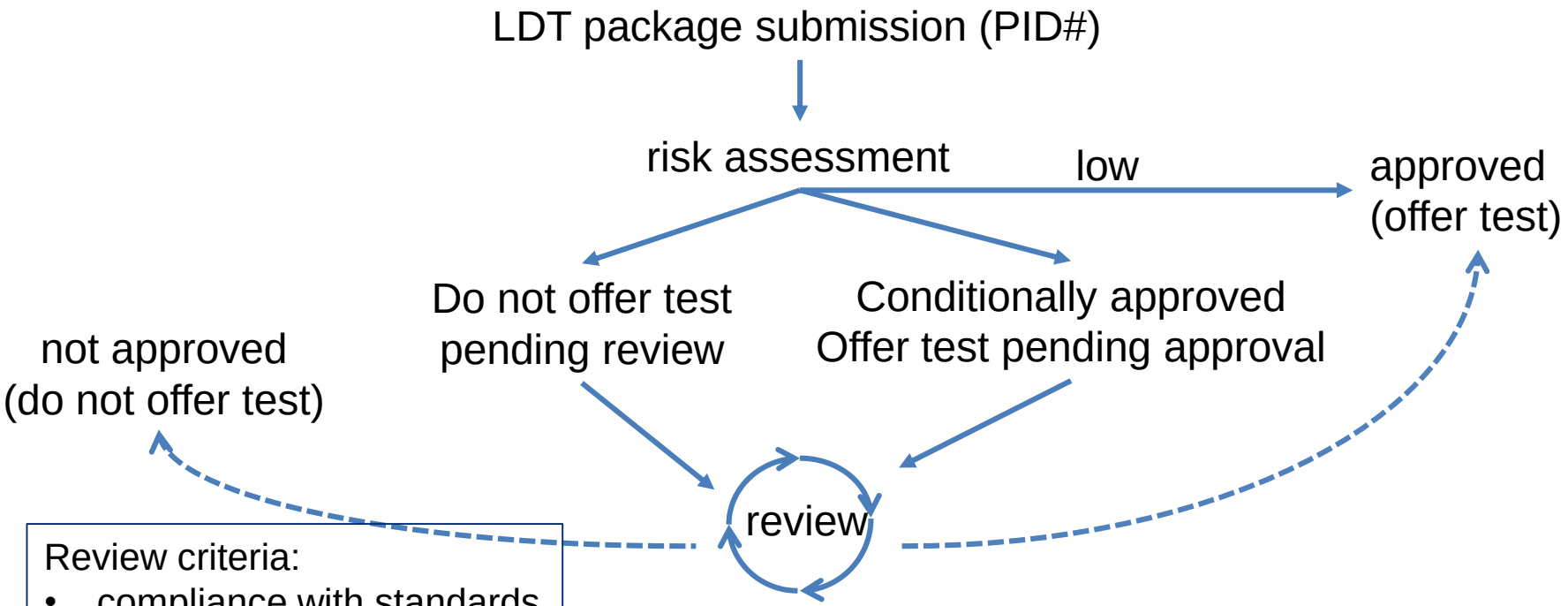
"Add Test Under Exemption" Form

Sample reports for all outcomes

Validation summary

(Informed consent)

Adding an LDT (after April 24, 2003)



Review criteria:
- compliance with standards
- analytical validity
- clinical validity

FDA Premarket Requirements for Devices

Prior to marketing in the U.S., a device intended for human use requires either FDA premarket *notification* or FDA premarket *approval*.

Premarket *approval* (PMA):

documentation to FDA to demonstrate the safety and effectiveness of the class III device

Premarket *notification* (510(k))

demonstrate that device is at least as safe and effective as a legally marketed device that is not subject to PMA. Generally, referred to as "substantially equivalent" to a "predicate device."

New York's 3rd party review program

June 2017 - FDA accredits NYS DOH/Wadsworth Center as a 3rd party reviewer under its Third Party Reviewer program as established by section 523 of the FDA Modernization Act of 1997.

Wadsworth may review selected premarket *notifications* (510(k)) for certain devices/tests.

Only devices/tests that have a predicate device/test already cleared as a 510(k) device and that are substantially equivalent are eligible.

TP review organizations cannot review all device types

- Class III devices
- Class II devices that:
  - Are permanently implantable
  - Are life sustaining/supporting, or
  - Require clinical data in 510(k)s
- 510(k)s that requires multi-Center review (e.g. 510(k) for combination products, consulting reviews outside of CDRH, etc.)

This has been relaxed under the 21st century cure act of 2016

Is 3rd party review appropriate for me?

NYS only considers 510(k) review requests

- from laboratories with a current NYS laboratory permit including the appropriate category, **AND**
- in conjunction with an application for CLEP review through its regular LDT review process, **AND**
- in specific FDA test categories – Clinical Chemistry, Immunology, Microbiology, Pathology, Toxicology

Requests for 3rd party review

- Must be made with original LDT submission to NYS
- Will be accepted at NYS' discretion.
- Will be acted on once all NYS requirements and FDA requirements have been met.
- Must include a draft decision summary, including a description of predicate device and special controls (class II) and supporting claim of substantial equivalence. See 21 CFR 807.

5. Conducting the substantive review.

Substantive review focuses on substantial equivalence

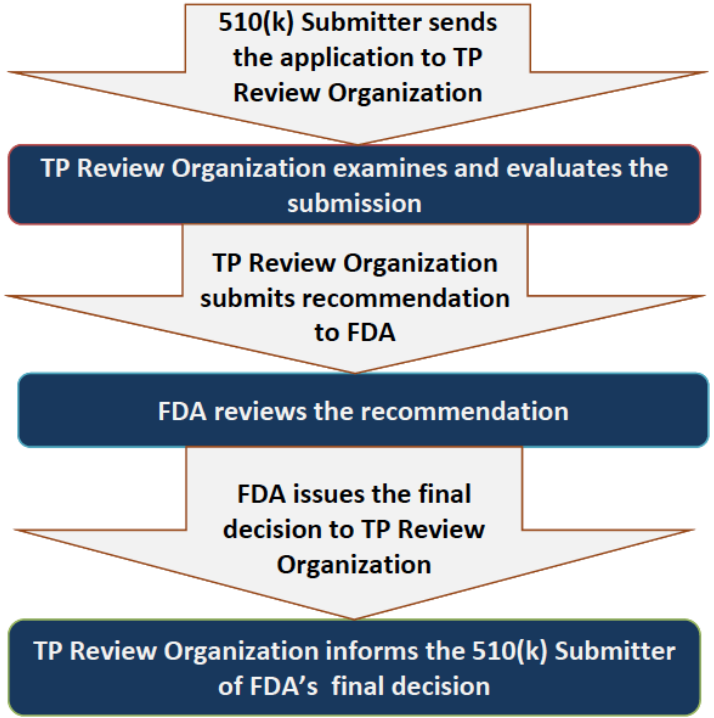
Establishing Substantial Equivalence

Decision Points From Flowchart

1. Is the predicate device legally marketed?
2. Do the devices have the same intended use?
3. Do the devices have the same technological characteristics?
4. Do the different technological characteristics of the devices raise different questions of safety and effectiveness?
5. Two Parts:
   a) Are the methods acceptable?
   b) Do the data demonstrate substantial equivalence?

Overview of TP paradigm

Note: NYS approval does not guarantee FDA clearance; the FDA will make the final decision about substantial equivalence to the predicate device.



TP organization is free to accept or reject the request to review. TP is NOT a consultant.

All communication goes through the TP reviewer

Further information about the 3rd party review process in general can be found on the FDA website at

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ThirdParyReview/ucm124005.htm

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ThirdParyReview/ucm123993.htm

FDA has multiple websites to check device eligibility in the TP program

1. List of Devices for Third Party Review: https://www.acessdata.fda.gov/scripts/cdrh/cfdocs/cfThirdParty/current.cfm

2. Product Classification Database: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm

3. Current List of Accredited Persons for 510(k) Review: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfthirdparty/accredit.cfm

A slide deck describing the third party review process is available by request from erasmus.schneider@health.ny.gov