Appendix 3A. Review Memorandum Template and Instructions for Assay and Instrument Combination Submissions

A. 510(k) Number:

Indicate the 510(k) tracking number assigned to the document.

B. Purpose for Submission:

Indicate the reason for submission of this 510(k), e.g., reagent formulation changes, labeling changes, software changes.

C. Measurand:

Identify the specific analyte to be tested.

D. Type of Test:

State whether the test is either quantitative or qualitative. Indicate the technology, e.g., ELISA, RT-PCR.

E. Applicant:

Provide name of the sponsor.

F. Proprietary and Established Names:

List all the proprietary and established names.

G. Regulatory Information:

1. Regulation section:

   Provide the relevant Code of Federal Regulations sections for the device, e.g., 21 CFR section 866.XXX, Tumor Associated Antigen Immunological Test System.

2. Classification:

   State whether the device is class I, II, or III.

3. Product code:

Indicate the specific analyte code for the device**.**

4. Panel:

   State the regulatory panel for the device: Chemistry (75), Hematology (81), Immunology (82), Microbiology (83), Pathology (88), Toxicology (91).

H. Intended Use:

State the final version of the intended use statement, i.e., as it will appear in the labeling of the device.

1. Intended use(s):

   State the specific intended use(s) for which the test will be used.

2. Indication(s) for use:

   State the specific indication(s) for which the test will be used.

3. Special conditions for use statement(s):

   Describe any special applications of the device (see 809.10) or specific contraindications or indications for use not addressed in the Intended Use Statement, if applicable, e.g., prescription use, OTC, waived, POC, home use.

4. Special instrument requirements:

   Briefly describe any special instrument requirements for the device.

I. Device Description:

Provide a brief description of the characteristics of the device, that is, the design, model, components, etc., (i.e., the make-up of the device).

J. Substantial Equivalence Information:

1. Predicate device name(s):

   In a list provide the name(s) of the legally marketed device(s) with the same intended use to which substantial equivalence is (are) claimed.

2. Predicate 510(k) number(s):

   In a list (in the same order as in J. 1. above) provide the 510(k) submission number(s) for the predicate device(s) for which substantial equivalence is (are) claimed.

3. Comparison with predicate:

   Provide a side-by-side comparison of the technological and analytical characteristics, for the new device and the predicate. For example, see table below:

Similarities		
Item	**Device**	**Predicate**

Differences		
Item	**Device**	**Predicate**

K. Standard/Guidance Document Referenced (if applicable):

List any recognized standards or relevant guidance referenced. Describe modification(s) to recognized standards (if any).

L. Test Principle:

Provide a description of the technology/ methodology utilized in the device. Discuss the principles of the device methodology, and indicate whether it is well established or new and unproven.

M. Performance Characteristics (if/when applicable):

The type of data to be provided in this section depends on the intended use, technological characteristics of the new device, and on claims made by the manufacturer.

1. Analytical performance:

   a. Precision/Reproducibility:

      i. Study design: Describe test methods. Include information such as sample types tested, number of samples or measurements, target concentrations. Indicate n for the parameters varied (e.g., observations, days, runs, operators, sites, lots, instruments, calibration). Describe statistical methods.

      ii. Results/Acceptance criteria: Include percent CV /Standard deviation for total and within-run precision (and other parameters e.g., between-site, between-instrument, where applicable).

   b. Linearity/assay reportable range:

i. Study design: Describe test methods. Include information such as sample types tested (e.g., unaltered patient sample, spiked or diluted patient sample, spiked patient pools, control material), target concentrations or range, number of samples, calculations/statistical methods. Include description of the test for high dose hook effect where appropriate.

ii. Results/Acceptance criteria: Identify the linear range and acceptable or maximum difference from linearity within the range.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Where applicable, briefly summarize the information about traceability of calibrators and method. Include, for example, methods and acceptance criteria for stability studies, traceability to reference material and description of value assignment, validation, and acceptance criteria.

d. Detection limit:

i. Study Design: Describe the test methods. Include information such as sample types tested, target concentrations/range, number of measurements, statistical methods. Describe which aspects of sensitivity were measured, for example: Limit of blank: usually mean of blank +2 to 3 SD, Limit of detection: lowest level detected > 95% of the time, Functional lower limit: Lowest analyte concentration where % CV is acceptable.

ii. Results/Acceptance criteria: Describe the sensitivity level for each measure of sensitivity assessed.

e. Analytical specificity:

i. Study design: Describe test methods. Include information such as sample types tested (e.g., samples spiked with interferent, samples naturally high in interferent etc.), concentrations or intervals of potential interferents or cross-reactants tested, and the concentration of intended use analyte (if present) in the sample. Define the comparator/control samples used (e.g. spiked samples containing analyte without interferent), statistical methods, definitions/calculations of cross-reactivity or recovery.

ii. Results/Acceptance criteria: Describe any interference observed (e.g., recoveries for interference levels tested). Describe any trends (e.g., "high levels of metabolite x may cause depressed results").

f. Assay cut-off:

Describe whether the cutoff was established previously in the literature (and whether it was established with this specific device) or in this submission. If the latter,

describe the study design including methods for determining the cutoff, including the population(s) studied (demographics/ selection/ inclusion and exclusion criteria, number of individuals included), reference method, or method of clinical diagnosis and statistical methods used to generate results. Define "gray zone," if applicable.

Results: sensitivity and specificity for chosen cutoffs values.

2. Comparison studies:

   a. Method comparison with predicate device:

      i. Study design: Describe test methods. Identify the comparator(s) (e.g., predicate device, reference method). Describe the sample type(s) (e.g., unaltered patient specimens, spiked or diluted patient specimens, spiked patient pools, and control material), matrix, number of samples, sample range. When appropriate include information such as number/types of sites, sample selection methods, inclusion/exclusion criteria, overall demographic description of patients represented by the samples (e.g., age, gender, race, how/whether samples represent the intended use population), number of individuals represented. Describe statistical methods used to generate results (e.g., regression methods, data exclusion, number of observations represented by each data point).

      ii. Results: Describe overall results and/or results for specific sites and patient groups, as appropriate. For quantitative tests, include information such as slope and intercept (with confidence intervals), correlation coefficient, measure of scatter around the regression line (e.g., sy..x), measure of bias at medical decision levels. In some cases, it may be helpful to include a graph (x-y graph or bias plot). For qualitative or semi-quantitative tests, include percent agreement with comparator for positive/negative samples, confidence intervals.

   b. Matrix comparison:

      i. Study design: For each matrix in the intended use, describe the method for comparison or determination of accuracy. Include information such as sample types tested, number of samples, sample range or target concentrations tested, and calculations/statistical methods.

      ii. Results/Acceptance criteria: Describe the accuracy of the new matrix or results of the matrix comparison.

3. Clinical studies:

   a. Clinical Sensitivity:

      i. Study design: Explain how "Clinical Truth" was determined. Include information such as method(s) of diagnosis, specimen types, patient demographics,

inclusion/exclusion criteria, number of specimens collected, (any discarded), number of individuals represented, number/types of sites, statistical methods. When appropriate include collection methods, other pertinent information.

ii. Results: Sensitivity, specificity, positive and negative predictive value with confidence intervals. Describe results for overall study and/or for specific patient groups or sites, as appropriate.

*b. Clinical specificity**:***

See Section 3.a.i.

c. Other clinical supportive data (when a. and b. are not applicable):

Provide other clinical supporting data such as clinical monitoring data, etc.

4. Clinical cut-off**:**

Describe whether the cutoff was established previously in the literature (and whether it was established with this specific device) or in this submission. If the latter, describe the study design including methods for determining the cutoff including the population(s) studied (demographics/ selection/ inclusion and exclusion criteria, number of individuals included), reference method, or method of clinical diagnosis and statistical methods used to generate results. Define "gray zone," if applicable.

Results: sensitivity and specificity for chosen cutoffs values.

5. Expected values/Reference range:

Describe whether the expected range was established in the literature (and whether it was established with this specific device) or in this submission. If the latter, describe the methods for determining the expected range including the population(s) studied (demographics/ selection/ inclusion and exclusion criteria, number of individuals), reference method or method of clinical diagnosis, statistical methods.

Results: Describe and define (e.g., 95th percentile) normal range values for relevant populations.

N. Instrument Name:

State the name of the manufacturer and the instrument name

O. System Descriptions:

1. Modes of Operation:

Describe modes of operation, i.e., random access, batch, stat, open tube, closed tube, automatic, mode.

2. Software:

   Describe the kind of software the system uses, i.e., operating system, user interface, data management, communications, laboratory information system. Also state whether FDA has reviewed the applicant's Hazard Analysis and Software Documentation previously.

3. Specimen Identification:

   Describe how specimens are identified, i.e., barcode, rack/position, instrument auto numbering.

4. Specimen Sampling and Handling:

   Describe how specimens are mixed (for whole blood), sampled (i.e., direct open tube or closed tube piercing), and handled (e.g., manual).

5. Calibration:

   Describe the calibration procedures for the system, i.e., use of whole blood and commercial calibration materials.

6. Quality Control (QC):

   Describe quality control procedures and use of commercial quality control materials. For Point-of-Care or home-use devices, i.e., handheld meters, describe any electronic QC procedures.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Describe any additional supporting information provided by the applicant that was evaluated as part of the substantial equivalence (SE) determination.

Q. Proposed Labeling

Indicate whether the labeling is sufficient and it satisfies the requirements of 21 CFR section 809.10.

R. Conclusion:

State the rationale for the SE decision.

S. Other Supportive Device and Instrument Information:

Describe any additional supporting information provided by the applicant that was evaluated as part of the review.

T. Administrative Information:

1. Applicant Contact Information:

   Report the mailing address and contact information of the applicant, and identify the contact person responsible for the information.

2. Review Documentation:

   Record all applicable information for the administrative record, e.g., the submission chronology, phone memos, faxes, e-mails, meeting minutes, discussions regarding labeling issues.

REVIEW MEMORANDUM
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:

B. Purpose for Submission:

C. Measurand:

D. Type of Test:

E. Applicant:

F. Proprietary and Established Names:

G. Regulatory Information:

1. Regulation section:
2. Classification:
3. Product code:
4. Panel:

H. Intended Use:

1. Intended use(s):
2. Indication(s) for use:
3. Special conditions for use statement(s):
4. Special instrument requirements:

I. Device Description:

J. Substantial Equivalence Information:

1. Predicate device name(s):
2. Predicate 510(k) number(s):

3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**

Differences		
Item	**Device**	**Predicate**

K. Standard/Guidance Document Referenced (if applicable):

L. Test Principle:

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   b. Linearity/assay reportable range:

   c. Traceability, Stability, Expected values (controls, calibrators, or methods):

   d. Detection limit:

   e. Analytical specificity:

   f. Assay cut-off:

2. Comparison studies:

   a. Method comparison with predicate device:

   b. *Matrix comparison:*

3. Clinical studies:

   a. Clinical Sensitivity:

   b. Clinical specificity:

   c. Other clinical supportive data (when a. and b. are not applicable):

4. Clinical cut-off**:**

5. Expected values/Reference range:

N. Instrument Name:

O. System Descriptions:

1. Modes of Operation:

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes _____ or No _____

3. Specimen Identification:

4. Specimen Sampling and Handling:

5. Calibration:

6. Quality Control:

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Q. Proposed Labeling:

R. Conclusion:

S. Other Supportive Device and Instrument Information:

T. Administrative Information:

1. Applicant Contact Information:

   a. Name of applicant:

   b. Mailing address:

   c. Phone #:

   d. Fax #:

e. E-mail address (optional):

f. Contact:

2. Review Documentation: