This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

Guidance Document for the Submission of Tumor Associated Antigen Premarket Notifications, [510(k)], to FDA

This document is intended to provide guidance in the preparation of a regulatory submission. It does not bind the FDA or the regulated industry in any manner.

Office of Device Evaluation
Division of Clinical Laboratory Devices
Immunology Branch

Document issued on: September 19, 1996

While this guidance document represents a final document, comments and suggestions may be submitted at any time for Agency consideration by writing to Peter E. Maxim, Ph.D., Chief, Immunology Branch, Food and Drug Administration, Center for Devices and Radiological Health, 2098 Gaither Road, HFZ-440, Rockville, Maryland 20850. For questions regarding the use or interpretation of this guidance, contact Peter E. Maxim, Ph.D. at (301) 594-1293.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Devices and Radiological Health

GUIDANCE FOR SUBMISSION OF TUMOR MARKER PREMARKET NOTIFICATIONS [510(k)s] TO Food and Drug Administration

Guidance Document For Submission of
Tumor Associated Antigen Premarket Notifications, 510(k), to FDA

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I. Summary

This document represents current FDA thinking and provides suggestions for 510 (k) submissions of Tumor Associated Antigen *in vitro* diagnostic devices employing immunochemistry methodology. It is based on 1) current basic science, 2) clinical experience, 3) the Safe Medical Device Act of 1990 and 4) FDA Code of Federal Regulations (CFR). As advances are made in science and medicine, these review criteria will be evaluated and revised as necessary.

II. Purpose of Guidance:

The purpose of this document is to provide guidance and clarification on the types of information and data needed by the Food and Drug Administration (FDA) before a device intended to measure tumor-associated antigen levels in serum, plasma, or other body fluids can be cleared for monitoring cancer patients.

A premarket notification [510(k)] submission must provide evidence that the device is accurate, safe, effective and substantially equivalent to a device legally marketed in the United States.

This document is an adjunct to the CFR and FDA 87-4224, The *In Vitro* Diagnostic Devices: Guidance for the Preparation of 510(k) Submissions manual. It is not to supersede those publications, but is to provide additional guidance and clarification on what information is necessary before the FDA can clear a device for marketing. We hope this will lead to more reliable, reproducible, and standardized commercial tests.

III. Definition of Device:

This generic type of device is intended for use in clinical laboratories as an *in vitro* diagnostic test for the qualitative or quantitative measurement of tumor-associated antigen levels in serum, plasma or other body fluids by immunoassay methodologies. This generic type of device does not include tissue receptor assays, immunohistochemical stains, or direct tests for oncogenes of other genetic markers associated with a predisposition to development of certain cancers.

Product Codes:	analyte specific
Classification:	Class II
Panel:	Immunology (82), Chemistry (75), Hematology (81), and Pathology (88)
Review Required:	Premarket Notification 510(k)

Regulation Section: 21 CFR Part 866.XXXX; Part 862.XXXX; Part 864.XXXX Tumor Associated Antigen Immunological Test Systems

Identification: A Tumor Associated Antigen Immunological Test System is a device that consists of a set of reagents used to measure, by immunochemical techniques, the levels of tumor-associated antigens in serum, plasma or other body fluids. Measurement of tumor-associated antigen levels may aid in the monitoring of patients for disease progression or response to therapy or for the detection of recurrent or residual disease. Tumor-associated antigen immunoassay systems intended for use in screening for the early detection or diagnosis of cancer in either the general population or in a high risk population, or in disease staging, are not included.

This category of devices does not include tissue receptor assays, immunohistochemical stains, or direct tests for oncogenes or other genetic markers associated with a predisposition to development of certain cancers.

A. Introduction

FDA began regulating tumor-associated antigen test systems as licensed biologicals in 1973. As a result of the Medical Devices Amendments of 1976, they were designated Transitional Devices and placed by statute into class III. This action was based on concerns at the time that the clinical application of these markers was, as yet, unsubstantiated. FDA has approved several specific types of serum tumor markers including: Carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), prostate specific antigen (PSA), CA 125 (residual epithelial ovarian cancer) and soluble Interleukin-2 (IL-2) receptor. A petition to reclassify such products was filed in 1995, proposing all tumor associated antigen tests used for monitoring be placed into class II. A review of the clinical history of these devices indicated that the use of special controls could provide adequate assurance of safety and effectiveness for use of the devices. This document is intended in part to serve as a special control for these devices.

These tests can be placed into several broad categories including the following:

- Oncofetal proteins, such as carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP).
- Hormones, such as ACTH, calcitonin, and human chorionic gonadotropin (HCG).
- Organ-specific antigens, such as prostate specific antigen (PSA).

- Monoclonal antibody-defined antigens, such as tumor associated glycoproteins CA 125, CA 19-9, CA 72-4, and CA 15-3.

- Enzymes, such as prostatic acid phosphatase.

Measurement of tumor associated antigen levels in various body fluids can aid in the monitoring of certain cancers. Monitoring is defined here as assessing the progression of tumor growth or as assessing the response of a tumor to therapy. This includes the serial measurement in patients with histologically confirmed diagnoses who are undergoing therapy for residual or advanced disease. Increasing tumor marker concentrations are indicative of progressive disease, decreasing concentrations often are indicative of response to therapy and constant serum tumor marker levels are associated with stable disease. Monitoring is further defined as serial measurements used as an aid in the detection of recurrent or residual disease in patients following primary curative treatment. Sustained elevations in marker concentrations are suggestive of residual disease, whereas increasing concentrations are indicative of recurring disease.

IV. Administrative

The requirements for a premarket notification submission are given in 21 CFR Part 807, Subpart E and should be consulted before filing an application with the FDA. Specific requirements that are often absent from submissions include:

1. A 510(k) summary of safety and effectiveness information as described in § 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, that is relevant to an assessment of substantial equivalence. The information could be descriptive information about the new and predicate device(s), or performance or clinical testing information.

2. A statement that the submitter 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 § 807.87(j).

3. An indications- for- use statement with all of the proposed clinical indications and intended uses of the device described. A separate form is available for this.

4. Documentation/data described in the special controls for these devices.

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

V. Instructions

Provide a concise discussion to include the following, as appropriate. Support the statements throughout the document with key literature citations or data.

1. Clinical indications, significance and intended use.

2 . Background description of the disease including the type of population affected (sex, age, etc.)

3. A brief historical summary of all test methodologies used to detect the serum tumor associated antigen levels.

4. Rules for determining statistical significance, and use clinical significance of test results. (An interpretative algorithm for appropriate test follow up, e.g. an upward pattern in test levels in successive time periods, or a test value exceeding a particular cutoff.)

5. Medical Significance of false positive and false negative results.

6. The clinical utility of this test.

7. The merits/advantages and limitations/disadvantages of the device methodology(ies) compared to other available clinical methodologies.

8. All specimen types/matrix(ices) used by the test methodology(ies). (Matrix is defined as the milieu containing the analyte in the patient specimen submitted for analysis.

9. A description of the technology/ methodology utilized in the device. Discuss the principles of the device methodology and whether it is well-established or new and unproven.

10. For new markers, a summary/discussion of the scientific and medical literature that relates the analyte to specific cancer(s) to be monitored. All device specific literature references should be included.

VI. Validation of Specific Performance Characteristics

FDA requests different types of data and statistical analyses in pre-market notification applications to market *in vitro* diagnostic devices. The type of data required depends on the intended use, technological characteristics of the new device, and on 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 and/or by other studies to determine the operating characteristics of the device. As an example, when the candidate 510(k) is declaring substantial equivalence to another legally marketed device, the information listed in VI (A) may be sufficient. For a new marker the information outlined in VI (A) and (B) may be required [excluding VI (A)(4)(a)].

All claims for substantial equivalence and specific performance characteristics for using the device must be supported by appropriate data. Clearly document all protocols for in house and external testing. Present test data results with analyses and conclusions. Summarize results and include explanations for unexpected results and any additional testing performed. Charts (scatter grams, histograms, etc.) may be used as part of the analyses and conclusions when appropriate. Raw unprocessed laboratory data may be requested.

A. Non-Clinical Laboratory Studies

1. Reagent Characterization

a. Characterize the antibody(ies) and antigens(s) used in the assay.

b. If any recombinant/monoclonal technology was used in the preparation of the antibody (ies) or antigen(s), describe the methods used.

2. Assay Specificity and Interfering substances

Any that are substances encountered in specific specimen types or conditions should be tested using the assay system, e.g., temperature, time, hemolysis, lipemia, microbial contamination, additional analytes, antibodies or other autoantibodies present.

Interfering Substances

Evaluate the potential for cross-reactions with appropriate substances that may occur commonly along with the analyte of interest i.e., anti cancer drugs, over-the-counter medications, dietary supplements, human anti-mouse antibodies (HAMA), etc.

3. Performance Characteristics

Include the following performance characteristics:

a. Analytical Sensitivity (If Applicable)

The analytical sensitivity or detection limit is defined as the lowest quantity differentiated from Zero. (95% confidence intervals or 2 standard deviations (SD) above the mean of the Zero control are commonly used). Run the Zero standard (Zero Diluent) at least 20-25 times in the same run and calculate the mean of the Zero standard and 2 SD of the mean (counts, OD's, etc.).

b. Linear Range

Validate the linear range of the assay with normal and abnormal specimens covering the entire reportable range of the assay.

c. Precision

The National Committee for Clinical Laboratory Standards (NCCLS) documents EP5-T2 and EP9-T recommend an experiment testing two clinically significant levels near medical decision limits (normal and elevated) of an analyte, in this case tumor associated antigens. Use controls simulating patient samples or actual patient specimens 3 times in the same run and in two different runs each day for 20 days. This permits separate estimation of between-day, between-run and within-day standard deviations (SDs), as well as within-run and total SDs.

i. Within-Run and Between-Run Variation Tests:

Calculate total, between- and within-day and between- and within-run means and coefficients of variation of imprecision for each set of values.

ii. Means, SD, and Coefficients of Variation

Report in the performance characteristic section of the package insert the appropriate means, SDs, and/or coefficients of variation with confidence levels according to number of times the sample is repeated. Report the number of runs per day.

d. High-Dose Hook Effect Studies

Test a sample with the highest value available, serially diluted and undiluted. 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.

4. Comparison Studies

a. Comparison to Another Legally Marketed Device

Compare the new device to a legally marketed device. Include the package insert for the legally marketed device.

It is recommended that a recognized reference method (if available) also be employed for comparison to enable a fair evaluation of the proposed device's performance characteristics, particularly if there are broad differences in methodology/technology between the new device and the legally marketed device. Evaluation of tests employing quantitative measurement techniques should include at a minimum an evaluation of random and systematic error in comparison to a legally marketed device. Comparisons may be direct between the two devices and/or indirect with the new and old devices compared to a reference method, definitive method, or designated comparative method. These studies should employ appropriate statistical analysis.

i. Linearity

When comparing two devices with substantially similar linear, performance, linear regression analysis may be used. Estimated slope and intercept and their 95% confidence intervals may be presented. When comparing two devices where one or both devices do not demonstrate linear performance or where the use of linear regression is not appropriate, other statistical evaluations, such as measures of concordance, McNemar's Test, etc., may be employed. For all tests, (and a requirement when statistically significant differences are noted between the new test and the legally marketed device) decision points for device use should be identified and an error analysis performed at each of these points.

ii. Reference Methods, Relative Sensitivity and Specificity

Where a legally marketed device or a recognized reference method is available, the relative sensitivity and specificity as determined by comparison to a legally marketed device or to a reference method may be determined and reported in the Performance Characteristics section of the package insert.

An assay may be determined to be quantitative only if a recognized reference material of known concentration is available for standardization of a calibrator or standard used in the assay to calculate the results.

If the same reference material is used in the new device as in the comparative device to substantiate the quantitative claim, comparison data may be presented to show correlation between the two assays when running the reference material as samples. Run the serially diluted reference material using the new device and the comparative device. Provide a linear regression analysis as described below.

Compare results obtained using positive tumor marker samples free from interfering substances from persons covering the whole assay range (from low to high levels of tumor markers).

Perform a linear regression analysis and report the slope, intercept. correlation coefficient, the assay range, and the nature of the samples tested. The statistical theory of linear regression analysis requires independence of data (i.e., only one sample pair from each patient) among various sample pairs for calculating slope, intercept, and their 95% confidence intervals.

iii. Resolution of Comparison Discrepancies

Discrepancies between the new device and the comparison method may be resolved using another recognized reference method or clinical diagnosis. Even when discrepancy resolution is done, unresolved performance statistics must still be given and should not be supplanted by resolved results, unless it can be shown mathematically that the resolved results are free of statistical bias.

5. Specimen Collection and Handling Conditions

State specimen collection, storage and handling conditions in the package insert and provide data or appropriate literature references in the submission to substantiate claims.

a. Verify that recommended storage conditions are compatible with the assay. State the optimal conditions based on specimen storage stability studies.

b. If the use of plasma is claimed, a study with each anticoagulant must be performed to show that each anticoagulant does not interfere with the assay.

For each anticoagulant, test an appropriate number of matched serum and plasma specimens which cover the working assay range.

c. If other matrices are claimed, studies must be performed to demonstrate that additives or preservatives do not interfere with the assay.

6. Stability

According to Good Manufacturing Practices (GMPs), the manufacturer must maintain a file on the stability of all of the components of the device. The manufacturer does not have to submit this data to the FDA, but must be able to provide the data in summary form if it is requested to establish safety and effectiveness of the device.

B. Clinical Evaluation Studies Comparing Test Performance to Accepted Diagnostic Procedure(s)

In order to demonstrate clinical utility as an aid in monitoring, evaluations of new tumor marker analytes should to demonstrate that the marker is a significant predictor of changing clinical status. This may be demonstrated by testing a suitable sample of patients and evaluating the predictive power of the marker against, or in conjunction with, other known clinical diagnostic variables (age, gender, disease stage, remission, recurrence and other conditions including prior treatment regimens). Appropriate statistical tests should be employed; e.g., logistic or discriminate regression analysis, to discern this in terms of clinical sensitivity, clinical specificity and positive and negative predictive power. Other approaches might also be used, such as Logistic Regression or Cox Regression, for measuring relative risk of recurrence associated with a positive test positive compared to a negative test result, if other relevant clinical variables with predictive power are included in the regression analysis.

1. Plan Clinical Evaluation Studies.

a. Support all diagnostic claims and specific parameters important for operating the device.
b. Describe all protocols for external evaluation studies. Clearly define the study population and inclusion and exclusion criteria and the chosen clinical endpoint.

c. Number of investigators: Use at least three investigators at separate sites with at least one in the United States.
d. Uniform protocols for all external evaluation sites must be established prior to study and followed consistently throughout the course of data collection.
e. Any changes in the study design should be clearly documented, justified, and reflected in data interpretation.
f. External evaluation studies must be performed under the review of an Institutional Review Board (IRB), when IRB oversight is required.

2. Sample Size: Sample size should be determined prior to beginning the clinical study. The sample size must have sufficient statistical power or ability to detect differences of substantial magnitude and clinical importance. In general, the sample size should be realistically obtainable. It is better to overestimate the size than to underestimate and need to justify an increase or an extension in follow-up. FDA takes into consideration the possibility of a "low" sample size with a disease condition having a low prevalence.

3. Sampling Method: Describe sampling method used in the selection and exclusion of patients. All statistical analysis is based on the "random sample" assumption (e.g., Probability sampling).

4. Pooling of Investigator's Data: Present test data with analyses and conclusions by each investigator and pooled over investigators, if statistically and clinically justified. This is justified when test performance was similar in each of the study sites with respect to the major endpoint variables.

5. Describe statistical methods used and provide confidence intervals for endpoint variables. Confidence intervals for proportions should be computed using the Binomial probability distribution unless the Normal approximation can be justified.

6. Representative Data: The data used to support the intended use claim for the device should be representative: it should be a sampling of all populations for whose use the device is intended, and of no other populations. For example, if the device is intended for women of child-bearing age, the sample should be of such women; children and post-menopausal women should not be includedunless data is used to demonstrate that device is inappropriate in such populations where they might otherwise be included.

   a. Include samples from individuals with diseases or conditions that may cause false positive or false negative results with the device, if appropriate. Ideally, a prospective study is preferred. However, if a

retrospective study is used, include all eligible patients who meet the patient selection criteria as specified in the protocol within the pre-specified collection time period. If any eligible patients are excluded from the study or any ineligible patients are included into the study, justify this fully. If only a sample of eligible patients is used, ensure that an appropriate statistical (probabilistic) sampling plan is used to justify the representativeness and unbiasedness of the sample data to the target population.

7. Account for all Patients and Samples. Perform appropriate data audits and verification before submitting to FDA. The specific reason for excluding any patient after enrollment in the study should be given.

8. Qualifications of Investigators

   List the names of the investigators and addresses of sites at which testing was performed. Give a one paragraph description of the credentials of each investigator to support the individuals suitability to investigate the device.

9. Responsibility of Principal Investigators of Clinical Studies

   When studies are performed at study sites other than the manufacturer's own facility, the responsible (principal) investigator(s) should sign off on the study indicating that a study protocol was in place, was followed throughout the study course, and that the investigator has reviewed and verified the data. Studies need to be monitored closely for adherence to protocol.

10. Quality Control for Studies Used in Submission

    Studies should be performed using appropriate methods for quality control. Data obtained when assays are out of control should not be used.

11. <u>Validation of the Clinical Decision point:</u>

    Furnish descriptive information and laboratory data to show how the cut-off point (distinction between positivity and negativity or medical decision limit) was determined and what performance characteristics the cutoff was intended to produce.

    a. Define the population(s) used, including the following information:

       i. Number of samples in the normal population with samples summarized according to appropriate demographic characteristics.

       ii. Number of specimens included in each disease group summarized

according to appropriate demographic characteristics.

iii. Geographical area(s) from which the population was derived.

iv. Graphical (e.g., scatter grams, histograms, etc.) representation of population characteristics.

b. The description of how the cutoff was determined should include the statistical method used (e.g. receiver operator curve).

c. Since the use of a single cutoff is dependent on the absence of the need for an equivocal zone, the absence of such a need needs to be established.

12. Reference Ranges

a. Normal Individuals

Number of Subjects: If the device results correlate well using linear regression (slope close to 1.0 and intercept close to zero) with a method that has a published reference range for healthy individuals. 40-60 subjects are sufficient to confirm agreement. If the device results do not correlate well, establish a reference range with samples from 120 to 200 normal persons and supply a characterization by age, sex, geographic location, any symptoms of disease and other factors that would influence the values obtained, e.g., pregnancy.

i. Statistical Method Used

State in the package insert the statistical method used to characterize the population.

b. Patient Groups (including related benign diseases and other malignancies)

A range of analyte values for samples from specified patient groups may also be provided.

i. Ranges for Diseases

Determine the ranges for which the device is intended. (include disease stage or status as appropriate, e.g., stage of malignancy with a tumor marker recurrence, remission, pre or post operative stage, therapy, radiation, chemo, surgery, menopausal state, age, etc.). See section 12 (a)(i), for the numbers of patients necessary to

confirm or establish ranges.

ii. False Results

Provide clinical reports of false positive and false negative results for each disease, if appropriate. Define the denominator and numerator used in the calculations.

13. Sample Types Claimed

Investigate all matrices claimed in the intended use statement.

14. Summary of Information Published and Unpublished Supplementary Data

Include a summary of all published and unpublished information and/or published clinical data pertinent to the device.

VII. Other Considerations

A. Devices Used for Generating Data for Submission

Studies should be performed with a product which is representative of the final product that will be marketed or that can clearly be related to that product thorough concurrent testing.

B. Statistical Methods for Evaluation of Device

The statistical methods used to evaluate a 510(k) submission should be appropriate for the study protocol, type of data collected and intended use of the device. The statistical methods used in the evaluation of a device should be selected from recognized sources and properly referenced in applicable submissions.

VIII. Labeling Considerations

A. Instructions

Assure that the labeling complies with Section 502(a) of the Act, that the directions for use are not false or misleading, and that according to Section 502(f)(1) of the Act, directions for use are adequate. (Section 201(n) of the Act defines misbranding due to misleading labeling.)

Follow 21 CFR § 809.10 for the requirements for labeling of in vitro diagnostic products. As stated in § 801.119, this will meet the regulations for compliance with

the Section 502(a) of the Act, Section 502 (f)(1) of the Act and 21 CFR Part 801, Labeling.

The following are additional details for some of the points in the above statues and regulations.

1. The Intended Use Statement [§ 809.10(b)(2)]

    a. Essential information:

        Provide a concise description of the essential information about the product to include the following information:

    b. Manufacturer's name.

    c. Product name.

    d. Whether the assay is a quantitative or qualitative, analyte.

2. Test methodology.

3. Special instrumentation requirements.

4. Specimen type(s).

5. Monitoring application:

    Whether it is for monitoring, recurrence or for response to therapy.

6. Clinical significance:

    Clinical significance, if it can be stated in a few words. (If the clinical significance is lengthy or complicated, create a separate heading entitled "Clinical Significance.")

B. Typical Intended Use Statement:

A typical intended use statement is: "ABC's companies (analyte) is an *in vitro* device intended for the quantitative determination of (analyte) levels in human serum or plasma. The test system is intended as an aid in monitoring cancer patients for recurrence of disease.

C. Conditions for Use

Describe any special applications of the device or specific contraindications or indications for use not addressed in the Intended Use Statement.

These conditions for use may be addressed further in either the Summary and Explanation, Limitations, or Performance Characteristics sections of the package insert.

D. Specimen collection and preparation for analysis [§809.10(b)(7)]

Include a description of:

1) Type of specimen:

   The type of specimen to be collected, e.g., plasma, serum, urine.

2) The amount of specimen required, both optimum and minimum.

3) Additives, preservatives, etc., necessary to maintain the integrity of the specimen.

4) Collection procedures:

   References for appropriate collection procedures including preservatives, e.g., NCCLS guidelines, textbooks, journals, etc.

5) Collection precautions:

   Special precautions regarding specimen collection including temperature and condition of the tissue, method of protein determination, etc. and special preparation of the patient (discontinued use of hormonal therapy, etc.) as it bears on the validity of the test.

6) Known interfering substances or conditions.

7) Handling of specimens:

   Storage, handling or shipping instructions for the protection and maintenance of specimens; and the length or stability of the specimens.

E. Procedure: Directions for Use [§809.10(b)(8)]

Instruction should be adequate for the intended site and user of the device.

F. Quality Control [§809.10(b)(8)(vi)]

Include the following information:

1) Controls:

Types of specimen or commercially available products that should be used for positive and negative control including recommended levels of analyte, if materials are not provided in the kit.

2) Quality control:

Recommendations for quality control parameters other than positive and negative controls, if appropriate.

3) Directions for performing quality control.

4) Interpretation of quality control:

Directions for interpretation of the results of quality control samples (satisfactory limits of performance).

5) Discrepancy of control results:

Conclude with a statement similar to the following: "If control results do not fall within stated parameters, assay results are invalid."

G. Limitations of the Procedure [§809.10(b)(10)]

1) Test limitations:

List important test limitations and all known contraindications, with references. This should include qualifications of personnel interpreting test results; that results should only be used in conjunction with other clinical and laboratory data; and the various patient and clinical factors that may affect marker levels; and those factors that should be considered when interpreting test results.

H. Expected Values [§809.10 (b)(11)]

Explain how to interpret test results:
1) Quantitative tests:

a) Ranges for defined disease groups and cut-off levels.

Interpretation of positive, negative, and equivocal/indeterminate/ borderline results including their clinical significance. This should be a description of clinical studies that includes false positives and false negatives. A warning should appear indicating that each lab should establish reference ranges for its own patient population.

The cut-off or threshold levels recommended for use with the device should be explained and justified.

b) How test results may vary depending on geographical location, age, sex of population studied, season of year, type of test employed, specimen collection and handling procedures, etc.

2.) Qualitative tests:

The cutoff or threshold levels recommended for use of the device should be explained and justified. Describe also criteria for borderline or equivocal results.

a) Provide a description of the clinical studies performed to establish the specificity and sensitivity of the device with adequate description of test negative and positive results. Appropriate 2x2 tables should also be presented.

b) How test results may vary depending on geographical location, age, sex of population studied, season of year, type of test employed, specimen collection and handling procedures, etc.

I. Performance Characteristics [§809.10(b)(12)]

1) Support data:

Summarize the data upon which the performance characteristics are based, e.g., accuracy, precision (repeatability), specificity, and sensitivity. The calculation of positive and negative predictive values requires knowledge about the prevalence of disease in the population sampled.

IX. Conclusion:

On December 1, 1995, the Immunology Devices Panel unanimously recommended that Tumor Associated Antigen Test Systems intended for monitoring be reclassified as class II medical devices. This document serves as guidance for the type of data and information that is needed for the FDA to review 510(k) submissions for these devices and serves as a special control for the reclassification. It is anticipated that this document will be revised

to accommodate advances in science and medicine, the development of additional voluntary standards and the experience of both the FDA and sponsors with these submissions.

X. References

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