BAKER & DANIELS

Est 1863 805 15th Street, NW, Suite 700 Washington, DC 20005 202 312 7440 Fax 202 312 7460 www.bakerdaniels.com

Bradley Merrill Thompson
Direct: (317) 569-4637
Fax: (317) 569-4800
email: brad.thompson@bakerd.com

VIA HAND DELIVERY

June 17, 2003

Dockets Management Branch (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Guidance Document Submission

Dear Sir or Madam:

Pursuant to 21 C.F.R. § 10.115(f)(3), we are submitting a draft of a proposed guidance document for the U.S. Food and Drug Administration ("FDA") to consider entitled "*In Vitro* Analytical Tests ("IVATs"); Draft Guidance for Industry and FDA." This proposed guidance document sets forth recommendations for the analytical information that would be included in a premarket notification for IVAT kits. Although the analytical kit concept as described in the proposed guidance applies only to class I and class II products, we believe the Center for Devices and Radiological Health should consider its application to products requiring a premarket approval ("PMA") on a case-by-case basis, and advise industry of this potential, especially for emerging threats such as SARS. Alternatively, another guidance document could address analytical PMAs for certain types of diagnostic tests.

In drafting the proposed guidance document, our intent was to describe a process that would bring innovative technologies to market while at the same time protect the public health through a review of its analytical performance, appropriate labeling restrictions and post-market controls. Indeed, for this proposed guidance to have value, in addition to improvements on existing technologies, it must also apply to innovative ones. We believe that FDA should keep these principles in mind and should be flexible in its application of the document. At a later date, we plan to develop and submit some examples of technologies for which this proposed guidance would seem to be suitable.

The proposed guidance document was developed by representatives from members of the IVD industry, specifically, BD, Gen-Probe Incorporated, Roche Diagnostics, and Roche Molecular Diagnostics. Concurrently with submitting this proposed guidance document to the agency, these representatives are also seeking input on the proposed guidance from other members of the IVD industry, including trade associations, as well as members of the clinical

03D-0334

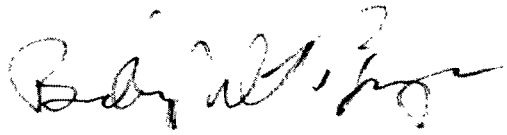
GDL 1

laboratory industry and clinicians. Therefore, we may in the future submit an enhanced draft to the agency based upon this input.

Please do not hesitate to contact me if you have any questions.

Respectfully submitted,

BAKER & DANIELS



By:_____
Bradley Merrill Thompson, on behalf of

Richard Naples, Roche Diagnostics
Karen Long, Roche Molecular Diagnostics
Patricia Shrader, BD
Glen Freiberg, Gen-Probe Incorporated

BMT/lrk
Enclosure

cc: David W. Feigal, Jr., M.D.
Steven I. Gutman, M.D.
Daniel E. Troy, Esq.

Version 06/17/03

In Vitro Analytical Tests (IVATs); Draft Guidance for Industry and FDA

Draft Guidance – Not for Implementation

This guidance document is being distributed for comment purposes only. Draft release for comment on: _____ ___, 2003

For questions regarding this document contact Steven I. Gutman, M.D., at (301) 594-3084 or by email at sig@cdrh.fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of *In Vitro* Diagnostic Device Evaluation and Safety

Preface

Public Comment

For 60 days following the date of publication in the *Federal Register* of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061 (HFA-305), Rockville, MD 20852.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/cdrh/[specific address], or CDRH Facts-On-Demand. In order to receive this document via your fax machine, call the CDRH Facts-On-Demand system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system. At the second voice prompt, press 1 to order a document. Enter the document number ((*Office GGP Rep will insert FOD number*) followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

Draft – Not for Implementation

In Vitro Analytical Tests (IVATs); Draft Guidance for Industry and FDA

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

Introduction

FDA has long been involved in regulation of test kits and systems. In particular, the agency has subjected test systems to general controls, which apply to all medical devices, and, when appropriate, special controls. Consistent with that approach, this document provides guidance to the regulated industry and the agency on a new category of *in vitro* diagnostic test ("IVD"), an *in vitro* analytical test ("IVAT") and an approach that may be used, under appropriate circumstances, to obtain a 510(k) premarket notification clearance for an IVAT. This guidance applies to any IVD for which the manufacturer chooses to pursue this analytical clearance, if the submission establishes analytical validity. The analytical requirements for the clearance will parallel the analytical data currently represented in diagnostic product package inserts. This document also addresses how IVATs will be regulated under existing FDA regulations.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be cleared for marketing. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document and that by creating this new category of 510(k) clearance, appropriately moderated the regulatory burden on FDA and industry for a specific category of products—namely IVATs. If, however, you believe that information is being requested that is not relevant to the regulatory decision for your pending application or that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Lease Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

Background

In recent years, FDA has made significant efforts to streamline the pre-market notification process in an effort to bring medical device technologies to market while simultaneously ensuring that the public health is adequately protected. For example, FDA has used its discretion to grant market clearance under the pre-market notification process to class II devices based on varying types of information, depending on the risk presented by the specific device, and has focused more on post-clearance requirements as a form of protection than on a pre-market analysis. Additionally, in our final guidance, *The New 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications*, we set forth the special and abbreviated 510(k) submission processes, which manufacturers may use in appropriate circumstances in lieu of the traditional 510(k) submission. This guidance document fits within that approach by bringing innovative technologies to market by an analytical clearance process, while protecting public health through appropriate labeling restrictions and post-market controls.

Definition of *In Vitro* Analytical Test ("IVAT")

An *in vitro* analytical test ("IVAT") is an *in vitro* diagnostic test ("IVD") for which analytical validity has been established. Analytical validity means the ability of a test to measure the property or characteristic that it was designed to measure (for example, specific mutations or analytical values in given units) by calculating such values as analytical specificity and sensitivity. Analytical sensitivity (i.e., minimum detection limit) means the lowest amount of an analyte that a test will detect when it is present in a specimen, and analytical specificity means the probability that a test will be negative when an analyte is absent from a specimen. Analytical sensitivity and specificity are usually expressed as percentages, copies per milligram or other appropriate unit. These concepts – analytical validity, specificity and sensitivity – are discussed in more detail below.

In vitro analytical tests are not restricted to a particular type of test – IVATs may be *any type* of test or test kit, as long as it meets these criteria (and the manufacturer obtains an analytical 510(k) clearance under 21 C.F.R. Part 807, Subpart E, as described more fully below).

Pre-Market Notification: Analytical 510(k) Clearance

In 21 C.F.R. 807.87, FDA established the content requirements for pre-market notification submissions to be submitted by device manufacturers in support of the substantial equivalence decision. FDA has, however, discretion in the type of information it deems necessary to meet the content requirements for pre-market notification submissions. For example, as explained above, in the *The New 510(k) Paradigm*, the agency set forth the requirements for special and abbreviated 510(k) submissions, which require different information than a traditional 510(k).

Consistent with that approach, this guidance document sets forth the pre-market clearance process by which manufacturers may obtain marketing clearance for *in vitro* analytical devices.

IVATs are subject to the requirements of 21 C.F.R. Part 807, Subpart E, and therefore must be cleared for marketing through a 510(k) submission. More specifically, IVATs will be cleared for marketing through an analytical 510(k) clearance that is based on review of the same analytical data that FDA now examines in premarket notification submissions. This guidance is complementary to the requirements of 21 C.F.R. 807.87 and other guidance documents on specific devices. Applicants may rely on other guidance documents as appropriate in preparing an analytical 510(k) submission. If an applicant chooses to use a device-specific guidance document in the preparation of an analytical 510(k) submission, the applicant should explain that in its submission and omit elements in the guidance that are needed only to support clinical claims beyond analytic claims. Because the amount of data that FDA will review in a 510(k) submission for an IVAT is less than that required in a traditional 510(k), the agency will make a determination of substantial equivalence within 60 days from the date of the submission.

The following section provides guidance to IVAT manufacturers on the content requirements for a 510(k) submission for an IVAT:

I. Device Description and Classification

IVATs are generic types of devices that are intended for use as *in vitro* diagnostic tests for the qualitative or quantitative measure of an analyte. Consistent with the claims for which they are cleared, IVATs will be classified by their analytical function. FDA believes that most of the existing classification regulations will apply to IVATs. These classifications are mainly found in 21 C.F.R. Parts 862 (Clinical chemistry and clinical toxicology devices), 864 (Hematology and pathology devices), and 866 (Immunology and microbiology devices). However, this should not be construed as a limitation to IVAT manufacturers. As always, manufacturers should identify the classification regulation that is appropriate for their particular device in their pre-market notification submission. See 21 C.F.R. 807.87(c). For example, 21 C.F.R. 864.7290 provides: "A factor deficiency test is a device used to diagnose specific coagulation defects, to monitor certain types of therapy, to detect coagulation inhibitors, and to detect a carrier state (a person carrying both a recessive gene for a coagulation factor deficiency such as hemophilia and the corresponding normal gene)." An IVAT for a factor deficiency test should show that a test for a carrier state, for example, was analytically valid (and must meet all other applicable requirements in 21 C.F.R. Part 807, Subpart E). However, the pre-market notification submission for the IVAT would not show a clinical application for that particular classification or the normal range for the analyte using that test. The laboratory must establish normal ranges for IVATs. Additionally, when deemed appropriate by the agency, applicants may also submit a *de novo* analytical 510(k) when a 510(k) submission has failed for lack of substantial equivalence to a predicate device. For more information on the *de novo* 510(k), please consult our guidance, *New Section*

513(f)(2): Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff.

In the IVAT 510(k), the submitter needs to provide the following information:

Generic device description

Code: Analyte specific test or test kit

Classification: I or II

Classification Panels: Clinical Chemistry (75), Hematology (81), Immunology (82), or Pathology (88)

Review required: Premarket Notification 510(k)

Regulation Section: Identify the specific classification regulation in 21 C.F.R. Part 862, 864, or 866

Identification: Describe IVAT here.

II. Identification of Predicate Device/Substantial Equivalence

A premarket notification submission should provide evidence that a device is, for its intended use, substantially equivalent to a legally marketed device in the United States (i.e., a predicate device). A predicate device can be any legally marketed device that was or is currently on the U.S. market and that is not in class III.

The agency has long been flexible in its consideration of predicate devices. For example, applicants may compare their device to one or more devices to support their substantial equivalency claims. Additionally, the performance of the device can be established by comparison to the predicate device(s) and/or by studies to determine the performance characteristics of the device. Consistent with its intention to make the analytical clearance process available for innovative technologies, the agency intends to continue this flexible approach with IVATs.

III. Administrative

The requirements for a premarket notification submission are given in 21 C.F.R. Part 807, Subpart E, and should be consulted before filing an application with the agency. Specific requirements include:

1. A 510(k) summary of safety and effectiveness information as described in 21 C.F.R. 807.93 or a 510(k) statement stating that such information would be

made available to interested individuals upon request as described in 807.93. Safety and effectiveness information refers to information in the premarket notification submission, including adverse safety and effectiveness information, which is relevant to an assessment of substantial equivalence. The information could be descriptive information about the new and predicate device(s) or performance information.

2. A statement that the applicant believes, to the best of his/her knowledge, that all data and information submitted are truthful and accurate, and that no material fact has been omitted as set forth in 21 C.F.R. 807.87(j).

3. An indication for use statement with all of the intended uses of the device described, but without clinical ranges for normality.

4. Documentation/data required by established special controls for these devices.

5. A table of contents and accurate pagination with consecutive numbering.

IV. Indications for Use

The indications for use statement should describe the analyte that the IVAT is intended to measure. The following is a suggested indications for use statement:

> Clinical Chemistry (75) or Hematology (81) or Immunology (82) or Pathology (88) – The (trade name) IVAT is a device intended for use in the measurement (or detection) of (specify the analyte(s)).

A separate optional form is available for the indications for use statement from the Office of Device Evaluation.

V. Validation of Specific Performance Characteristics

Analytical validation is the action or process of proving that a procedure, process, system, equipment, or method used works as expected and achieves the intended result. Thus, the IVAT manufacturer should provide assurance that the test does what it is supposed to do, i.e., the test accurately measures either the property or characteristic that it is expected to measure. For example, the analytical validity of a genetic test defines its ability to measure accurately and reliably the presence of a sequence, a change or the genotype of interest.

FDA requests several types of data and statistical analyses in pre-market notification submissions to market *in vitro* diagnostic devices, depending on the intended use, technological characteristics of the device, and on analytical claims made by the manufacturer. The performance of the device can be established by comparison to any

legally marketed medical device with the same intended use (i.e., a predicate device) and/or by other studies to determine the operating characteristics of the device. In any event, the applicant must support all claims for substantial equivalence and specific performance characteristics for using the device with appropriate data, analysis and conclusions commensurate with analytical data in traditional 510(k) submissions. The applicant should summarize results and include explanations for unexpected results and any additional testing performed. The applicant may also use charts as part of the analyses and conclusions when appropriate. When evaluating an application, FDA may request raw unprocessed laboratory data.

As appropriate, an applicant should assess the following performance characteristics:

A. ***Design and Manufacturing***

Where required, product design, manufacturing, and controls must conform with applicable parts of the Quality System regulation (QSR) as set forth in 21 C.F.R. Part 820. Specifically, the following elements of IVATs should be well-characterized: design, any controls used including internal controls, unique conditions for producing IVATs, and composition of the IVAT. We require that submissions include analytical data that demonstrate that the IVAT performs accurately and reliably under given conditions; this may include:

1. ***Specimen/sample***

The applicant should identify the specimen/sample and also describe preparation and acceptance criteria where applicable, as well as methods for determining label incorporation and/or binding, where appropriate. The applicant should also describe specimen collection, storage, and handling conditions.

2. ***Assay Components***

The applicant should describe the assay components including, if applicable, buffers, enzymes, signal detection systems, instruments, and software. For example, if the assay is for use on a closed system, that system would be specified. If it is for an open system, examples may be given.

3. ***Controls and/or Calibrators***

An applicant should describe all negative and positive controls and should characterize these as internal and/or external. Where calibration is

required, the package insert should provide instructions or recommend a reference.

B. *Analytical Laboratory Studies*

1. *Validation of Cut-Off or Reference Range*

The cutoff concentration of an assay is the specific concentration of an analyte in a sample or specimen that is chosen as a limit to distinguish a presumptive positive from a negative test result. The applicant should explain the rationale for the determination of the assay cut-off(s). In particular, an applicant should furnish appropriate descriptive analytical information and laboratory data to show how the cut-off point (distinction between positivity and negativity) or reference range was determined by the assay. For example, the applicant could recommend a cut-off, using analytical data to support that recommendation, or the applicant could determine a point that is likely to become the cut-off, using precision/reproducibility studies to show the reliability of this point. In either event, as already noted, the laboratory using the IVAT would need to validate the cut-off under CLIA. When relevant to the test, the applicant should also describe population and prevalence issues that are relevant to the analytical portion of the 510(k) submission. As appropriate, the description should also define the statistical method used to determine the cut-off point(s), define the basis for the equivocal zone, if any, and present a Receiver Operator Curve (ROC) analysis of cut-off point selection, or other graphical representations for the decision on positive or negative results.

2. *Assay Range*

Where applicable, the applicant should validate the linear range of the assay with normal and abnormal specimens covering the entire reportable range of the assay.

3. *Effect of Excess Sample and Limiting Sample*

The applicant should investigate the sample concentrations and conditions that reproducibly yield acceptable results.

4. *Analytical Sensitivity*

Analytical sensitivity defines how effectively the test identifies the analyte that is present in a sample and is determined using samples with the

analyte. For example, the analytical sensitivity of a genetic mutation would be determined using samples with a known mutation, based on DNA sequencing, consensus finding (e.g., proficiency testing (PT) samples, controls available from cell banks), or comparison to a reference method (e.g., intra-laboratory method comparison or inter-laboratory sample exchange). It could also be based on a fluorescent probe compared to a cytogenetic stain result. With regard to immunological test kits, for example, sensitivity may be determined by end-point dilution, earliest detectable reactivity in groups of serially collected samples, comparison to (standard) reference materials, comparing results for an analyte-positive specimen with an analyte concentration determined by one or more independent methods, or other appropriate methods. An adequate statistical justification should support the chosen sample size. In the case of diseases for which no standard reference materials are available (for example, a rare genetic disease), the applicant should state the limitations on analytical sensitivity imposed by the supply of samples. The applicant should also consider factors such as the number of different analytes to be tested and available supporting literature in the calculation of the sample size. Submitters should report their estimates with associated confidence intervals.

5. ***Analytical Specificity***

Analytical specificity defines how effectively the test correctly classifies samples that do not have the analyte. Analytical specificity is determined using samples that are truly negative. An applicant should ensure that negative samples are determined by reference methods. Alternatively, an applicant may generate test samples and *verify* that those testing positive are true positives by performing testing by another reference method. This approach will reveal any false positives. The applicant should use the confidence intervals described above in analytical sensitivity. To determine analytic specificity, the applicant should use at least as many samples as were used for analytic sensitivity. In appropriate circumstances, an applicant may also determine specificity, for example, by searching Genbank (National Center for Biotechnology Information, http://www.ncbi.nlm.nih.gov) or other comprehensive nucleic-acid databases for similarity between sequences of the assay's analyte-specific reagents and those of other entities or by performing nucleic-acid detection studies on well-characterized isolates and strains of microorganisms (e.g., American Type Culture Collection (ATCC) or WHO reference strains).

6. *Interfering Substances*

The term interference describes the effect that a compound, whether exogenous or endogenous, has on the accuracy of test measurement. The applicant should test, using the assay system, potentially cross-reacting or interfering substances encountered in specific specimen types or conditions, for example, temperature, time, hemolysis, lipemia, microbial contamination, or additional analytes or autoantibodies present. Similarly, the applicant should evaluate the potential for cross-reactions with appropriate substances that may occur commonly along with the analyte of interest. The agency also suggests that the applicant verify that recommended storage conditions are compatible with the assay. Specifically, the applicant should state the optimal conditions based on specimen storage stability studies.

7. *Precision/Reproducibility*

Precision is the ability of a test to produce the same value during repeated measurements. For a quantitative test, the precision of the test is the closeness of agreement between independent results of measurements obtained under stated conditions. The applicant should consult NCCLS EP-5A and EP-12A for more information on reproducibility studies, http://www.nccls.org/. For qualitative tests, repeat testing of samples under identical conditions should be performed, and agreement of results reported.

8. *High Dose Hook Effect Studies*

If applicable, an applicant should test a sample with the highest value available, serially diluted and undiluted. Consistent with these test results, the applicant should state in the Performance Characteristics section of the package insert the level at which high-dose need was detected and a procedure for the user to follow to correct the problem.

C. *Data Processing*

We recommend that the applicant describe the optimization of multiple simultaneous target detection and/or differentiation (for example, hybridization conditions, concentration of reactants, and control of specificity.) The applicant should also describe the IVAT's potential for sample carryover, as well as computational methods for data processing. The agency recommends that the applicant develop computational methods using the CDRH software development and validation guidance documents that are available at

http://www.fda.gov/search/databases.html. Finally, the applicant should describe any limiting factors of the IVAT.

D. *Validation of Instrumentation*

If an IVAT will be supplied by the applicant as a system, the agency recommends that the applicant validate instruments used in the assay, as appropriate. For example, the application should characterize instruments used in the assay, including how the instrument assigns values to or interprets assay variables such as feature location, size, concentration, volume, drying of small samples, effect on small volume reactions and its impact on test results. Furthermore, as appropriate, the application should also describe instrument calibration and sources and estimates of uncertainties in results introduced by hardware components. The agency's expectation is that instrument systems will be cleared under traditional 510(k)s.

E. *Reagent Characterization*

As appropriate, the submission should also provide a brief description of the reagents used in the assay. Additionally, if any recombinant technology was used in the preparation of the antigen(s), the submission should describe the method used.

F. *Reconstitution Stability*

According to Quality Systems Regulation, the manufacturer must maintain a file on the stability of all the components of the device. The manufacturer does not have to submit these data to FDA, but must be able to provide the data in summary form it if is requested to establish safety and effectiveness of the device.

The above provides a summary of the analytical data that may be appropriate in an analytical 510(k) submission. Applicants may want to look to additional guidance documents for instruction on issues that are not unique to IVATs. Additionally, as explained above, applicants may also rely on other device-specific guidance documents in preparing their analytical 510(k) submission, omitting the elements that are only required to support clinical claims, beyond analytic claims.

VI. Correlation Studies

Where correlation studies are appropriate to establish performance of an IVAT, a sponsor may support its submission in a variety of ways. First, the sponsor could compare the IVAT to another device. This method would utilize results of correlation or comparison studies with another well-characterized, predicate device and would usually be reported

as percent agreement. Second, the sponsor could compare the IVAT to a reference method, when available. This method would utilize results of comparison or correlation studies to a validated reference method and is usually reported as sensitivity and specificity. Third, the sponsor could do a resolution of comparison discrepancies. If this method is used, the sponsor should report results of discrepancy testing, and resolution should be performed using only unbiased statistical techniques. A fourth method is to identify analytical/technical false positive or false negative results, including estimates of expected assay failure rates. A final method is to evaluate tests by employing quantitative measurement techniques, including evaluation of random and systematic error in comparison to the predicate or reference method.

VII. Labeling

The sponsor should ensure that the labeling complies with Section 502(a) of the Act, that the directions for use are not false or misleading, and that as required by Section 502(f)(1) of the Act, directions for use are adequate (Section 201(n) of the Act defines misbranding due to misleading labeling). The following are *additional* points to consider in applying the Act and the *in vitro* diagnostic device labeling regulations, 21 C.F.R. 801 and 809.10(a), (b).

A. *Indication for Use*

Both the label and the labeling accompanying an IVAT will need to describe the indications for use of the test as required by 21 C.F.R. 809.10(a)(2), (b)(2). However, IVAT manufacturers should not make clinical utility claims (for example, normal ranges using the assay) in their labeling, advertising or other promotional materials. Additionally, to avoid being subject to an FDA enforcement action, IVAT manufacturers are encouraged to incorporate the warnings and disclaimers discussed below in their labeling.

B. *Warnings and Disclaimers*

The regulations require the label and labeling of an IVAT to contain the standard disclaimer "For In Vitro Diagnostic Use," as well as any other limiting statement that is appropriate to the intended use of the test. 21 C.F.R. 809.10(a)(4), (b)(5)(ii). FDA believes that a statement providing that a clinical evaluation of the test has not been submitted to FDA, along with the proprietary and established name of the IVAT, is an appropriate accompaniment of the intended use statements for IVAT tests and suggests the following language: "This test has received analytical clearance by the U.S. Food and Drug Administration. [Where applicable:] Its appropriate role in diagnosis has not yet been evaluated." FDA will use its enforcement discretion to prosecute IVAT manufacturers that do not

incorporate an appropriate limitation statement with the intended use statement or promote beyond the boundaries of the analytical clearance.

C. *Expected Values*

The labeling of IVDs is also required to state the ranges of expected values for the product. 21 C.F.R. 809.10(b)(11). With regard to this requirement, an IVAT manufacturer or distributor should provide only the analytical ranges tested or a statement of "positive" or "negative" for qualitative tests. For example, in the case of a genetic test or other qualitative test, absence or presence of an analyte (e.g., a gene or gene product) would not be accompanied by the clinical implications, just that the analyte, gene or gene product was measured as present or absent. Similarly, in the case of a quantifiable genetic product, (e.g, Fragile X syndrome), the number of base pair repeats quantified would be an acceptable analytical result. Manufacturers or distributors that provide "normal" clinical ranges would be at risk of being subject to an enforcement action, as the agency believes that this implies that the test has been cleared for a clinical indication.

Consistent with the clearance for IVATs for analytical claims, FDA encourages IVAT manufacturers to confirm to FDA that the manufacturer will sell IVATs only to clinical laboratories regulated under the Clinical Laboratory Improvement Amendments of 1988 ("CLIA") as qualified to perform testing under 42 C.F.R. Part 493. With regard to the 510(k) summary, IVAT sponsors will not be required to submit a description of the clinical uses for the device, as is contemplated in 807.92(a)(5), although some literature submitted to FDA may discuss the clinical uses. Similarly, the sponsor does not need to submit any clinical data, so there would be no such data to discuss under 807.92(b). A sponsor should, however, discuss all non-clinical testing as contemplated by that subsection.

VIII. Other Considerations

A. *A Note on the Use of Published Literature*

Peer-reviewed literature may be used to support the analytical validity of a test, provided that an applicant can make an adequate justification and explain how the cited literature is directly applicable to the subject test. FDA will use the following factors to determine whether literature-based evidence is acceptable:

- the test that is the subject of the article is comparable in design and performance to the test that is the subject of the submission (similar identity), such that the results of the literature are directly applicable to the proposed test

- the information reported in the referenced article(s) constitutes valid scientific evidence
- the referenced articles have been published in well-recognized, peer reviewed scientific journals
- the findings across the reported studies are consistent or the differences can be explained
- the same protocols and methodologies are used in the referenced article and in the study protocol for the in-house test, or failing that, an reasonable explanation of the differences is provided along with justification for the use of the article.
- the article(s) of interest contain sufficient, detailed, objective data for all those sections in the submission for which it is cited

The quality and detail of the data in the referenced literature will affect the ability to rely on those reports. The published literature frequently does not contain complete, or entirely accurate, description of all the information needed to fill the submission. These factors may reduce the value of the referenced literature in some cases, and might preclude its use as direct supporting evidence of safety and effectiveness. Therefore, an applicant should evaluate selected articles for their acceptability. Access to the underlying data and other detailed information that is not provided in a referenced article increases its value as either supporting or sole evidence for the submission.

B. *Clearance for Marketing*

Upon submission of an IVAT 510(k), FDA will review the submission and within 60 days will make a determination regarding whether to clear the IVAT for marketing. Should FDA have questions for the product sponsor toward the end of the 60 day review period, those questions will be sent to the sponsor with complete comments on the proposed package insert. When the agency clears an IVAT for marketing, the IVAT submitter may make analytical claims with regard to the test. That is, manufacturers may claim that their test measures the property or characteristic that it is designed to measure. IVAT manufacturers that make claims with regard to the clinical application of the test or clinically normal ranges will be subject to an enforcement action. In order to make clinical claims with regard to a device, manufacturers will be required to pursue a traditional 510(k) clearance based upon sufficient clinical data, as determined by FDA. Therefore, FDA encourages manufacturers to continue actively collecting data and pursuing a full 510(k) clearance, which will then enable them to make claims about the clinical application of their device. The analytical clearance will not

result in any FDA export restrictions that are different than other products cleared by the 510(k) process.

C. ***User Fees***

IVAT pre-market notification submissions are subject to the Medical Device User Fee and Modernization Act of 2002 ("MDUFMA").

Additional Regulations

As medical devices, IVATs are subject to other regulations, including:

A. ***Device Registration and Listing***

As medical devices, IVATs are subject to the device registration and listing requirements. See 21 C.F.R. Part 807.

B. ***Quality System Regulation (Good Manufacturing Practices)***

As IVDs, IVATs would automatically be subject to existing good manufacturing practices under the quality system regulation. Consistent with this, IVAT manufacturers are subject to routine inspections to ensure compliance with the GMP requirements.

C. ***Medical Device Reports***

Manufacturers and importers of IVATs will also be subject to medical device reporting ("MDR"). The MDR regulations contemplate that medical device reports may be submitted by three different entities: (1) manufacturers, (2) importers, and (3) user facilities. See 21 C.F.R. Part 803. The agency believes that with respect to these entities, the MDR regulations will apply as they do to all other medical devices.

D. ***Corrections, Removals and Recalls***

IVATs will also be subject to the applicable regulations on corrections and removals that typically apply to medical devices. See 21 C.F.R. Parts 7 and 810. Similarly, IVAT manufacturers are also subject to all recall regulations. This means that they will be able to avail themselves of the voluntary recall provisions and will also be subject to, although rare, mandatory recall by FDA.

A Note on Clinical Laboratories

This guidance document is not intended in any way to supercede or modify CLIA and its application to clinical laboratories. While clinical laboratories may register, list, and obtain analytical clearance for any IVATs they wish to make, as contemplated by this guidance, we anticipate that laboratories will typically be users of IVATs rather than manufacturers. The agency contemplates that clinical laboratories will remain subject to CLIA requirements for validation. The guidelines for CMS surveyors provide for inspection of the files showing that laboratories adequately validate their tests.