

510 (k) Review (Part 1)

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**Center for Devices and Radiological Health
(CDRH)**

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Questions Answered During Review

- Proof of concept – Intended use
- Do the benefits of using the results outweigh the risks of a false positive or false negative results?
- Is it necessary to restrict use of the test system to certain types of laboratories?
- Can effectiveness of the test system for its recommended use be reliably predicted from data and information provided?

OIVD Decision Summaries

- For products cleared since November 2003
- Find information:
 - What types of clinical studies were done by other manufacturers?
 - How FDA reviewed data to grant substantial equivalence?
- Go to <http://www.fda.gov/cdrh/oivd/>
 - click on *Find All In Vitro Diagnostic Products and Decision Summaries Since November 2003* under Approvals & Clearances (on the right)
 - search by test, company, or other key word
 - select a product from the list
 - scroll down to the entry marked Decision Summary

Objectives of the Pre-market Review

➤ **EFFECTIVENESS**

- Is the intended use claim supported by the data provided?
- Do the data demonstrate the device to be effective for its recommended use?
- Are the directions and conditions for use clearly stated?
- What about the warnings and limitations of the device?

➤ **SAFETY**

- What are the risks of misdiagnosis ?
- What are the potential medical and social consequences of misdiagnosis?

➤ **SUBSTANTIAL EQUIVALENCE**

- Is the device at least as effective as a legally marketed device not requiring a PMA?

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY/ASSAY-ONLY 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. Indications 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:
- K. **Standard/Guidance Document Referenced (if applicable):**
- L. **Test Principle:**
- M. **Performance Characteristics:**
 - 1. Analytical performance:
 - a. Precision/Reproducibility:
 - b. Linearity/assay reportable range:
 - c. Traceability, Stability, (controls, calibrators, 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
 - 4. Clinical cut-off:
 - 5. Expected values/Reference range:

Administrative Elements (Sections A-F)

- All the required forms (FDA-3601, FDA-3514, FDA-3674, etc.)
- Cover Letter with contact information
- Detailed Table of Contents
- 510(k) Summary
- Truth and Accuracy Statement

General 510(k) Submission requirements

- Information organized logically
- All pages numbered, sections separated by tabs
- A copy of the predicate labeling
- Copies of labeling for any assays used during the course of studies
- The clinical study protocol which was sent to the sites
- All raw data from analytical studies
- All line data from clinical studies
- All proposed labels, package inserts, service and operator manuals, instructions for use, advertising and/or promotional materials.

(G) Regulatory Information

Example: 21 CFR 866.3510

- Rubella virus serological reagents
- Class II
- CLSI guidelines (I/LA6, I/LA18, D13, EP5, EP10)
- CDC Controls:
 - a) low titer standard
 - b) reference panel (well characterized rubella sera)
- WHO – International Rubella Standard

(H) Intended Use

- Do the data support the intended use?
- Do the data demonstrate the device to be effective for its recommended use?
- Do the benefits outweigh the risks of a false positive or a false negative result?
- What limitations apply?

(I) Device Description

- Principle of the assay
- Assay components / Critical reagents
- Calibrators traceability
- Testing platform
- Sample requirements and preparation
- Signal generation
- Interpretation of results

(J) Predicate

- An FDA cleared device
- Side-by-side comparison (table or chart)
- Similarities and differences
 - intended use
 - indications for use
 - assay design
 - technology
 - performance
 - target population

(K) Standards

- CLSI guidelines
- FDA guidance documents

Note: Different from 'Reference Standard' or 'Reference Method'

(L) Test Principle

➤ Technology

Examples-

- Chemiluminescent Immunoassay
- ELISA
- Enzymatic colorimetric
- Colorimetric oxidation
- Radioimmunoassay
- NAAT

(M) Performance Characteristics

Types of FDA questions:

- Study design - described?
- Concentrations of samples - near the cutoff or medical decision points?
 - Informative in the context of intended use?
- All matrices evaluated?
- Pre-analytical steps included in the evaluation?

(M) Performance Characteristics

➤ Analytical

- Use patient samples, where appropriate
(Check decision summaries for acceptable samples)
- Establish basic performance parameters
- Use traceable reference materials and methods, if available

(M) Performance Characteristics

➤ Clinical

- Study design should include the target population
 - Signs and symptoms
 - Pregnant women (rubella)
- Prospectively collected samples strongly recommended

(M) Performance Characteristics

➤ Clinical (cont'd)

- Matrix considerations, depending on the sample types claimed in the intended use
- Urine vs. vaginal swabs for Chlamydia
- Nasal swabs vs. nasal wash aspirates for respiratory infections

(a) Precision/Reproducibility

- Develop a sample panel of 3-6 members
 - Use clinical matrix
- Cover the measurement range of the assay
- Levels below and above clinical decision points
- Qualitative assays
 - Prepare samples at concentrations near the cutoff
- Include all pre-analytical steps

Precision/Reproducibility

FDA SE Decision Summary

Example 1- ACE Diagnostics

Within-run and within-lab precision were determined at the manufacturer's site, using serum based QC materials, according to the CLSI EP-5A, with 2 replicates per run, two runs per day for 22 days, n=88 observations. Samples were randomized. Calibration was performed once a week. Results are shown below:

Sample	Mean IU/mL	N	Within-run SD	Within-lab SD
Level 1	4.0	88	0.36	0.39
Level 2	25.5	88	0.52	0.63
Level 3	56.5	88	1.2	2.3

Precision/Reproducibility

FDA SE Decision Summary

Example 1- ACE Diagnostics (Cont'd)

- Precision was also estimated using multiple patient serum pools across the range of approximately 3-5 IU/mL
- Standard deviations were calculated based on 8 replicates, for each of 3 reagent lots, i.e. total of 24 observations at each concentration. (One run per lot)
- Results: across the concentration range tested, SD's calculated for each lot and over all lots were < 0.4 IU/mL

Precision/Reproducibility 510(k)

Example 2 - RIVAL Diagnostics

Between-run precision studies were done on serum-based material at 3 levels using the *SuperFast* Instrument System. Results are summarized below.

	Sample 1	Sample 2	Sample 3
N	25	25	25
Mean ($\mu\text{g/ml}$)	0.3	0.8	1.4
SD	0.03	0.05	0.05
%CV	9.8	4.5	2.7

Precision/Reproducibility 510(k)

Example 3 -Preparation of Serum Pools

Confirmed positive samples were initially diluted in a negative serum pool (consisting of 8 individual sera, total volume ~ 2295ml) to create five samples:

HIGH NEG1	Target = 0.9*	Measured = 0.89
HIGH NEG2	Target = 0.9	Measured = 0.92
LOW POS1	Target = 1.1	Measured = 1.06
LOW POS2	Target = 1.1	Measured = 1.14
POSITIVE	Target = 2.0	Measured = 2.05

*(all concentrations expressed as COI)

Reproducibility data tables show 3 samples:

- HSP1 Mean = 0.960
- HSP2 Mean = 1.199
- HSP3 Mean = 2.184

Precision/Reproducibility 510(k)

Example 4- UserFriendly Diagnostics

- Intended use: The *User Friendly*® **Point of Care System** is intended to quantitatively measure YF analyte in serum, plasma or **whole blood** samples over the range of 0.5-10.0 mg/dL
- The clinical cutoff is **0.7 mg/dL**
- Two samples of serum controls (low and high) containing approximately 2.0 and 8.0 mg/dL YF analyte were each assayed in 3 runs over 15 days (n=45 per level)
- The % CVs were **15.2** for the low and **5.3** for the high sample.

(b) Linearity

(examples of FDA review questions)

➤ Study design:

- Sample types/preparation?
- Target concentrations-calculations?
- Traceable standards used?
- What methods of determination?
- Acceptance criteria?
- What statistical approaches used?

Linearity FDA SE Decision Summary

Example 5 - ACE Diagnostics

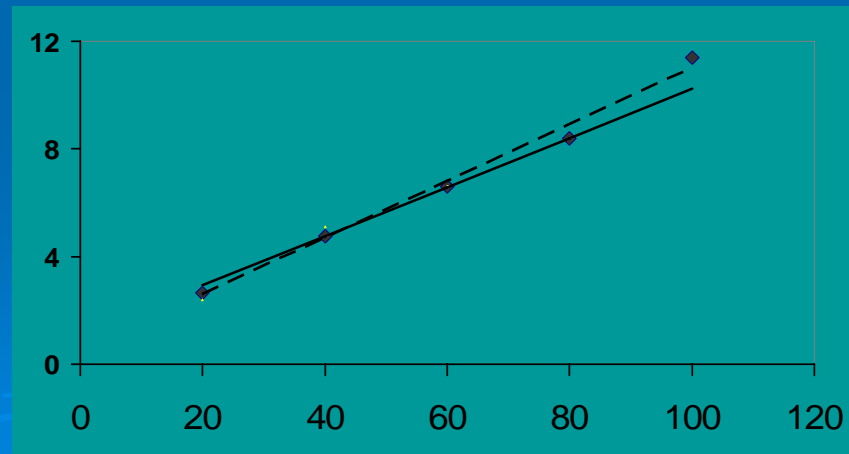
- A negative serum pool was spiked with a stock solution prepared from material traceable to WHO/USP standard to a concentration of 60 mg/ml analyte (“high pool”). The “high pool” was serially diluted with negative serum to prepare 10 samples with concentrations evenly distributed across the assay range.
- All samples were analyzed by the *Ace Diagnostics* assay in replicates (n=5) and average values determined.
- Expected concentrations were based on the independently quantified stock solution times dilution factors.
- For samples in the range of 2-60 mg/ml, observed/expected values were within the acceptance limits of +/-15%.

Linearity FDA SE Decision Summary

Example 6 - RIVAL Diagnostics

Serial dilutions of a suitable control were tested and the observed value compared to known expected or calculated expected result. Percent deviations were calculated. Linearity claim is based on percent deviations of $< 5\%$ at the 2 highest analyte concentrations.

_____ fit points 1-3
..... fit points 2-4



(d) Limit of Detection

- Minimum detectable concentration
- CLSI-EP-17 - *Protocols for Determination of Limits of Detection and Limits of Quantitation*
- What types of studies were done?
- LoD crucial in qualitative assays
- LoQ crucial in quantitative assays

(e) Analytical Specificity

➤ Interference

- Chemical

 - Hemoglobin (hemolysis)

 - Bilirubin

 - Triglycerides

- Cross Reactivity

 - Which organisms/substances likely to cross react?

 - Common antibodies (i.e. RA, CMV)

- Must use high titer /concentration of potential cross-reactants

(f) Assay Cutoff/Clinical Cutoff

- How was it determined?
 - Analytical samples?
 - Analysis of ROC curves?
 - Determine the best level of specificity, w/o sacrificing sensitivity
- CDC-based on epidemiologic studies
- International standards – traceability
- Secondary (working) standards

Method Comparison

(examples of FDA review questions)

- Description of the study design?
- How many sites?
- Were real clinical samples used? (vs. cell lines, control materials, etc.)
- Prospective vs. Retrospective samples
- Data stratified appropriately?
- Sensitivity/Specificity vs. % Agreement

Example 7 -Matrix Comparison Serum/Plasma Validation

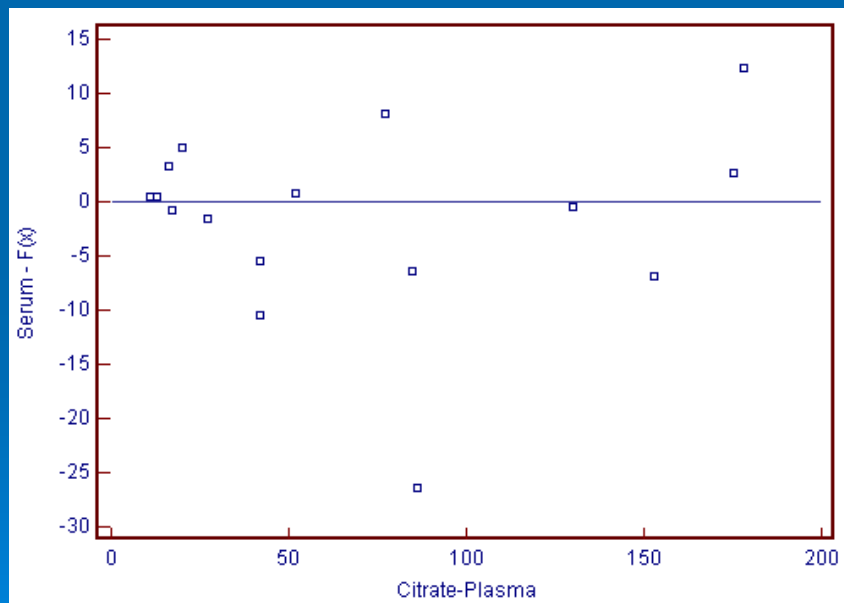
Information provided:

- Four quadruples of each the serum and the corresponding citrate plasma were serially diluted and the dilutions determined in [assay].
- The dilutions cover all concentrations in the diagnostically important range.
- Passing-Bablok regression was calculated.

Regression equation	$y = -2.28 + 1.07 x$
Intercept A = -2.28	95% C.I.: -6.27 to 0.83
Slope B = 1.07	95% C.I.: 0.98 to 1.16
- The ideal correlation was within the 95% C.I.'s of slope and intercept (n = 16).

Example 7 -Matrix Comparison Serum/Plasma Validation (cont'd)

No **significant deviation** from linearity was detected by means of the Cusum test. The results are shown in the diagram below.



Studies to Support Intended Use Claims

- Intended Use statement drives the review of the submission
- Carefully crafted Intended Use will determine the type of studies needed
- Example:

Device for the detection of IgG antibodies to Rubella virus

Example of Intended Use

For the quantitative determination of IgG antibodies to rubella virus in human serum and K₃ EDTA and sodium citrate plasma to aid in the assessment of a patient's immune status to rubella, including pregnant women and women of childbearing age. This assay is intended to be used on the *SuperPlus* Automated EIA Processor. This product is not FDA cleared for use in screening blood and plasma donors.

Intended Use – Part 1

"... quantitative determination of IgG antibodies to rubella virus in human serum and K₃ EDTA and sodium citrate plasma ..."

- ✓ Linear range?
- ✓ WHO reference standard?
- ✓ Traceability?
- ✓ CDC Panel testing?
- ✓ CLSI I/LA6-A – How many samples required for % positive and % negative agreement?
- ✓ Matrix testing completed?

Intended Use - Part 2

"...to aid in the assessment of a patient's immune status to rubella..." "

- ✓ Check the CDC current guidelines
- ✓ Established cut off in US is 10 IU/mL
- ✓ European cut off may be different
- ✓ Studies around the cut off will be essential
- ✓ Know your disease and clinical considerations

Intended Use - Part 3

“...including pregnant women and women of childbearing age”

- ✓ Was the appropriate patient population tested?
- ✓ Stratify the data by gender, age.
- ✓ Present data from pregnant women separately.

Intended Use - Part 3 (cont'd)

- The main intended use population (for a rubella assay) should contain (as per the CLSI document):
 - At least 100 negative specimens
 - At least 50 low positive samples (10-20 IU/mL)
 - At least 50 high positive samples (above 20 IU/mL).
- Satisfactory performance at cut off:
 - Point estimates of at least 95% for both, positive percent agreement and negative percent agreement with the predicate.

Intended Use – Part 4

“... This assay is intended to be used on the *SuperPlus* Automated EIA Processor”

- ✓ All analytical and clinical data must be generated on the claimed device
- ✓ All clinical samples must be also analyzed on the predicate device

Limitation: “Performance on automated equipment other than *SuperPlus*... has not been established”

Intended Use – Part 5

“...This product is not FDA cleared for use in screening blood and plasma donors.”

Limitations, as relevant to the device:

- Studies in sub-population of prenatal women?
 - No – “Performance characteristics have not been established for pre-natal screening”
- Studies in sub-pop of newborns?
 - No – “Performance characteristics have not been established for newborns”
- Studies in immunocompromised patients?
 - No – “Performance characteristics have not been established in immunocompromised patients”

Common Problems

- Unorganized submissions
- Poor analysis of data
- Missing data
- Administrative gaps, missing documents
- Apparent lack of monitoring/auditing of clinical sites

Tips /Notes

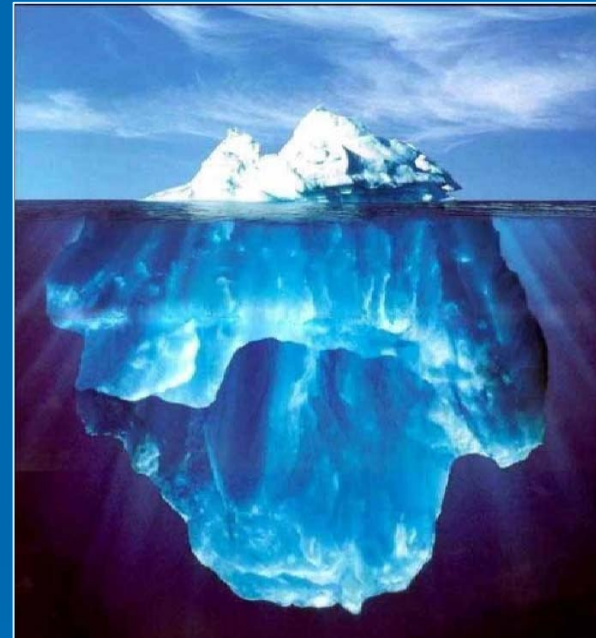
- Perform quality review before sending your submission to FDA
- Avoid inconsistencies (we will find them)
- Utilize the published decision summaries for predicates to answer questions related to your device
- For difficult questions, contact OIVD

We are your partners!

Information: CDRH Homepage

www.fda.gov/cdrh

- **Device Classification Database**
- **Device Advice**
 - <http://www.fda.gov/cdrh/devadvice>
- **Register for “What’s New”**
- **Guidance Documents**
- **Device regulation and guidance**
 - <http://www.fda.gov/cdrh/devadvice/ide/index.shtml>
- **Much more...**





THANK YOU

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