STATE OF NEW YORK
DEPARTMENT OF HEALTH

Wadsworth Center The Governor Nelson A. Rockefeller Empire State Plaza P.O. Box 509 Albany, New York, 12201-0509

COMPREHENSIVE TEST APPROVAL POLICY AND SUBMISSION GUIDELINES

Subsection 58-1.10(g) of Part 58 of Title 10 (Health) of the Official Compilation of Codes, Rules and Regulations of the State of New York states that *all technical procedures employed in a laboratory shall be of proven reliability and generally accepted by leading authorities in the specialties of laboratory medicine and/or approved by the Department*. A laboratory can perform only those assays for which the performance characteristics have been *established and validated*, or if already established (typically by a manufacturer) *verified* at the site where the assay will be performed. The laboratory must also hold the appropriate permit category for the test and must meet all other requirements related to on-site survey, personnel and proficiency testing. This guidance document will describe the types of tests that require specific review and approval from the Department and provide forms and instructions for submitting test approval materials. Due to the variety of test methods available, ancillary requirements, notification forms and checklists for submissions in certain specialties are included as appendices to this document. Contact Program staff at clepval@health.state.ny.us for questions, or for guidance on situations not explained here.

APPLICATION PROCEDURES

Description of Assay/Test	How to Apply	Requirements / Guidance
FDA-approved assays Assays cleared (510k), approved (PMA), or exempted by the United States Food and Drug Administration (FDA) that have not been modified to change the procedure or the intended use. FDA clearance or approval status can be found at FDA's Medical Devices website. A separate FDA site lists Approved Donor Screening Assays for Infectious Agents and HIV Diagnostic Assays. This includes Investigational Use Only (IUO)-labeled tests ONLY when utilized under a specific FDA Investigational Device Exemption (IDE).	If your laboratory already holds a NYS permit, submit the test addition via eCLEP. You may also make an Add Category request via eCLEP if the laboratory does not hold the appropriate category. If you are not certain which permit category is required for an assay, you can refer to the category/analyte list included in the Guide to Program Requirements and Services available on our website, or contact program staff for assistance. Laboratories applying for an initial permit may include FDA-approved assays on the test list included in the initial permit application, no additional forms are necessary. *Exception: Genetic Testing – Molecular, refer to Application for Assay Approval in Genetic Testing - Molecular	Laboratories holding a permit in the required category may perform FDA-approved assays once they have submitted the test addition notification via eCLEP and have met their own quality management systems requirements. Laboratories applying for a category, or applying for an initial permit, may begin testing once the permit has been amended or issued. Verification data will be reviewed during the initial survey (for new permits and categories) or during the next on-site survey (for laboratories already holding a permit). The Department may, based on survey findings or other concerns about the performance of the assay, request additional documentation and verification data. Refer to requirements in the Clinical Laboratory Standards of Practice (Examination Practices Validation/VAL S5).
Standard Method A standard method is defined as an assay that has an established record of reliability and clinical validity, and which employs a standardized protocol that is universally applied in laboratories that employ the method for the analyte, such application being consistent with industry standards recognized by leading authorities in laboratory science. These are, in general, methods in use prior to FDA's 1976 Medical Device Amendments.	Follow instructions for **FDA-approved assays**. If upon review it is determined that the assay does not qualify as a standard method, additional documentation and validation data may be requested.	Follow requirements for **FDA-approved assays.** If the method is determined not to qualify as a standard method, additional documentation and validation data may be requested.

APPLICATION PROCEDURES, continued

Description of Assay/Test	How to Apply	Requirements / Guidance
Modifications to FDA cleared / approved, OR to previously NYS-approved assays that affect the assay's intended use Change from intended use is a change in the specimen type; the type of analysis (e.g., qualitative vs. quantitative); the purpose of the assay (e.g., screening, diagnosis, prognosis, monitoring, and /or confirmation); or the target population(s) as specified in the NYS approval letter, or by the FDA, as described in the package insert, including any specific *Limitation* or *Restriction* statements in the insert.	Specific requirements, notification forms and checklists for submissions in several permit categories / specialties are included as appendices to this document. For these assay types, complete and submit the information outlined in the Appendices as appropriate to the assay and permit category. Minimally, description of the modification and a summary of the validation performed are required. Additional data, including your laboratory-specific SOPM and independent validation summaries and data, may be requested for review. If you are not sure whether the modification requires a submission, contact Program staff at clepval@health.state.ny.us	Requirements will vary dependent upon the assay details, technology, permit category, and the modification itself.
Tests using commercially distributed assays or test kits NOT cleared/approved by the FDA Variously labeled (e.g., RUO, IUO) or without labeling, these require review by the Department prior to use to determine the extent to which the manufacturer has established the performance characteristics of the assay.	For these assay types, complete and submit the information outlined in the Appendices as appropriate to the assay and permit category.	Clinical use of kits labeled RUO, IUO, or unlabeled and not cleared/approved by the FDA, requires written approval from the Department. Assays approved based upon review of package insert/sample reports alone will undergo validation review during on-site inspection. Any laboratory test using Analyte-Specific Reagents (ASR) is, by FDA definition, a laboratory-developed test. ASR-labeled immunohistochemical (IHC) stains and classic *in-situ* hybridization (ISH) probes used for tissue pathology are considered standard methods when used as part of the MD pathologist-guided processes. (see Standard Methods)
Laboratory-developed tests (LDTs) LDTs are non-FDA cleared or approved assays that are developed by the laboratory offering the assay. LDTs may include a combination of reagents and/or kits prepared by the laboratory, labeled as Analyte Specific Reagents (ASR), Research Use Only (RUO), or Investigational Use Only (IUO).	For these assay types, complete and submit the information included in the Appendices as appropriate to the assay and permit category.	Written approval is required by the Department in order to offer these assay types for New York State. The laboratory is responsible for establishing and validating the performance characteristics of the assay (or verifying performance characteristics that a manufacturer had established, for any commercially-distributed components) at the site where the assay will be performed. Under certain circumstances, a laboratory may receive a limited exemption from the submission of a comprehensive validation package for each test they wish to offer. See Requests for Exemption from Comprehensive Submissions

APPLICATION PROCEDURES, continued

Description of Assay/Test	How to Apply	Requirements / Guidance
Clinical Trials and Research Tests Not Approved by the FDA Tests performed on specimens from trial participants for participant management under IRB-approved research or clinical trials protocols, where the results are reported and are used for clinical decision making. Examples of testing performed for participant management include those that influence enrollment (exclusion or inclusion), safety, or dosing.	If results of the tests are used in participant management as described follow the instructions for either commercially-distributed or laboratory developed assays, as appropriate.	If the results of the tests are **not** used in participant management, then permit and assay approval is not required. Examples of tests that do not require review and approval include retrospective biomarkers measurements or assays to measure drug concentrations for pharmacokinetic/pharmacodynamic evaluation, and are used to collect aggregate data on drug or treatment efficacy.
Requests for Exemption from Comprehensive Submissions Laboratories may request an exemption from comprehensive reviews of validation packages. It is very common for a laboratory to use a standardized methodology to test for numerous analytes. For example, a cytogenetics laboratory may routinely use fluorescent in-situ hybridization (FISH) to identify the presence or absence of specific DNA sequences. While the probes used may differ, the technology is the same and there should be a standardized protocol used for validation. If the laboratory is able to demonstrate that an appropriate validation protocol is followed on a consistent basis over time for the FISH assays they use, it would be appropriate for the laboratory to request an exemption from a comprehensive review for any additional FISH assays that may be developed and validated.	Laboratories interested in an exemption should submit a request in writing. In general, exemptions are granted for assays of common methodology within a category, e.g., FISH-based assays in the cytogenetics category and LC-tandem MS-based test in endocrinology. Laboratories that routinely develop assays should submit a standardized protocol for method validation. Such a protocol would include a description of the laboratory's general principles and practices for assay development and initial validation, an algorithm for assay validation using reference assays and/or clinical findings, and laboratory-specific protocols for on-going validation, including quality control procedures and quality assurance indicators. For clarification of the exemption process as it relates to your particular circumstances or assistance in applying for an exemption, contact program staff. Note: Exemptions are not considered for forensic identity testing, forensic paternity testing, or DNA databasing.	In order to be considered for an exemption from the requirement to submit methods for review and approval, a laboratory must first have a sufficient number of representative methods approved through comprehensive validation review process, to demonstrate that an appropriate validation protocol is followed on a consistent basis over time. Laboratories qualifying for an exemption will receive written approval. Subsequent to the granting of the specific exemption for an approved group of assays, the laboratory can request approval to offer additional assays under their exemption. The request for additional approvals should be accompanied by the information included in the Sections I and II of the appropriate Appendix, including a summary of the data analysis, and sample reports for all possible outcomes, including test interpretation. The department may request additional information as necessary for these additions (which may include a full validation package). If these additional submissions are found to be deficient so as not to support performance claims, or there is evidence that the laboratory's validation practices have varied substantially from its established (and approved) validation protocol, approvals granted under the exemption will be re-examined.

GENERAL REQUIREMENTS FOR ASSAY VALIDATION

The Department requires all testing to be both analytically and clinically valid. Analytical validity means the ability of the assay to meet technical performance specifications noted in (i) of the standard referenced below. Clinical validity means the proven ability of an assay to reliably identify a specific condition in a test subject. The general requirements for assay validation are described in CLEP's Clinical Laboratory Standards of Practice: Validation Sustaining Standard of Practice 5 (Validation S5a) (http://www.wadsworth.org/labcert/clep/files/NYSDOHStandardsPart1GeneralSystems.pdf):

For methods not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures); for commercialized methods where performance specifications are not provided by the manufacturer (IUO, RUO); and for modified FDA-cleared or approved test systems, the laboratory shall:

i. establish performance specifications for accuracy, precision, reportable range of test results, reference interval(s) (normal values), analytical sensitivity and specificity (to include interfering substances); and other applicable performance characteristics, including the clinical sensitivity and specificity of novel assays without comparative methods;

ii. assure that the established reference interval is appropriate for the laboratory's population; and,

iii. submit validation data and SOPM for review by CLRS staff in accordance with established guidelines as provided in the relevant appendices (e.g., for Nucleic Acid Amplification Tests for Infectious Agents; Trace Elements)

When the test comprises multiple individual assays and/or analytes combined as a panel and interpreted as such, the laboratory must clearly describe its composition and clinical use. The submission must include comprehensive procedures and validation of each individual assay; the actual algorithm used for the interpretation; and how the analytical and clinical performance characteristics of the individual assays and their combination using the interpretive algorithm were established.

Where Departmental assay design and validation guidance and requirements are not provided, it is the submitting laboratory's responsibility to design and implement procedures for analytical and clinical validation of assays. Validation protocols can be based on clinical laboratory industry consensus guidelines (e.g., ACMG, CLSI, and FDA). With few exceptions, the Department will not define numbers of specimens to be used in validation studies. The submitting laboratory must design a validation study with numbers and types of materials that are statistically defensible and scientifically appropriate, and must include both positive and negative samples.

TRACKING THE PROGRESS OF YOUR SUBMISSION

Laboratories participating in the New York State Electronic Proficiency Test Reporting System (EPTRS) can track the progress of test approval submissions via the **Test Approval Status** link on the EPTRS home page available on the Department's Health Commerce System (HCS). Approved methods are shared with referring laboratories, consumers and health care providers upon request, so it is important to regularly review your list of approved methods to ensure a method is still being offered. If a test or test method has been discontinued, you may send an email as described below. Once a submission is received and logged, it is assigned a Project ID (PID) number and included in the **Test Approval Status** list showing the current status.

To inquire about a submission, you can send an email to clepval@health.state.ny.us . Please reference your laboratory's four-digit permanent facility identifier (PFI) and the PID number in the subject line of your email.

CONFIDENTIALITY AND FREEDOM OF INFORMATION LAW (FOIL)

Materials submitted, including related data packages, cannot be returned to the laboratory. All materials are maintained under strict confidentiality. As relates to New York State's Freedom of Information Law (commonly called FOIL): The Department's Records Access Officer has advised Wadsworth Center that if documents are marked "proprietary"; "confidential"; or with any labeling indicative of the submitter's desire for an increased level of protection based on the submission content, such protection from immediate release based on a FOIL request is justified. Laboratories will be given an opportunity to block information release if a request for the material is filed under the FOIL, by presenting evidence that the materials contain trade secrets. Marking should minimally appear on the cover page of each unit of material. Documents not marked with such terms will not block release of the submission through a FOIL request.

PATENT AND INTELLECTUAL PROPERTY LAW

The Department's review of method validation documentation is conducted to evaluate the laboratory's demonstration of technical and clinical validity and to determine if the performance of the assay is as claimed; the review does not consider the existence or relevance of intellectual property issues or patent rights. Consideration of, and compliance with, any applicable intellectual property or patent law requirements is the responsibility of the submitting laboratory.