510 (k) Review (Part 1): Decision Summaries

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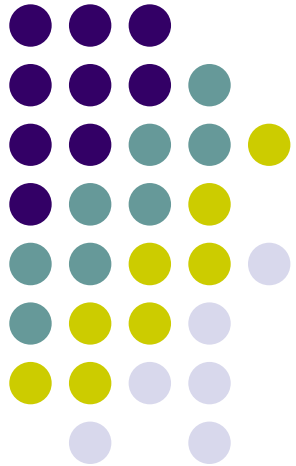
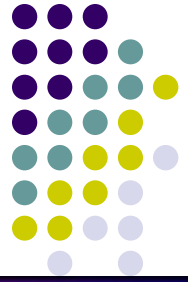
Center for Devices and Radiological Health (CDRH)

April 25, 2011



Objectives of the Pre-market Review



- **EFFECTIVENESS**
  - Is the intended use 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?

OIVD Decision Summaries

- Allows manufacturers to see what was done for similar devices
- All decision summaries are posted online 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

-OR-

  - Go to http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
  - search by test, company, or other key word
  - Click on FDA Review - Decision Summary

510(k) SE DETERMINATION DECISION SUMMARY TEMPLATE

A. 510(k) Number:

B. Purpose for Submission:

C. Measureand:

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:

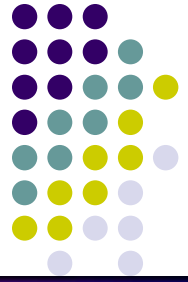
2. Comparison studies:
- a. Method comparison with predicate device:
- b. Matrix comparison:

3. Clinical studies:
- a. Clinical Sensitivity:
- b. Clinical specificity**:**
- c. Other clinical supportive data

4. Clinical cut-off:

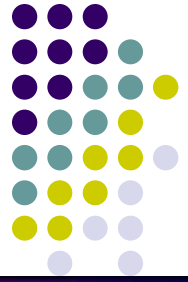
5. Expected values/Reference range:

General 510(k) Submission Requirements



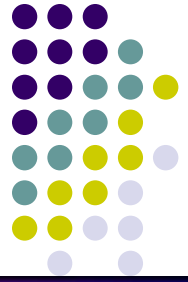
- All the required forms (FDA-3601, FDA-3514, FDA-3674, etc.)
- Cover Letter with contact information
- Detailed Table of Contents
- 510(k) Summary
- Truth and Accuracy Statement

General Items to Include with your 510(k) Submission



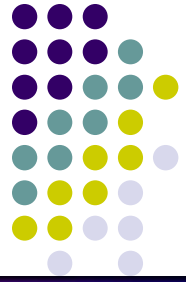
- Information should be organized logically
  - All pages numbered
  - Sections separated by tabs
  - Include a detailed TOC
- A copy of the labeling (package insert) for the predicate device(s) should be included
- A copy of labeling for any other assays used during the course of studies
- The clinical study protocol for the subject device which was sent to the sites, copy of informed consent (when applicable), and IRB approval
- All raw data from analytical studies and clinical studies
- All proposed labels, package inserts, service and operator manuals, instructions for use, advertising and/or promotional materials, and press releases.

Administrative Elements (Sections A-F)



- Sections A-F provide administrative information for the device and manufacturer
  A. 510(k) number
  B. Purpose of the Submission
  C. Measureand
  D. Type of Test
  E. Applicant
  F. Proprietary and Established Names

(G) Regulatory Information



- Section G summarizes the regulatory information including the Regulation Section, Classification, Product Code, and Panel
  - Example of a multiplexed respiratory assay
  - 21 CFR 866.3980 - Respiratory Viral Multiplex Nucleic Acid Assay
  - Classification II
  - Product Code - OCC
  - Panel - MI

(H) Intended Use

- This section contains the final intended use of the subject device. The review of the submission includes the evaluation of the submitted information to answer the following questions:
  - Do the data support the intended use, including the specimen type and patient population?
  - 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?
  - Are there special instrument or software requirements?

(I) Device Description

- This section gives an in-depth summary of the device including:
  - Principle of the assay – underlying technology
  - Assay components / Critical reagents
  - Calibrator traceability
  - Testing platform
  - Specimen types and processing/preparation
  - How the signal is generated and detected
  - Interpretation of results

(J) Predicate

- This Section compares and contrasts the subject device to the predicate device(s).
  - All predicate devices are FDA cleared, or were legally marketed prior to May 28, 1976
  - Side-by-side comparison (table or chart) containing the following information at a minimum (Similarities and Differences):
    - Intended use
    - Indications for use
    - Assay design
    - Technology
    - Performance
    - Target population

(K) Standards

- This section summarizes any reference standards or guidance documents that were referenced in the submission
  - CLSI guidelines (I/LA6, I/LA18, D13, EP5, EP10, etc.)
  - FDA guidance documents
  - CDC controls
  - WHO International Standard
  - These items will be covered in detail later in the workshop (Standards – Commonly used, How to Modify, and Statistical Input)

Note: These are different from the ‘Reference Method’ that may be used during the clinical evaluation to establish clinical performance of a device.

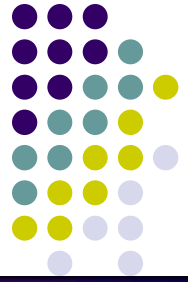
(L) Test Principle

- This section details the technology utilized in the subject device including any aspect relating to generation of the result
  - Examples of technology frequently encountered in submissions
    - Chemiluminescent Immunoassay
    - ELISA
    - Enzymatic/oxidative colorimetric assay
    - Radioimmunoassay
    - NAAT
    - Mass Spec

(M) Performance Characteristics

- This section contains a summary of the analytical and clinical validation data used to determine substantial equivalence.
  - Study design – accurately described and implemented?
  - Concentrations of test samples correct - near the cutoff or medical decision points and informative in the context of intended use?
  - Were all specimen types included?
  - Were all matrices evaluated?
  - Pre-analytical steps included in the evaluation? (i.e., sample extraction, processing, etc.)

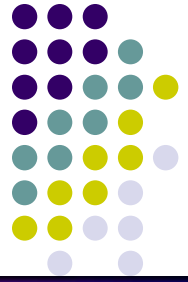
(M) Performance Characteristics



- Analytical
  - Use patient samples, where appropriate

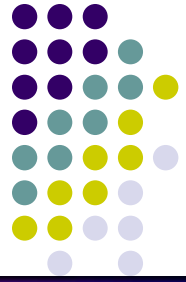
    (Check decision summaries for acceptable samples)
  - Establish basic performance parameters
  - Use traceable reference materials and methods, if available

(M) Performance Characteristics



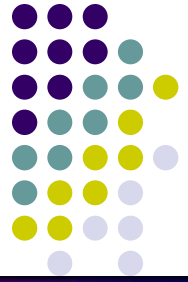
- Clinical
  - Study design should include the target population included in the intended use
    - Signs and symptoms
    - Other special patient populations (pregnant, neonates, etc)
  - Prospectively collected samples are strongly recommended to validate clinical performance.

(M) Performance Characteristics



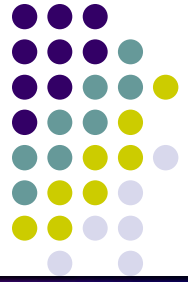
- Clinical (cont'd)
  - Matrix considerations - depending on the sample types claimed in the intended use, multiple sample types may need to be represented in the clinical study
    - Urine vs. vaginal swabs for Chlamydia
    - Nasal swabs vs. nasal wash/aspirates for respiratory infections
  - The claim for each sample type should be substantiated with the appropriate number of samples.

(M) Performance Characteristics (subsections a-f)



- The following slides will cover various subsections that may be included in your evaluation of the device. In each case there are examples of devices used to highlight some of the issues that are encountered while under review.

(a) Precision/Reproducibility Examples of FDA review questions



- Was multisite study to establish the reproducibility of an assay performed?
- Was the study performed in the appropriate setting (i.e. lab complexity representative of the end user)?
- Were the appropriate levels tested?
- Were all pre-analytical steps included in the study?
  - Develop a sample panel of 3-6 members
    - Use negative clinical matrix
- For quantitative assays
  - Cover the measurement range of the assay
  - Levels below and above clinical decision points
- For qualitative assays
  - Include samples at concentrations at or near the LoD

Precision/Reproducibility

FDA SE Decision Summary

Example 1- ACE Diagnostics

- Within-run and within-lab precision were determined, 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

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

Example 2 - RIVAL Diagnostics

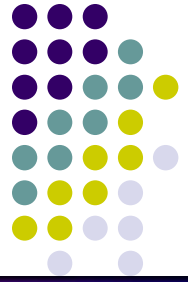
Between-run precision studies were done on serum-based material at 3 levels using the ***S**uper**F**ast* Instrument System. Results are summarized below.

	Sample 1	Sample 2	Sample 3
N	25	25	25
Mean (µg/ml)	0.3	0.8	1.4
SD	0.03	0.05	0.05
%CV	9.8	4.5	2.7

(b) Linearity
(examples of FDA review questions)

- Study design:
  - Sample types/preparation?
  - Target concentrations-calculations?
  - Traceable standards used?
  - What methods of determination of Linearity was used?
  - Acceptance criteria?
  - What statistical approaches were used?

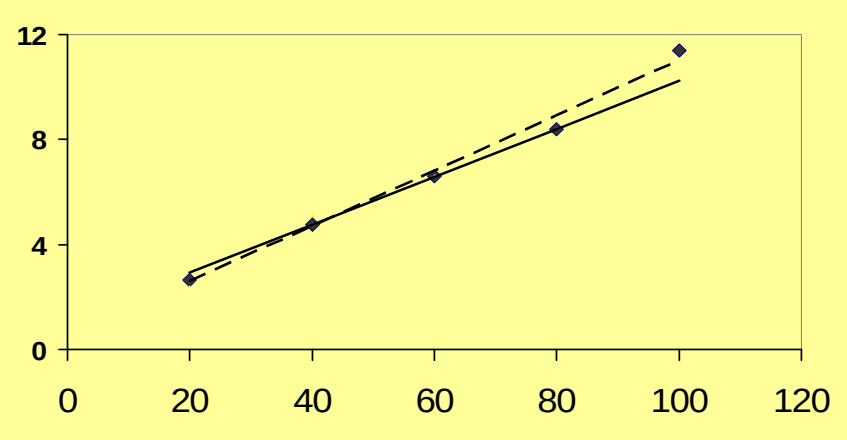
Linearity FDA SE Decision Summary
Example 5 - ACE Diagnostics



- 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%.

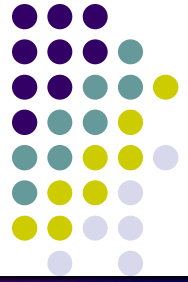
Linearity FDA SE Decision Summary
Example 6 - RIVAL Diagnostics

- 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.



- No information was provided as to how or what the sample is being tested. No information given for the number of replicates. No clear indication of what the values on the X/Y axis are.

(c) Matrix Comparison



- Study design questions:
  - Matrix types/preparation?
    - Are all claimed matrices included
  - Target concentrations?
  - Was a traceable standard used if available?
  - Acceptance criteria?
  - What statistical approach was used?

Example 7 -Matrix Comparison Serum/Plasma Validation

Information provided:

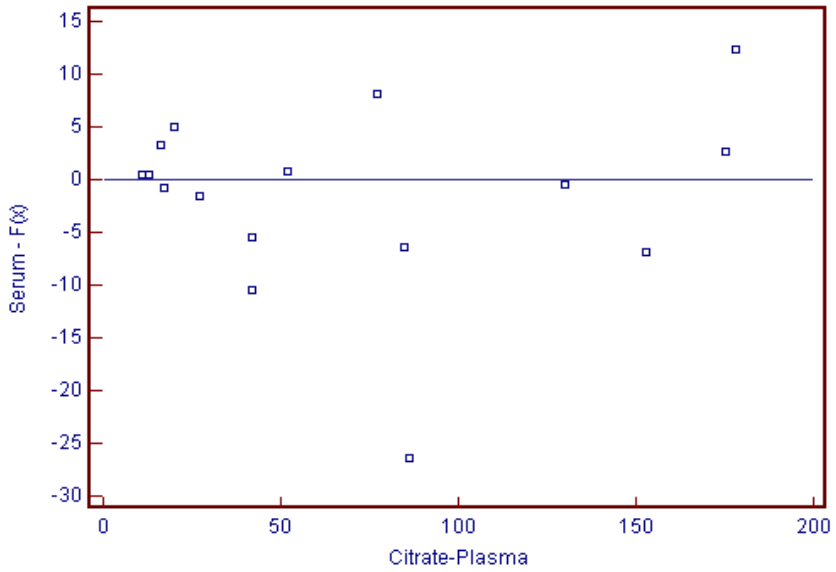
- Four measurements of each serum and the corresponding citrate plasma were serially diluted and the dilutions determined in [assay].
- The dilutions cover all concentrations in the diagnostically important range.
- Passing-Bablok regression was calculated.

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).
- Sponsor provided what was measured, how it was measured, the number of replicate measurements, the test range and how it relates to the clinical range and provided the regression analysis data.

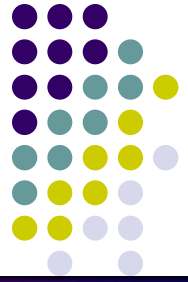
Example 7 -Matrix Comparison Serum/Plasma Validation (cont'd)

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



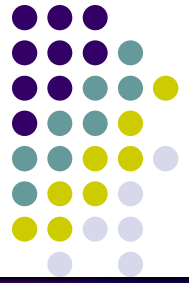
- The sponsor failed to describe what was being tested and at what levels and failed to describe the statistical method used, in this case a Cusum test. From the information provided the reviewer can not evaluate the matrix comparison data.

(d) Limit of Detection
(examples of FDA review questions)



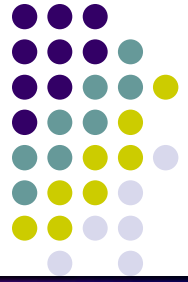
- What is the minimum detectable concentration?
- Was a standard or guidance used to design experiments for the studies? For example, CLSI-EP-17 - *Protocols for Determination of Limits of Detection and Limits of Quantitation.*
- What types of studies were done?
  - Note: Determination of LoD is crucial in qualitative assays
  - Note: Determination of LoQ is crucial in quantitative assays

(e) Analytical Specificity
(examples of FDA review questions)



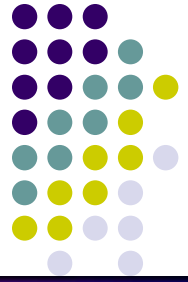
- Interference - endogenous and exogenous interfering substances that could create a false result
  - Chemical
    - Were the proper interfering substances found in clinical samples tested?
    - Were the substances tested at a relevant level?
    - Were the appropriate analyte levels used to determine potential negative affects from interfering substances?
      - Hemoglobin (hemolysis)
      - Bilirubin
      - Triglycerides
      - Mucus
      - Other substances that may be found in clinical sample
  - Cross Reactivity
    - Which organisms/substances likely to cross react?
    - For immuno-assays were common antibodies found in many clinical samples analyzed to demonstrate any cross-reactivity. (i.e. RA, CMV, HAMA)
    - Were near neighbors or other pathogens potentially found in the clinical specimen analyzed?

(f) Assay Cutoff/Clinical Cutoff



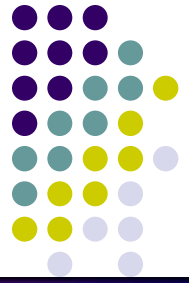
- How was the cut-off determined?
  - Analytical samples?
  - Was the analysis of ROC curves done correctly?
  - Determine the best level of specificity, w/o sacrificing sensitivity
- CDC-based on epidemiologic studies
- International standards – traceability

Method Comparison
(examples of FDA review questions)



- Was a description of the study design provided?
- How many sites were used and where were they located?
- Were real clinical samples used? (vs. cell lines, control materials, etc.)
- Prospective vs. Retrospective samples
- Was the data stratified appropriately?
- Sensitivity/Specificity vs. % Agreement

Studies to Support Intended Use Claims



- Intended Use statement drives the review of the submission
- A clearly and precisely crafted Intended Use determines the type of studies needed to determine substantial equivalence
- Example - Device for the detection of viral nucleic acids from Influenza A, 2009 H1N1, and Influenza B.
- The following slides will dissect an intended use statement and highlight the critical elements

Example of Intended Use

- The BestFlu Assay is **intended for use on the PERFECT instrument system** for ***in vitro*** **qualitative detection and differentiation of Influenza A, 2009 H1N1, and Influenza B viral nucleic acids** isolated from **nasopharyngeal (NP) swab and nasopharyngeal aspirates (NPA) specimens** obtained **from patients with signs and symptoms of respiratory infection**. Negative results do not preclude influenza virus infection and should not be used as the sole basis for patient management decisions.

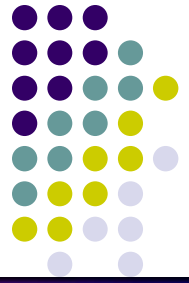
Intended Use - Part 1

"…intended for use on the PERFECT instrument system…"

- All analytical and clinical data must be generated on the claimed device
  - Was the claimed instrument used at all sites for the clinical studies and throughout the analytical validation?
  - Were the pre-analytical procedures associated with the PERFECT instrument used in all studies?
- All clinical samples must be also analyzed on the comparator device

Limitation: "Performance on automated equipment other than the PERFECT… has not been established"

Intended Use – Part 2



"… ***in vitro*** **qualitative detection and differentiation of Influenza A, 2009 H1N1, and Influenza B viral nucleic acids** …"

- ✓ Analytical Validity – Does the device correctly detect the claimed analytes?
- ✓ How many samples are required for % positive and % negative agreement?
- ✓ Are the number of positives statistically appropriate?
- ✓ Point estimate and 95% CI

Intended Use - Part 3

"…nasopharyngeal (NP) swab and nasopharyngeal aspirates (NPA) specimens…"

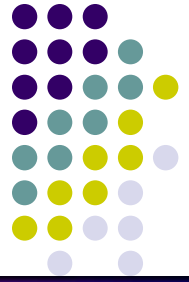
- ✓ Was each sample type represented with sufficient number in the clinical evaluation?
- ✓ Was each sample type included in the analytical validation as appropriate?
- ✓ If different pre-analytical techniques are necessary for each sample type are they accounted for in the clinical evaluation?

Intended Use - Part 4

"…from patients with signs and symptoms of respiratory infection…"

- Was the appropriate patient population tested?
- Was the data stratified by gender and age.
- Was the indicated patient population, as well as the inclusion/exclusion criteria for patient enrollment clearly stated in the information submitted to the clinical sites conducting the evaluation
- Was informed consent obtained if applicable?

Common Problems



- Unorganized submissions
  - Missing/incorrect TOC
  - No pagination
  - Sections not clearly marked
- Poorly QC'd submissions
  - Cut/paste errors
  - Incorrect data
- Poor analysis of data
- Missing data
- Administrative gaps
  - Missing documents
  - Unsigned documents
- Apparent lack of monitoring/auditing of clinical sites

Tips /Notes

- Please engage with us early in your development effort through the pre-IDE mechanism.
  - Allows you to get specific feedback directly related to your device from us.
- Utilize the published decision summaries for predicates to answer questions related to your device
- Avoid inconsistencies (we will find them)
- Perform quality review before sending your submission to FDA
- For difficult questions, contact OIVD

We are here to help!

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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