SMF Awareness Seminar 2014

Clinical Evaluation for
In Vitro Diagnostic Medical Devices

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Medical Device Branch
Definition of IVD
(from Medical Devices Regulations 2007)

“In vitro diagnostic product” means

Any reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination, that is intended by its manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:-

- concerning a physiological or pathological state;
- concerning a congenital abnormality;
- to determine the safety and compatibility of donations including blood and tissue donations, with potential recipients;
- to monitor therapeutic measures,

and includes a specimen receptacle but not a product for general laboratory use, unless that product, in view of its characteristics is specifically intended by its manufacturer to be used for in vitro diagnostic examinations.
Background: In Vitro Diagnostics (IVDs)

- In vitro diagnostics are tests performed on biological samples to **diagnose** or rule out a disease. They are used for disease screening, monitoring therapy and to ensure the safety of the blood used in transfusions.

- Includes tests used in laboratory or other health professional settings and tests used by lay users in non-clinical settings at home.
# Background

## Risk Associated with the Use of IVDs

### To public health
- Spread of infectious disease
- Unsafe blood transfusion

### To individual health
- Misdiagnosis/Delayed diagnosis
- Delayed or inappropriate treatment
- Incompatible tissue transplantation

<table>
<thead>
<tr>
<th>Risk Class</th>
<th>Risk to Individual Health</th>
<th>Risk to Public Health</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Low</td>
<td>No or minimal</td>
<td>Clinical chemistry analyzer</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>Low</td>
<td>Vitamin B12, Pregnancy self-testing</td>
</tr>
<tr>
<td>C</td>
<td>High</td>
<td>Moderate</td>
<td>Blood glucose self-testing, HLA typing</td>
</tr>
<tr>
<td>D</td>
<td>High</td>
<td>High</td>
<td>HIV blood donor screening, HIV diagnostic</td>
</tr>
</tbody>
</table>
Background
Pre-market Requirements for IVDs

To place an in vitro diagnostic (IVD) medical device on the market, the manufacturer must demonstrate that the device complies with the Essential Principles of Safety and Performance of Medical Devices.

Generally, from a clinical evidence perspective, it is expected that the manufacturer has demonstrated the device achieves its intended performance during normal conditions of use in the intended environment (e.g. laboratories, physician’s offices, healthcare centres, home environments) and in the intended use population.
SCOPE

- What is Clinical Evidence?
- How to Demonstrate Clinical Evidence?
- What Regulators Look for When Evaluating Clinical Evidence?
- Issues related to RUO/IUO in Clinical Diagnostic Use
SCOPE

- What is Clinical Evidence?
- How to Demonstrate Clinical Evidence?
- What Regulators Look for When Evaluating Clinical Evidence?
- Issues related to RUO/IUO in Clinical Diagnostic Use
Clinical Evidence

*Definition:* All the information that support the scientific validity and performance for its use as intended by the manufacturer.

- Allows a manufacturer to demonstrate the Safety and Performance of an IVD

Source: GHTF/SG5/N6:2012
Clinical Evidence Elements

- Clinical Evidence
  - Scientific Validity
  - Performance
    - Analytical Performance
    - Clinical Performance
  - Clinical Performance

Intended Use
Intended Use

- Objective intent of the manufacturer regarding the use of the IVD
- reflected in the intended use statement

- ACE HIV Rapid Test is intended to detect anti-HIV-1/2 antibodies and HIV-1 p24 antigen in human serum, plasma, venous blood and capillary blood. This kit is intended for blood donor screening and HIV diagnosis.

- Zen Blood Glucose Monitoring System is designed to quantitatively measure the concentration of glucose in capillary whole blood by persons with diabetes in the home or by health care professionals in health care facilities. Professionals may use the test strips to test capillary, venous, arterial, and neonate (including cord) blood samples; lay use is limited to capillary whole blood testing.
Scientific Validity

**Definition:** The association of an analyte (i.e. substance detected or measured) to a clinical condition/physiological state.

- Is the IVD testing a right marker?

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Clinical Condition/physiological status</th>
<th>Scientific Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>hCG</td>
<td>Pregnancy</td>
<td>Well established</td>
</tr>
<tr>
<td>Calcium in serum</td>
<td>Bone disease</td>
<td>Well established</td>
</tr>
<tr>
<td>HIV p24 Ag</td>
<td>HIV infection</td>
<td>Well established</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>Detection of Inflammatory disorders</td>
<td>Well established</td>
</tr>
<tr>
<td></td>
<td>Risk of cardiac diseases</td>
<td>Emerging</td>
</tr>
</tbody>
</table>
Performance

Definition: Ability of an IVD medical device to achieve its intended use as claimed by the manufacturer.

- Can the IVD achieve what is claimed?
  
  – Analytical performance:  
    ability to detect or measure a particular analyte.
  
  – Clinical performance:  
    ability to yield results that are correlated with a particular clinical condition/physiological state (target population and intended user).
Pre-market Requirement for Clinical Evidence

The manufacturer is expected to demonstrate **clinical evidence** for an IVD medical devices.
SCOPE

- What is Clinical Evidence?
- How to Demonstrate Clinical Evidence?
- What Regulators Look for When Evaluating Clinical Evidence?
- Issues related to RUO/IUO in Clinical Diagnostic Use
How to Establish Scientific Validity?

- Identified from academic research
- Supported by studies evaluating the analyte for potential clinical applications
- Literature review
- Feasibility and/or scientific validity studies performed by the manufacturer
Example of Scientific Validity
HIV Infection: a Well Established Marker

**Intended use statement:**

ACE HIV Rapid Test is intended to detect anti-HIV-1/2 antibodies and HIV-1 p24 antigen in human serum, plasma, venous blood and capillary blood. This kit is intended for blood donor screening and HIV diagnosis.

**Scientific Validity for ACE HIV Rapid Test**

The association of the presence of the anti-HIV and HIV antigens in human blood with the HIV infection is very well known.

The combination of the P24 antigen and antibody tests could increase the diagnostic efficiency for early diagnosis of HIV infection, as widely described in literatures [1,2].

**Reference**

Scientific Validity Example (2)
Personalized Cancer Medicine: An Emerging Marker

Intended use statement:
The KRAS/BRAF Mutation Analysis Kit is intended for the detection of KRAS exon 2, 3, 4 and BRAF exon 15 mutations (listed in Table 1) in genomic DNA from tumors of patients diagnosed with metastatic colorectal or lung cancers.

Scientific Validity for detection of KRAS and BRAF mutations:
4.1 Background Notes
The KRAS gene encodes a small GTPase that plays a key role in transducing signals from the epidermal growth factor receptor (EGFR) and several studies have demonstrated that tumors carrying any of these mutant forms of the KRAS gene are less likely to respond to anti-EGFR antibody therapy. [2,3] The American Society of Clinical Oncology (ASCO) recently reported that not all mCRC patients with wild-type KRAS tumors respond to anti-EGFR therapy. This suggests that additional genes and/or pathways may be involved in the mechanism of resistance to these drugs. Mutations in BRAF, another downstream effector of the EGF-activated pathway, have been identified in up to 8% of mCRC tumors. [5-7] Studies with mCRC patients have shown resistance to anti-EGFR therapy in patients with tumors expressing mutated BRAF. Those same individuals also had decreased progression-free (PFS) and overall (OS) survival when treated with EGFR antagonists.

These findings strongly suggest that screening for both KRAS and BRAF mutations is necessary to more accurately identify patients who will not respond to anti-EGFR therapy.
Performance

*Definition*: Ability of an IVD medical device to achieve its intended use as claimed by the manufacturer.

- Can the IVD achieve what is claimed?
Analytical Performance

Ability to detect or measure a particular analyte.

- Accuracy (trueness + precision)
- Analytical sensitivity (e.g. LOD, LOB, LOQ, etc)
- Analytical specificity (interference substances endogenous/exogenous)
- Linearity
- Cut-off
- Measuring interval (range)
- Carry-over
- Appropriate specimen collection and handling

Ref. GN-18: Guidance on Preparation of a Product Registration Submission for IVD MD using the ASEAN CSDT
Clinical Performance

Ability to yield results that are correlated with a particular clinical condition/physiological state (target population and intended user).

- Diagnostic specificity
- Diagnostic sensitivity
- Positive predictive value
- Negative predictive value
- Likelihood ratio
- Expected values in normal and affected populations

Ref. GN-18: Guidance on Preparation of a Product Registration Submission for IVD MD using the ASEAN CSDT
Clinical Performance Study

• **Definition:** A study undertaken to establish or confirm the clinical performance of an IVD medical device.

**NOTE:**
• Synonymous with ‘clinical trial’ and ‘clinical study’.
• Clinical performance study may not be required for all IVD products
• Study design:
  – normal conditions of use
  – in the intended environment (e.g. laboratories, physician’s offices, healthcare centres, home environments) and
  – in the intended use population
Compilation of Clinical Evidence

• Prepare clinical evidence report
  – Scientific validity
  – Analytical performance
  – Clinical performance

• Example

1.1 CLINICAL EVIDENCE .................................................................................................. 5
1.1.1 SCIENTIFIC VALIDITY ............................................................................................... 5
1.1.2 ANALYTICAL PERFORMANCE .................................................................................... 6
1.1.3 CLINICAL PERFORMANCE ......................................................................................... 8
CONCLUSION CLINICAL EVIDENCE .................................................................................. 16

• To support pre-market application
SCOPE

- What is Clinical Evidence?
- How to Demonstrate Clinical Evidence?
- What Regulators Look for When Evaluating Clinical Evidence?
- Issues related to RUO/IUO in Clinical Diagnostic Use
Clinical Evidence Elements

- Clinical Evidence
  - Scientific Validity
  - Performance
    - Analytical Performance
    - Clinical Performance
  - Clinical Performance

Intended Use
What is Required for Performance Evaluation?

Least burden approach

• Are the **analytical performance** data in conjunction with the **scientific validity** sufficient to demonstrate conformity with the relevant Essential Principle?

• If yes, then **clinical performance** data is **NOT** required.
What is required for Performance Evaluation?

<table>
<thead>
<tr>
<th>Test Category</th>
<th>Scientific Validity</th>
<th>Analytical Performance Required?</th>
<th>Clinical Performance Required?</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Established and Standard</td>
<td>Yes</td>
<td>Yes</td>
<td>Not required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early pregnancy test (hCG level)</td>
</tr>
<tr>
<td>II</td>
<td>Established and Non-Standard</td>
<td>Yes</td>
<td>Yes</td>
<td>Will often be required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatitis C diagnosis (anti-HCV antibodies)</td>
</tr>
<tr>
<td>III</td>
<td>Novel</td>
<td>Yes</td>
<td>Yes</td>
<td>Most likely be required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-invasive prenatal testing (NIPT) cell free DNA in mother blood</td>
</tr>
</tbody>
</table>
Clinical Evidence Assessment

• Assessment and analysis of data to establish or verify the performance of an IVD medical device

• Study design
  – during normal conditions of use
  – in the intended environment
    • laboratories,
    • physician’s offices,
    • healthcare centres,
    • home environments
  – in the intended use population.

• Statistical analysis/considerations

→ Overall conclusions: favorable benefit-to-risk ratio
Product Specific Performance Requirements

- Recognized Standards:
  e.g. Blood Glucose Monitoring System: ISO15197:2013

- Common Technical Specifications:
  e.g. Blood Donor Screening Test (e.g. HIV): EU Common Technical Specifications for Annex II List A products

- Product Specific Guidelines from Reference Agencies:
  e.g. MTB, Influenza, HPV: USFDA OIVD Guidelines

- If none of the above exists, e.g. first of this kind
  - First-principle: to demonstrate the performance for the intended use
  - Discuss with HSA...
Case Study 1: HIV Test Kit

**Intended Use:**
ACE HIV Rapid Test is intended to detect anti-HIV-1/2 antibodies and HIV-1 p24 antigen in human serum, plasma, venous blood and capillary blood. This kit is intended for blood donor screening and HIV diagnosis.

**Common Technical Specifications:**

COMMISSION DECISION
of 3 February 2009
amending Decision 2002/364/EC on common technical specifications for in vitro-diagnostic medical devices
Performance Characteristics for HIV Screening Assay

Table 1: “Screening” assays: anti-HIV 1 and 2,

<table>
<thead>
<tr>
<th>Diagnostic sensitivity</th>
<th>Anti-HIV-1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive specimens</td>
<td>400 HIV-1</td>
</tr>
<tr>
<td></td>
<td>100 HIV-2</td>
</tr>
<tr>
<td></td>
<td>including 40 non-B-subtypes, all available</td>
</tr>
<tr>
<td></td>
<td>HIV/1 subtypes should be represented by at least 3</td>
</tr>
<tr>
<td></td>
<td>samples per subtype</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Seroconversion panels</th>
<th>20 panels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 further panels (at Notified Body or manufacturer)</td>
</tr>
</tbody>
</table>
Performance Characteristics for HIV Screening Assay

Table 1: “Screening” assays: anti-HIV 1 and 2,

<table>
<thead>
<tr>
<th>Analytical sensitivity</th>
<th>Standards</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>Unselected donors (including first-time donors)</td>
<td>5000</td>
</tr>
<tr>
<td></td>
<td>Hospitalised patients</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Potentially cross-reacting blood-specimens (RF+, related viruses, pregnant women, etc.)</td>
<td>100</td>
</tr>
</tbody>
</table>
Performance Characteristics for HIV Screening Assay

Table 3: Rapid test: anti-HIV 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Anti-HIV 1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic sensitivity</strong></td>
<td>Positive specimens</td>
</tr>
<tr>
<td></td>
<td>Same criteria as for screening assays</td>
</tr>
<tr>
<td></td>
<td>Seroconversion panels</td>
</tr>
<tr>
<td></td>
<td>Same criteria as for screening assays</td>
</tr>
<tr>
<td><strong>Diagnostic specificity</strong></td>
<td>Negative specimens</td>
</tr>
<tr>
<td></td>
<td>1,000 blood donations</td>
</tr>
<tr>
<td></td>
<td>200 clinical specimens</td>
</tr>
<tr>
<td></td>
<td>200 samples from pregnant women</td>
</tr>
<tr>
<td></td>
<td>100 potentially interfering samples</td>
</tr>
</tbody>
</table>
Case Study 2: Blood-Glucose Monitoring System for self-testing

Intended Use:
Zen Blood Glucose Monitoring System is designed to quantitatively measure the concentration of glucose in capillary whole blood by persons with diabetes in the home or by health care professionals in health care facilities. Professionals may use the test strips to test capillary, venous, arterial, and neonate (including cord) blood samples; lay use is limited to capillary whole blood testing.
Case Study 2: Blood-Glucose Monitoring System for self-testing

INTERNATIONAL STANDARD

ISO 15197

Second edition
2013-05-15

In vitro diagnostic test systems — Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus
Case Study 2: Blood Glucose Monitoring System for Self-Testing

8 User performance evaluation

The user performance evaluation shall demonstrate that intended users are able to obtain accurate glucose measured values when operating the blood-glucose monitoring system, given only the instructions and training materials routinely provided with the system.

Accuracy of capillary blood-glucose values measured by lay persons shall be compared to capillary blood-glucose values measured by the reference measurement procedure.

Blood-glucose monitoring systems for self-testing shall be evaluated in a setting that allows lay persons to perform blood-glucose measurements without outside influence. Rationale for selection of the evaluation sites shall be documented in the study report.
Case Study 2: Blood-Glucose Monitoring System for self-testing

User Performance Evaluation

7.5.1 User Results compared to YSI 2300 STAT Plus results

7.5.2 User Results compared to Technician results

7.5.3 Technician results compared to YSI 2300 STAT Plus results

The results of the Consensus Error Grid show that when comparing the technician results to the plasma glucose reference value obtained by the YSI, 51/52 (98%) of the results results were in Zone A. All (52/52) of the results were within Zones A and B.
Case Study 2: Blood-Glucose Monitoring System for self-testing

8.8. Evaluation of Instruction for Use

8.8 Evaluation of instructions for use

8.8.1 General

The instructions for use and messages displayed on the meter shall be evaluated for clarity and usefulness.

The evaluation shall be performed by the subjects participating in the user performance evaluation. Other lay persons may also participate in the evaluation.

8.8.2 Evaluation method

The evaluation method shall be conducted by a questionnaire designed to assess whether the users understood how to use the device correctly.

A typical questionnaire may consist of a series of statements, where evaluation participants are asked to indicate their degree of agreement with each statement on a scale of 1 to 5 (1 = strongly disagree; 3 = neutral; 5 = strongly agree).

EXAMPLE The questionnaire can include statements such as:

— The instructions were easy to follow.
— The test results displayed on the meter were easy to see.
— It was easy to understand the test results.
— The instructions clearly explain what to do if an error message is displayed on the glucose monitor.

Study participants shall also be given an opportunity to provide unrestricted comments on their experience when using the blood-glucose monitoring system and the instructions for use.

To avoid biasing the study results, the questionnaire shall be completed after the subject’s self-testing has been completed.
Clinical Evidence Report

• A compilation of the scientific validity, analytical and clinical performance.
• The level of detail in the report content will vary
  – Risk classification of the IVD
  – Evaluation route (abridged or full evaluation)
• Least burden approach
SCOPE

- What is Clinical Evidence?
- How to Demonstrate Clinical Evidence?
- What Regulators Look for When Evaluating Clinical Evidence?
- Issues related to RUO/IUO in Clinical Diagnostic Use
Risk of using unregistered IVD in Clinical Diagnostic

- Unproven performance characteristics;
- Manufacturing controls are inadequate to ensure consistent production of the finished product

→ Mislead healthcare providers
→ Cause serious adverse health consequence to patients
## RUO, IUO and IVD

<table>
<thead>
<tr>
<th>For Research Use</th>
<th>For Clinical Diagnostic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RUO</strong></td>
<td></td>
</tr>
<tr>
<td>• Not subject to MD control</td>
<td></td>
</tr>
<tr>
<td>- For discovering and developing medical knowledge related to human diseases/conditions</td>
<td></td>
</tr>
<tr>
<td>- Not intended to produce results for clinical use</td>
<td></td>
</tr>
<tr>
<td>• Off-label use</td>
<td></td>
</tr>
<tr>
<td>- May risk public health</td>
<td></td>
</tr>
<tr>
<td>- Subject to QMS of clinical diagnostic lab</td>
<td></td>
</tr>
<tr>
<td>• Dealers of RUO shall not promote it for IVD use</td>
<td></td>
</tr>
<tr>
<td><strong>IVD</strong></td>
<td></td>
</tr>
<tr>
<td>• Registered IVD</td>
<td></td>
</tr>
<tr>
<td>- No objection letter from HSA</td>
<td></td>
</tr>
<tr>
<td>• Unregistered IVD</td>
<td></td>
</tr>
<tr>
<td>- Authorization Route (GN-29)</td>
<td></td>
</tr>
<tr>
<td>• Subject to MD control</td>
<td></td>
</tr>
<tr>
<td>- Product registration</td>
<td></td>
</tr>
<tr>
<td>- Dealer’s licencing</td>
<td></td>
</tr>
<tr>
<td><strong>IUO</strong></td>
<td></td>
</tr>
<tr>
<td>• Investigational Use Only</td>
<td></td>
</tr>
<tr>
<td>- NOT used to carry out research but are themselves the object of the research.</td>
<td></td>
</tr>
<tr>
<td>- Import requires HSA approval (CTM for Medical Devices)</td>
<td></td>
</tr>
<tr>
<td>• Off-label use</td>
<td></td>
</tr>
<tr>
<td>- May risk public health</td>
<td></td>
</tr>
<tr>
<td>- Subject to QMS of clinical diagnostic lab</td>
<td></td>
</tr>
<tr>
<td>• Dealers of IUO shall not promote it for IVD use</td>
<td></td>
</tr>
</tbody>
</table>
Take Home…

Clinical Evidence → Intended Use

Scientific Validity

Performance

Always required

Analytical Performance

Clinical Performance

not always required

Intended Use
Take Home…

• Clinical evidence = scientific validity + performance
  – allows the manufacturer to demonstrate safety & performance

• All IVDs require analytical performance; but not all require clinical performance
  – Novel device requests both

• The evaluator expects that the manufacturer has demonstrated the device achieves its intended performance during normal conditions of use in the intended environment and in the intended use population.

• RUO device shall not be promoted for clinical diagnostic use
Resources & Links

• GHTF/SG5/N6:2012 Clinical Evidence for IVD Medical Devices – Key Definitions and Concepts

• GHTF/SG5/N7:2012 Clinical Evidence for IVD Medical Devices – Scientific Validity and Performance Evaluation

• GHTF/SG5/N8:2012 Clinical Evidence for IVD Medical Devices – Clinical Performance Studies for In Vitro Diagnostic Devices

Queries?

Submit Health Product Enquiry Form
http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Medical_Devices/Application_Registration/e-Services_and_Forms.html

Email us at: HSA_MD_INFO@hsa.gov.sg
Thank You