

Pre-IDE Information Packet

Office of In Vitro Diagnostic Device
Evaluation and Safety

TABLE OF CONTENTS

- I. Introduction
- II. Administrative Requirements
- III. Intended Use and Indications for Use
- IV. Device Description
- V. Analytical Performance
- VI. Method Comparison
- VII. Clinical Performance
- VIII. Glossary

I. INTRODUCTION

This document was prepared by the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) to assist manufacturers in preparing pre-IDEs (protocols) and submissions for new devices.

Throughout the document, definitions of underlined terms can be found in the Glossary (Section VIII).

What is a pre-IDE?

The pre-IDE process can be thought of as a “pre-submission” process. It may involve sending analytical or clinical protocols to FDA for review and comment before proceeding with studies. The process may also involve a meeting with FDA to discuss protocols and/or possible regulatory pathways. Pre-IDE submissions and meetings are strictly *voluntary*, and any comments or recommendations made in the review of protocols or during these meetings are **not binding** on the Agency or the Sponsor. A submission made under the pre-IDE process is not an official IDE application as described in 21 CFR Part 812. In fact, most *in vitro* diagnostic devices (IVDs) are exempt from the medical device IDE regulations as long as conditions in 21 CFR 812.2(c)(3)¹ are met.

When do I file a pre-IDE?

It is appropriate to file a pre-IDE for a protocol review with the FDA when:

- The new product involves cutting edge technology and it will be helpful to familiarize FDA with the technology in advance of the submission;
- Assistance is needed in defining possible regulatory pathways;
- The studies involve complex data and/or statistical approaches and assistance is needed in defining appropriate analyses;
- The study designs are complex and you are seeking advice on ways to simplify and focus them on the studies needed to support your claim.

You may refer to the Q & A document for additional information on the pre-IDE process.

What information is needed to file a pre-IDE, and what is the relationship of the protocol to my premarket notification 510(k) or premarket application (PMA) submission?

A pre-IDE focuses on how information will be gathered by the manufacturer to support the intended use and indications for use as proposed. Generally, when preparing a pre-

¹ The conditions stated in 21 CFR 812.2(c) (3) are that the sponsor comply with the applicable requirements in 21 CFR 809.10(c) and that testing (1) is noninvasive; (2) does not require an invasive sampling procedure that represents significant risk; (3) does not by design or intention introduce energy into a subject; and (4) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

IDE, a manufacturer provides administrative information (Section II), proposed intended use and indications for use (Section III), a brief description of the device/principle of operation, and a proposal or study protocol for method comparison (Section VI) or clinical study (Section VII). The subsequent premarket notification (510(k)) contains results of those studies, as well as information on the analytical characterization and performance of the assay (Section IV and V).

Premarket applications (PMA) will include assay characterization and analytical performance data. However, the method comparison will usually be either to a reference method or often to clinical measures or diagnosis (Section VII). Additional PMA submission requirements can be found in 21 CFR 814, and manufacturing requirements in 21 CFR 820.

Throughout the document, definitions of underlined terms can be found in the Glossary (Section VIII).

FDA understands that different devices used in different medical disciplines will have different analytical and/or clinical issues. Thus, some of the elements discussed in this document may not be required in your protocol or submission. Please contact the appropriate division in OIVD for assistance, particularly if you are a new manufacturer, or if your device is for a new analyte.

Chemistry and Toxicology	(301) 594-1243
Immunology and Hematology	(301) 594-1293
Microbiology	(301) 594-2096

II. ADMINISTRATIVE

The following administrative information is required for all submissions, including pre-IDEs, 510(k)s and PMAs. The cover letter should state if your device is new or if you are providing supplementary information to a previously submitted document. If supplementary information is being submitted, please provide the original document number. For pre-IDEs, it is helpful for us to know whether a feasibility study has been performed. FDA typically reviews study protocols for which the study has not yet been initiated. Please direct any questions to the director of the division that would receive the protocol or submission. If you have questions regarding the protocol of an on-going study, please make it clear to the FDA staff that the study has already started.

- A. Contact Information
- Name of Manufacturer
 - Manufacturer Street Address
 - City, State, Zip
 - Phone Number
 - Fax Number
 - Contact person for all communications

- Address, phone, fax of contact person for all communications (if different from manufacturer information)
 - Email (optional)
- B. Device Information
- Trade name (proprietary name)
 - Common name (usual name)
- C. Regulatory Information for 510(k) submissions only (not for pre-IDE)
- Regulation (if known), as indicated in the Code of Federal Regulations (CFR) for the specific device.
 - Predicate device. The predicate device is a legally marketed device that has the same intended use and/or the same or similar technological characteristics. Some technological differences are acceptable if they do not affect safety and effectiveness. Technological differences may include modification in design, materials, or energy sources, medical and scientific differences.
 - Please include the document number (if known) and a package insert (see 21 CFR 809.10) for both the proposed and the predicate device. It is helpful if a summary table demonstrating similarities and differences between the predicate and the proposed device is provided (see 21 CFR 807.87(f)).

III. INTENDED USE AND INDICATIONS FOR USE

A. Intended Use

The intended use statement describes how the device is to be used. It includes the following information:

1. Analyte to be measured or organism to be identified or detected;
2. Whether the test is quantitative, semi-quantitative, and/or qualitative;
3. Specimen type(s) or matrix(-ces).

Examples include: blood (include source, e.g., venipuncture, heel or finger stick), serum, plasma (include anti-coagulants), stool, hair, swab (include source, e.g., cervical, nasopharyngeal, throat), urine (include time collected), saliva, cerebrospinal fluid (CSF), sweat, tears, etc.

4. Conditions for use.

Examples include: Prescription use (hospital laboratory, point of care, physician's office, home use, workplace) or over-the-counter.

B. Indications for use.

The Indications for use describes for what or for whom the device is to be used (e.g., disease, condition or patient population).

The following are some examples of information included in the indications for use:

1. The condition(s) or disease(s) to be screened, monitored, treated or diagnosed (e.g., diabetes, hepatitis);
2. Target patient population (e.g., pediatric);
3. Frequency of use (e.g., after meals);
4. Physiological purpose (e.g., determine glucose level).

FDA understands that a manufacturer may not have a clear statement of intended use or indications for use prior to the initiation of a clinical study. However, your hypothesis(es), clearly stated in the pre-IDE, allows FDA to determine if the proposed study will support the proposed use(s) [see Section VI, Method Comparison or Section VII Clinical performance for additional information].

For the submission, you should have a clear statement of your intended use and indications for use. It is often helpful for manufacturers to describe how their device aids in diagnosing or identifying a disease or condition, including discussion of the impact of the information in patient management. This is different from merely demonstrating that a device functions in accordance with its design.

IV. DEVICE DESCRIPTION

A pre-IDE submission should briefly summarize the principles of operation and active reagents in the proposed test system. The information that follows is provided so that you are aware of the types of information that may be requested when you file a 510(k) or PMA. The submission should summarize or provide data relative to the following information, where appropriate for your device and the type of regulatory action you are seeking (i.e., clearance or approval):

A. Reagents and test components.

1. List all components in the assay. Include source, volumes, concentrations, form (e.g., liquid or lyophilized). Identify hazardous material if appropriate.

2. Characterize the active reagents in the assay. It is important to ensure that an adequate supply of these critical reagents is available to avoid frequent material changes to new lots.
 - a. If produced internally, briefly describe the manufacturing process.
 - i) Demonstrate reagent, analyte, antigen, antibody purity using biochemical, immunochemical, or immunological techniques.
 - ii) Identify potentially cross-reacting or interfering substances (e.g., antigens, immunoglobulin, drugs, anticoagulants, etc.) that may give a false analytical result.
 - iii) Determine stability (real-time or accelerated) of the reagents. Indicate if there are any special handling considerations for assay components with unique storage requirements, such as reduced shelf-life after reconstitution, aliquoting and freezing after reconstitution, or storage in reduced light.
 - b. If purchased from a vender, provide a certificate of analysis and describe criteria for accepting and releasing new lots.
3. List other reagents, materials, equipment that are needed to run the assay but are not provided in the kit.
4. Describe calibrators (See FDA Guidance: "Abbreviated 510(k) Submissions for In Vitro Diagnostic Calibrators") and/or controls (See FDA Guidance: "Points to Consider Guidance Document on Assayed and Unassayed Quality control Material") used in the system. Calibrators should cover the measurement range of the assay. Controls should span the clinically relevant decision points.

Indicate if the calibrator/control material is under review as part of the submission. If not, indicate whether they are: exempt from review by regulation; to be reviewed in a separate submission; provided/purchased by the user; already cleared/approved (include document number).

If to be reviewed as part of the submission for the proposed device, the following information should be included:

- a. Describe the calibrator/control matrix or source material. Indicate if controls are internal or external.
 - b. Indicate if the material is standardized or traceable to a national or international reference material.
 - c. Describe the process by which values are assigned and the relationship of the values to the decision point (positive/negative).
-

- d. Determine the stability of the materials.
5. Controls
- a. The control material should be furnished in all matrices claimed in the Intended Use statement.
 - b. If the assay is a single use device, the positive and negative controls should assess the reliability of the assay procedural elements, all reagents, and components (i.e., the controls are not mechanical controls such as, for the flow rate across a membrane).
 - c. If this assay is considered qualitative, the positive control level should fall close to the critical clinical cutoff level in order to challenge the assay.

B. Instruments

The study protocol should state whether there are special instrument or software requirements. Please refer to Guidance for FDA reviewers and Industry for aid in completing this section. See “Guidance for the Content of Premarket Submissions for Software contained in Medical Devices – May 29, 1998” at <http://www.fda.gov/cdrh/ode/57.html>.

- 1. Instrument Component. Provide an Instrument Appendix detailing:
 - i) Instrument Name
 - ii) System descriptions with clearly outlined specifications
 - iii) Mode of operation (random access, batch or stat)
- 2. Software Component. FDA guidance on off-the-shelf software can be found at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfggp/search.cfm>. Relevant documents are: “General Principles of Software Validation; Final Guidance for Industry and FDA Staff “Guidance for Off-the-Shelf Software Use in Medical Devices; Final”, and Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices; Final.” If the software is unique or proprietary to the proposed device, describe:
 - i) The operating system
 - ii) Data management accessories (software function(s))
 - iii) User interface
 - iv) Communications system
- 3. Describe how the sample would be identified (e.g., positive specimen ID, bar code).
- 4. Describe how specimens are sampled or handled.

5. Describe all assay types handled by instrument/software (e.g., immunoassay, chemistry, serology).
 6. Describe all calibration parameters for the system
 7. Describe all installation parameters and requirements.
 8. Describe user definable parameters. State whether system is open or closed.
 9. Describe internal process controls related to the system. Detail quality control procedures applicable to the system.
 10. State whether the reagents are stored on the platform and whether temperature regulation is used.
 11. Indicate whether the software development processes for the particular line of product has been previously submitted or reviewed by FDA.
 12. Determine the level of concern for the software (e.g., major, moderate or minor). FDA/CDRH uses the term “level of concern” as an estimate of the severity of injury that a device could permit or inflict (directly or indirectly) on a patient or operator as a result of latent failures, design flaws or using the medical device software.
- C. Describe the sample/specimen type and procedures for specimen collection, handling (storage and transportation) and processing. [References: NCCLS documents H21-A2 for specimen collection and handling of plasma for coagulation testing. Other applicable documents for hematology are: H18-A, H1-A4 and H11-A3].
- D. Describe the principle of operation for the methodology.

V. ANALYTICAL PERFORMANCE

General Comments

Pre-IDEs for analytical performance are generally submitted to facilitate feedback from the FDA on the appropriateness of the proposed cut-off (see C below) or method comparison (Section VI). The analytical performance parameters described in this section should be addressed in the sponsor’s submission (510(k) or PMA) to the Agency.

A manufacturer must comply with 21 CFR 807.87 in order for FDA to make a determination of substantial equivalence for a 510(k) submission. For all studies, describe the study design including population(s) studied, the number of samples, type of sample (e.g., spiked), matrix, dilution, and target concentrations where appropriate. Test data

should be presented with analyses and conclusions, and include a brief description of how the data were generated and in what target population(s). Summarize results and include explanations for unexpected results and any additional testing performed. When appropriate, charts (scattergrams, histograms, receiver operator curves (ROC), etc.) may be used as part of analyses and conclusions. Describe the statistical methods used in the analyses. Include estimates of robustness for each parameter, where appropriate (e.g., confidence interval, coefficient of variation). Provide acceptance criteria or other pertinent observations.

PMA submissions should address parameters for analytical performance. However, PMA devices, because of their novelty, have to demonstrate safety and effectiveness (21 CFR 860.7), and provide valid scientific evidence of clinical use (21 CFR 860.7(c)(2)).

Specific Performance Parameters

A. Precision

Precision studies should be with specimens at the cutoff (e.g., control(s) diluted to extinction); see NCCLS, EP12-A.

1. Perform separate calculations for each specimen tested for within-run and total precision for each instrument or method used.
2. For qualitative assays, provide the percentage of results that are negative, borderline/equivocal (if appropriate), or positive for each test procedure in a frequency table. Calculate the %positive, %negative and total agreement between methods.
3. For quantitative/semi-quantitative assays, present the coefficient of variation (CV) for each set of values for with-in run and total precision.

B. Reproducibility (inter-assay, see NCCLS EP12-A)

Reproducibility is calculated similarly to precision above, using test results assayed between users/sites, and over time (e.g., day to day) where those variables have the potential to contribute significantly to total error in the system (e.g., if method is particularly complex site-to-site reliability should be calculated; if the test is expected to have a high volume, the manufacturer may want to assess the drift in results over time). FDA prefers that reproducibility be assessed in at least three testing sites, with at least one of those sites in the United States.

C. Normal Range/Cut-off (see NCCLS C28, NCCLS EP-12)

The normal range or cut-off value should be determined in both a healthy, asymptomatic population and/or in a population with similar signs or symptoms as the target population for the device. If submitting a pre-IDE for the proposed device, the manufacturer should describe the population used to derive the normal range or cut-off, including the sample size, and pertinent demographic information (age, gender, etc), and should include the appropriate statistical analyses.

A submission should include the results of the studies, and should also include data validating the value(s) in an independent population that is similar to that described in the indications for use of the device. A manufacturer may reference literature for a normal or expected value, however, that value should be independently validated in the population(s) that the device is intended.

- D. Analytical sensitivity describes the lower limits of assay. This can be calculated several ways (NCCLS I/LA21-P).
1. Limit of blank: usually the mean of the blank determinations \pm 2-3 standard deviations
 2. Limit of detection: lowest level of analyte detected \geq 95% of the time
 3. Analytical sensitivity: intercept of calibration curve when the concentration = 0
 4. Functional sensitivity: lowest analyte concentration where the %coefficient of variation (CV) is acceptable, typically %CV < 20%.
- E. Analytical Specificity (NCCLS EP7-P, Interference)
- Assessing specificity includes a determination of any potentially cross-reacting or interfering substances that may be encountered in specific specimen types or under specific assay conditions.
- For the Microbiology Division: If the assay is semi-quantitative and detects IgG, data should be furnished to support the interpretation of a significant increase in antibody level. If semi-quantitative and detects IgM, data should be furnished to support a clinically useful interpretation.
- F. Accuracy (NCCLS GP10-A 1995, Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots; Approved Guideline)
- Accuracy is calculated as the agreement of the new test result with the result of a standard or reference method. Accuracy is calculated as the number of samples positive by both methods plus the number of samples negative by both methods divided by the total number of samples tested.
- G. Matrix comparison, if appropriate.
- You should plan verify relevant performance characteristics (e.g., correlation, precision) for each matrix claimed in your intended use. The comparison should be performed using samples with both high and low values of the analyte being measured, and/or within the dynamic range of the assay.
- H. Other studies (quantitative or semi-quantitative assays)
-

1. Linearity over the reportable range (refer to NCCLS EP-6P, H20-A and H26-A)
2. High dose hook effect
3. Recovery

VI. METHOD COMPARISON

General Comments

Method comparison is important to validate your device (see NCCLS EP9-A 1995, Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline). If your device is similar to other devices already on the market (for the same intended use), one option is that you may submit an analytical study comparing the performance of your device with the predicate device. FDA may request that your analytical study be performed using clinical specimens from the target population.

If there is no FDA cleared product on the market that you can compare to and your device is of moderate or low risk, you may be eligible for a de novo 510(k) in which you compare your device to a reference method or clinical diagnosis (see also Section VII, Clinical Performance). Sometimes, even when a predicate device with the same intended use exists, sponsors will want to compare their device to either diagnosis or a reference method in order to support different or expanded claims or uses.

For the following comparisons, a pre-IDE should address how the information will be collected, in what patient population(s), and give a plan for how the data will be analyzed. In the submission, the results of the study should be presented.

A. Predicate Device

If comparing your device to a predicate device, we recommend that you describe the following:

- the type and number of site(s),
- experience of test operator(s) with the device,
- how samples are selected with inclusion/exclusion criteria;
- the sample demographics,
- number of samples, measurements per sample and number of individuals represented, with an explanation of multiple measurements per individual

We recommend that the sample distribution cover the measurement range of the assay and ensure that samples cover important decision points, such as at a cut-off. In your pre-IDE, explain how results will be displayed (e.g., agreement, regression)

B. Reference method (Gold Standard comparisons)

The difference between a method comparison to a predicate device and comparison to a reference method is that the reference method is recognized by the general laboratory, the medical community, or FDA as a gold standard. We recommend that you describe:

- the reference method and provide any literature support that is available;
- the type and number of site(s),
- experience of test operator(s) with your device and the reference method,
- how samples are selected with inclusion/exclusion criteria;
- the sample demographics,
- number of samples, measurements per sample and number of individuals represented, with an explanation of multiple measurements per individual.
- how discrepant or equivocal results will be presented or analyzed

We recommend that the sample distribution cover the measurement range of the assay and ensure that samples cover important decision points, such as at a cut-off.

C. Literature Comparison

You may use peer-reviewed literature in support of analytical claims. However, the referenced studies should have been performed with your device as you intend it to be marketed (i.e., not a prototype).

You may use literature to support the clinical claims, particularly where clinical specimens are difficult to obtain. If submitting a pre-IDE, we recommend you provide the referenced literature with the protocol and indicate how it will be used. The studies in the literature should be consistent with your intended use and indications for use (i.e., target population).

VII. CLINICAL PERFORMANCE

A clinical study is an evaluation in which patients are pre-selected for study by virtue of the presence or absence of a condition, disease, signs or symptoms. The comparison is often to diagnosis or other surrogate marker of disease. The clinical investigation is often stratified by demographic variables (age, gender). A clinical study enables determinations of effectiveness and should not be confused with an analytical study (i.e. study that evaluates test results in comparison with another method) using clinical specimens. In the latter case, the clinical specimens are often selected merely because they span a range of analytical results, and not because of the health status of the patient (though normal and abnormal results are represented, prevalence is not preserved in the study population).

For many devices, clinical performance data are not required. However, if the device is a new analyte, has a new intended use or indications for use, or represents a novel methodology, then clinical data may be required. Most pre-IDE submissions seek

interactive, informal feedback from FDA on a manufacturer's proposed study design before the study is initiated. The pre-IDE submission will contain the study protocol, drafted in terms of how data will be collected to support the intended use or indications for use as proposed. The 510(k) submission then will summarize how data were collected, identify and any deviations from the clinical protocol, and will describe all relevant results, analyses, and applications thereof. The submission may include interpretative guidelines, or precautions, warnings or limitations that are identified during the course of clinical study.

- A. Study design
 - 1. Give the number and location of study sites. FDA recommends at least three sites.
 - 2. Describe the study investigators and their level of expertise/experience with device. Discuss if investigators or sites will require training in order to perform testing. Ensure that if institutional review board (IRB) approval is required, it is obtained (21 CFR 50 or 56). Describe relevant informed consent procedures.

 - B. Patient samples or specimens
 - 1. Provide inclusion/exclusion criteria.
 - 2. Describe the clinical status (diagnosis, stage of illness, signs/symptoms). Indicate how (criteria, laboratory tests, physical examination) and by whom (i.e., specialist, generalist) diagnosis was made.
 - 3. Provide demographic information and the prevalence of disease, condition, signs/symptoms
 - 4. Describe samples to be used. The matrix should be consistent with intended population. Indicate if specimens will be collected fresh or if they were archived. If archived, indicate how they will be stored and how their integrity is assessed. Describe how stored specimens are selected for inclusion in the studies.
 - 5. Provide a sound statistical basis for the determination of sample size (N).

 - C. Analyses
 - 1. Present a plan for how data will be analyzed (e.g., identify independent and dependent variables)
 - 2. Describe how the cut-off or reference range is determined and validated (NCCLS GP10-A; also see Analytical Performance, Section V, Part C).
 - 3. Describe expected results. Define or explain calculations. Determine equivocal zones and describe if and how discrepant results will be resolved.
 - 4. Provide the expected rate of clinical false positives, false negatives if known.
-

- D. Interpretation
1. Provide interpretation criteria and/or cite literature for the meaning of positive, negative, or equivocal results.
 2. Describe the consequence of misdiagnoses.
 3. Provide recommendations for results in equivocal zone (if appropriate)

VIII. GLOSSARY

[**Not in text]

These terms are commonly used in the review of in vitro diagnostic device performance. In some cases, these definitions are broader or narrower than used in clinical laboratories or research facilities.

Ref = refer to; NRSCL = National Reference standard for the Clinical Laboratory;
EP = NCCLS Evaluation Protocols;

510(k): See premarket notification.

Acceptance criteria: A range of values derived by consensus with the manufacturer and/or the FDA that define when a particular analysis is considered valid.

Accuracy: Closeness of the test results to truth; free of bias. See also bias. For information on how to collect data to address accuracy, see sensitivity and specificity [See also NCCLS EP9-T, Method Comparison]

Analyte: The substance/target the test measures [ref NRSCL8].

Analytical sensitivity: The analyte concentration at which 95% of the test results are positive. This is determined by performing multiple runs of the zero calibrator. It can be determined by the intercept of the calibration curve when the concentration of analyte is zero. See sensitivity. The study to address analytical sensitivity typically uses spiked samples or otherwise non-clinical samples. [ref see EP12-P]

Analytical specificity: For quantitative tests, the ability of an analytical method to determine only the component it purports to measure or the extent to which the assay responds only to all subsets of a specific analyte and not to other substances present in the sample. See specificity. The study to address analytical specificity typically uses non-clinical samples. For information on how to collect data to address analytical sensitivity [ref EP12-P].

****Adulterant:** Something added to the sample after the sample is removed from the body with the intent to sabotage the assay result

Assay: Amount, activity, or potency of a specific analyte or substance [ref NRSCL8]

****Bias:** The systematic deviation of test results from the accepted reference value. See accuracy [ref NRSCL8].

Calibration: The process of testing and adjusting an instrument, kit or test system to provide a known relationship between the measurement response and the value of the

substance being measured by the test procedure. Calibration involves measurement of the assay or instrument response to special samples called calibrators. Calibrators are materials whose concentrations are known and to which the test sample is compared in order to determine the concentration of the substance being measured. Calibrators are used to standardize an instrument or assay method [ref NRSCL8].

****Calibration interval:** Time period where calibration is stable [ref NRSCL8].

****Carry-over:** Analyzed carried from one specimen to another subsequent specimen. Carry-over is not a form of interference. For information on how to collect data to address carry-over [ref NRSCL8].

****Central laboratory:** A laboratory staffed with trained personnel capable of performing high complexity testing.

Classification, Section 513, Federal Food, Drug and Cosmetic Act (FD&C Act): FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulation classes based on the level of control necessary to assure the safety and effectiveness of the device. The three classes and the requirements which apply to them are:

Class I:

Class I devices require only general controls. General controls are the baseline requirements of the FD&C Act that apply to all medical devices. Unless specifically exempted by regulation, general controls contain requirements for device manufacturers or other designated persons to register their establishment with FDA; list their devices with FDA; comply with labeling regulations; submit a premarket notification [510(k)] to FDA; and design and produce devices under good manufacturing practices (GMP).

Class II:

Class II devices include any device for which reasonable assurance of safety and effectiveness can be obtained by applying "special controls" in addition to general controls. Special controls may include special labeling requirements, mandatory performance standards, patient registries and postmarket surveillance.

Class III:

Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure their safety and effectiveness. These devices require a premarket approval (PMA) application in order to obtain marketing clearance.

CLIA: Congress passed the Clinical Laboratory Improvement Amendments (CLIA) in 1988 establishing quality standards for all laboratory testing to ensure the accuracy, reliability, and timeliness of patient test results. CLIA requires regulation of laboratories based on test complexity, not test site.

CLIA - Test Complexity: The final CLIA regulations were published on February 28, 1992 and are based on the complexity of the test method; thus, the more complex the test, the more stringent the requirements. The three categories of tests are: waived, moderate complexity and high complexity. Commercially marketed test systems are scored for complexity based on seven criteria (knowledge; training and experience; reagents and materials preparation; characteristics of operational steps; calibration, quality control and proficiency testing materials; test system troubleshooting and equipment maintenance; and interpretation and judgment. Each test system is given a score of 1, 2, 3 for each of these criteria.

CLIA - Moderately Complex Tests: Commercially-marketed tests receiving scores of 12 or less will be categorized as moderate complexity,

CLIA - Highly Complex Tests: Commercially marketed tests receiving scores above 12

CLIA - Waived Tests: Simple laboratory tests which-- (1) Are cleared by FDA for home use; (2) Employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible; or (3) Pose no reasonable risk of harm to the patient if the test is performed incorrectly.

Clinical sensitivity: See also sensitivity and positive percent agreement. The proportion of patients with well-defined clinical disorders whose test values are positive or are above the defined limit. The objective clinical endpoints must be determined independent of the assay. The study to address clinical sensitivity uses samples obtained from patients. Either banked or prospective samples are used depending on the assay. For information on how to collect data to address clinical sensitivity [ref NRSCL8 and EP12-P]

Clinical specificity: See also specificity and negative percent agreement. The proportion of subjects evaluated who do not have a specified clinical disorder whose test results are negative or are below the defined limit. The objective clinical endpoints must be determined independent of the assay. The study to address clinical specificity uses samples obtained from patients. Either banked or prospective samples are used depending on the assay. For information on how to collect data to address clinical specificity [ref NRSCL8 and EP12-P]

Clinical Utility: The device is effective for its intended use and will provide clinically significant results in a large portion of the target population.

Comparator: For a 510(k) premarket notification (PMN); can be a predicate, a peer reviewed reference standard, or an objective clinical endpoint.

****Contraindications:** A piece of the label which identified situations where the device should not be used because the risk of use outweighs any possible benefit. This includes known hazards.

Correlation: A measure of the degree of linear relationship between two variables. Correlation (r) varies from -1.00 to +1.00. Negative correlation means that as one variable decreases, the other increases. Positive correlation means that the variables change in the same direction (i.e., both increase or both decrease).

Cross-reactivity: Shared or similar antigenic response to the analyte which falsely elevates the signal measuring the analyte. See interference. For information on how to collect data to address cross-reactivity [ref NRSCL8].

Cut-off: See also decision level and medical decision point. A test value that marks the upper or lower boundary between a negative and a positive interpretation of the test result when the test is qualitative. Theoretically, when testing a sample at the cut-off, half the results will be positive and half will be negative. Some quantitative tests include more than one medical decision points or cut-offs [ref NRSCL8].

Data: Individual or body of facts, statistics, observation, or numbers that provide information about the performance of the device [ref NRSCL8].

Decision level/decision points: See cut-off.

Demographics: Age, race, gender, geographic location and/or education level of subjects in a clinical study.

****Diagnostic test:** A measurement or examination of a diagnostic specimen for the purpose of diagnosis, prevention, or treatment of any disease or the assessment of health or impairment of health of an individual patient [ref US CFR 493 February 29, 1992].

****Discrepancy resolution:** Using the results from a third test to reflect truth when experimental assay and the cleared comparator assay disagree.

****Efficacy:** The ability of a medical device to achieve the expected result in attaining diagnosis or treatment in an ideal setting [ref ISO Guide 63-2.4].

Equivocal zone: The range surrounding the cut-off where a sample has an equal probability of being positive or negative.

Error: See also precision. Deviation from truth or from an accepted, expected true or reference individual value. In other words, an individual measurement minus its true value [ref NRSCL8].

Random error: Non-directional, patternless differences between successive results obtained.

Systematic error: Equal to random error subtracted from total error.

False results: False positive (FP) occurs when a sample is truly clinically negative, but the assay result indicates the sample is positive. A false negative result (FN) occurs when a sample is truly clinically positive, but the assay result indicates the sample is negative [ref NRSCL8].

Functional sensitivity: See also sensitivity. This is the lowest level the device can measure plus 2 standard deviations. This is determined by the lowest analyte concentration where %CV is acceptable, typically when the CVC is less than 20%. When used, this is usually the lowest part of the assay range that a result can be reported.

Gold Standard: A term applied to assays or standards that give a result as close to truth as is possible. For example, culturing an etiologic agent from an aseptically obtained blood sample is a positive gold standard [ref NRSCL8].

Hook effect: This effect occurs when the analyte concentration is so high in the sample that the reaction is saturated and the test result reads negative. Assays are evaluated to determine if values become negative at very high concentration causing false negative results.

Hypothesis testing: The testing of 2 or more statistical hypotheses that is mutually exclusive so that exactly one hypothesis can be accepted at a specified confidence interval [ref NRSCL8].

In control: The process when results from the control solution are within acceptable control range. This suggests that the assay is capable of performing according to the label given those parts of the assay the controls are designed to evaluate [ref NRSCL8].

***In vitro* diagnostic (IVD):** A term used to describe those reagents, instruments, and systems for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, or treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body [refNRSCL8].

Inclusion/Exclusion criteria - Conditions of clinical patients or clinical samples that cause them to be included or excluded from clinical trials.

Intended use/Indication for use: The device description of what the manufacturer intends the product to be used for. It includes the analyte(s), the matrix, the disease or condition to use the device with, subpopulations where the device is intended, whether the device is prescription or over-the-counter, or prescription home use, whether it is for diagnosis, screening or monitoring.

Intercept: See also method comparison. This term is relative to comparing 2 devices showing substantial equivalence. The y-intercept is the value of “y” in the equation

$y=mx+b$ when $X=0$. Ideally, if the devices perform identically, the intercept = 0 [ref NRSCL8].

Interference: See also cross-reactivity. Something, other than the analyte, that causes the apparent concentration or intensity of the reagent or signal to increase [ref NRSCL8]

Endogenous Interference: an interferent typical or inherent in the sample such as bilirubin, triglycerides, cholesterol, uric acid, rheumatoid factor, hematocrit, albumin, gamma globulin, HAMA or dehydration.

External Interference: Any interferent whether added to the body altering the sample (e.g. alcohol, medications, or citric acid), or some cross-reacting metabolites, or a biproduct of sample processing such as an anticoagulant or preservative.

****Internal Quality Control:** Procedures run in association with the measurement of patients' specimens to evaluate whether the assay is capable of performing according to the label within predefined tolerance limits [ref NRSCL8].

Investigational review board (IRB): A group of scientists who evaluate the ethics of a proposal for a clinical study.

Limit of detection: See also sensitivity. The lowest amount of analyte which can be detected within acceptable precision and accuracy, e.g lowest limit detected $\geq 95\%$ of the time [ref NRSCL8].

Limit of blank: Blank determinations plus 2-3 standard deviations.

****Line identity:** See also intercept and method of comparison. The line best describing a method comparison.

Linearity: The ability of the assay, within a given range, to provide results that are directly proportional to the concentration of the analyte in the test sample. This is determined with known concentrations of analyte using the matrix of the intended sample. Linearity is reserved for quantitative assays [ref NRSCL8].

****Lot release criteria:** The criteria met before a new batch of consumable device components can be marketed after being manufactured, e.g., reagents, test strips.

Matrix: The type of sample, e.g. saliva, urine, spinal fluid, tears, blood, plasma, serum, hair [ref NRSCL8].

****Matrix effect:** The impact of changing a matrix on the performance of the assay compared to the matrix used when the assay was last cleared. See interference. This is evaluated by a matrix comparison study [ref NRSCL8].

Medical decision point: See also cut-off. The value above or below which a physician will alter their medical therapy or interpretation of the disease or condition.

Method comparison: A comparison of results where an assay and either a predicate assay or a reference method are compared over the range of the new assay. The mathematical equation describing the comparison is $y = mx + b$ where y is the intercept and m is the slope of the line generated by the comparison. See also intercept. A study to address method comparison involves comparing data from the assay to that of the predicate using correlation design with regression analysis.

****Near patient testing:** Testing performed outside a central laboratory (e.g., home use, workplace, emergency room, physician office).

Negative predictive value: The likelihood that an individual with a negative test result does not have the particular disease or other condition that the test is designed to detect [ref NRSCL8].

****Objective clinical endpoints:** See also clinical sensitivity and specificity. Clinical signs, symptoms, and other indicators that are well recognized in the standard practice of medicine to indicate the disease or condition for the intended use of the assay [ref NRSCL8].

Package insert: Informational material that accompanies the instruments, reagents, and other laboratory products that gives the instructions for use of the device; contains precautions, warnings and limitations.

****Percent agreement:** The proportion of results obtained with the proposed device that agrees with the results of the comparative method (the predicate device, reference method or gold standard, or clinical diagnosis).

Positive percent agreement: The proportion of positive results obtained with the proposed device and the comparative method out of the total number of positive results for the comparative method; equals clinical sensitivity if the comparative method is a gold standard or clinical diagnosis.

Negative percent agreement: The proportion of negative results obtained with the proposed device and the comparative method out of the total number of negative results for the comparative method; equals clinical specificity if the comparative method is a gold standard or clinical diagnosis.

Performance Characteristic: A property of a test that is used to describe its quality e.g. accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference range [ref NRSCL8 and US CFR 493 February 28, 1992].

Population: The totality of samples tested. The patients or patient samples should be a represented subgroup of the target population for which device is intended for use [ref NRSCL8].

Positive predictive value: The likelihood that an individual with a positive test result has a particular disease or other condition, that the test is designed to detect [ref NRSCL8].

Precision: See also Reproducibility and Repeatability. The closeness in agreement between independent test results obtained under stipulated conditions. It is typically reported as standard deviations (SD) or coefficient of variation (CV) which describes imprecision [ref NRSCL8, I/LA21-P, and EP12-P].

Predicate: A legally marketed device with the same or similar indications for use.

Premarket application (PMA): An application for marketing a new (i.e., no predicate) or high risk device; submissions are evaluated for safety and effectiveness.

Premarket notification (PMN or 510(k)): An application for marketing a low or moderate risk device that is substantially equivalent to a device already on the market.

****Prescription home use:** Prescription home use in- vitro diagnostic devices are intended to detect and/or measure analytes e.g. antigens, antibodies, hormones etc. in clinical specimens. They are essentially the same as other clinical lab devices but differ in that they are used by a lay person in the home setting on the order of a physician.

Prevalence: A fraction where the numerator is the number in the group affected by the disease or condition compared to the denominator, the total number in a specified group [ref NRSCL8].

Product insert: See package insert.

Quality control (QC): The expected reaction or concentration of analytes is within known limits to cause either positive or negative results when used in place of a human sample. They are materials that contain assay-specific analyte in an assay-compatible matrix are tested with patient samples to ascertain the reliability of the assay. The purpose in running an assay using QC material is to assure users that the device is functioning according to its labeling within the limit of what the material is designed to control for [ref NCCLS EP12-P].

Quantitative assay: The assay produces a quantitative numeric result, sometimes it is required that a quantitative test is traceable to a standard.

Semiquantitative: The assay produces a positive or negative result and provides information such that the positive result can be associated with a numeric result thereby providing categories or levels for qualitative results.

Qualitative assay: The assay produces a positive or negative result.

****Quality Systems Regulations (QSR):** QSR regulations define appropriate quality systems for medical devices. Manufacturers establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications. (See 21 CFR Part 820). The quality systems for FDA regulated products are known as

current good manufacturing practices (cGMPs). In 1996 the good manufacturing practice requirements were revised to include the area of Design Controls.

Range: The smallest to the largest observed value. The total span of values a device can provide results [ref NRSCL8, NCCLS C28-A].

Reference range: The range of test values expected for a designated population of individuals. Demographic information is submitted when data is presented [ref NRSCL8].

Reportable range: The range of test values over which the device response is valid. Data for linearity, dilution testing, parallelism, or spiked recovery (see recovery) may be used to support the reportable range [ref NRSCL8].

Recovery: See also reportable range. The increase in analyte concentration or activity after adding a known amount of the analyte to a sample [ref NRSCL8]

Reference method: A thoroughly investigated method, in which exact and clear descriptions of the necessary conditions and procedures are given for the accurate determination of one or more property values, and in which documented accuracy and precision of the method are commensurate with the method's use for assessing the accuracy of other methods for measuring the same property values or for assigning reference method values to reference materials. Peer reviewed reference methods are adopted by standard setting organizations [ref NRSCL8].

Reference standard: See reference method.

Reference material: See also reference method. Materials used in the reference method.

****Repeatability:** See also precision. The closeness of agreement between the results of successive measurements of the same samples carried out under the same conditions of measurement e.g. within run precision [ref NCCLS I/LA21-P].

Reproducibility: See also precision. The closeness in agreement of repeated testing where the test conditions are changed. Changes most often involve time e.g. between run precision [ref EP12-P and I/LA21-P].

Samples: The type of material obtained from the body to be assayed e.g. saliva, blood, hair, nail.

Retrospective: Samples that were banked or stored materials obtained from patients. The samples were usually obtained for general purposes unrelated to the evaluation of a new assay.

Prospective: Samples are obtained directly from patients enrolled in a study whose purpose is to investigate the performance of the device.

Sensitivity: This is defined by how low an assay can detect the analyte. The test's ability to obtain a positive result compared to the reference method for that assay. Can

use Limit of detection, Functional sensitivity, or analytical sensitivity. See clinical sensitivity, analytical sensitivity, functional sensitivity, limit of detection. Another term used is relative sensitivity. Cross-reactivity may impact sensitivity [ref NRSCL8].

Specificity: How specific an assay is at measuring just the analyte in the presence of potential interfering substances. The test's ability to obtain negative results compared to the reference method for that assay. Also, lack of specificity occurs when competing substances cross-react with the analyte for binding sites. See cross-reactivity and analytical specificity. Studies include clinical and/or analytical as appropriate. Also interference and cross-reactivity data impact specificity [ref NRSCL8 and NCCLS EP-7].

Stability/Storage: The duration a diagnostic device or its components maintain their integrity such that they can perform according to their labeling. Real time, accelerated and stress evaluations are performed to determine duration of constituted and unconstituted reagents; open and closed packaging; and in analyzer and chilled reagents.

Real-time stability studies establish the expiration dating for the entire kit and its individual components under recommended storage conditions, and this information is provided on the label.

Accelerated stability studies can be conducted at elevated temperatures for materials that are suitable for testing by these methods.

Standard: Peer reviewed descriptions, processes or material on how to perform evaluations for the purpose of defining device performance.

****Statistically significant:** The decision to reject a null hypothesis based on the comparison of the probability of observing the data if the null hypothesis is true (p-value) and the probability that a Type 1 (alpha) error can occur. A type 1 error is the probability of rejecting the null hypothesis when it is really true.

Study: All of the investigation(s) to address an aspect of device performance. For example, an investigation to determine the sensitivity of an assay may have been performed at three clinical sites.

****Substance:** Element, ion, compound, factor, infectious agent, cell, organelle, activity (enzymatic, hormonal, immunological), property, presence or absence, concentration, activity, intensity or other characteristic that can be measured [ref NRSCL8].

****Substantial equivalence:** Equivalent to a predicate; mutual agreement by device manufacturer and FDA review staff that sufficient information was presented in the application to support the claims that the results from the new test will have the same level of safety for patients as the predicated.

Traceable: The connection between reference material and calibrators or controls.

Trial: Investigations at a particular clinical site.

****Trueness:** The closeness in agreement between the average values obtained from a large series of test results and an accepted reference value [ref NRSCL8].

Validation: End users test the product to determine if the performance is within the specifications given by the manufacturer, given risks identified and mitigated according to the instructions for use.

****Verification:** Analytical and benchtop evaluation of performance by manufacturer to identify potential risks and determine if mitigating attempts successful in averting risks.

Warnings: Information to make users aware of potential serious adverse events or safety hazards that may occur if device used improperly.