Precision of IVDMIA (In Vitro Diagnostic Multivariate Index Assay) with Individual Analytes

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Marina V. Kondratovich, PhD
Associate Director for Clinical Studies, OIR, CDRH, FDA

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A device that:

- **Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result** (e.g., a “classification”, “score”, “index”, etc) that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease

Draft Guidance for Industry, Clinical laboratories, and FDA Staff “In Vitro Diagnostic Multivariate Index Assays”, published on July 26, 2007
IVDMIA Paradigm

\[ X_1 \quad X_2 \quad X_3 \quad X_4 \quad \ldots \quad X_K \]

Interpretation Function
Score, Cutoff(s)

Low Risk  Medium Risk  High Risk
Multi-analyte

K outputs

Patient characteristics, imaging, IVD analytes are combined

IVDMIA

Only IVD analytes are combined

Analytes are quantitative, qualitative or semi-quantitative

Individual and multiplex analytes

OVA1

Analytes are only qualitative

Multiplex analytes

Analytes are only quantitative

Individual analytes
## Precision

Multi-analyte (K individual analytes)

<table>
<thead>
<tr>
<th>Current Approach:</th>
<th>Precision experiment for Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example: Score</td>
<td>Score = F(X₁, X₂, X₃, X₄, X₅), Xᵢ – individual analytes (proteins)</td>
</tr>
<tr>
<td></td>
<td>5 samples with mean Score values: 3.1, 3.8, 5.7, 6.9, 9.9</td>
</tr>
<tr>
<td></td>
<td>cutoff for Score = 5.0</td>
</tr>
</tbody>
</table>
Basic Points

- The usual precision study provides information about precision for some particular combinations of the individual analytes amounts which were present in the samples of the precision studies described above.

- There are many possible combinations of the individual analytes amounts which give the same value of the test score and therefore, the samples with the same score but different combinations of the individual analyte amounts can have different precisions.

- The additional simulation provides information about precision profile of the test score system for different combinations on individual analytes values.
For more details about Monte Carlo simulation of precision, see

Class II Special Controls Guidance Document: Ovarian Adnexal Mass Assessment Score Test System

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm237299.htm

Section VI.B “Repeatability/Reproducibility”
Pages 11-13
For sake of simplicity, consider two individual analytes $X_1$ and $X_2$, score is $f(X_1, X_2)$.

Within-laboratory precision for each analyte is available:
- Precision of $X_1$: 3-5 concentrations, SD, %CV
- Precision of $X_2$: 3-5 concentrations, SD, %CV
• Score can be calculated at 16 points
• Precision can be evaluated using Monte Carlo simulation with normal distributions of measurement errors for each $X_i$
• Random measurement errors of analytes $X_1$, $X_2$, ..., $X_K$ are not correlated (because analytes are measured individually)
Example: Score = f(X₁, X₂) = 5* X₁ + 3* X₂

<table>
<thead>
<tr>
<th>X₁</th>
<th>Mean</th>
<th>5.0</th>
<th>20.0</th>
<th>200.0</th>
<th>2000.0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SD</td>
<td>1.0</td>
<td>2.0</td>
<td>20.0</td>
<td>300.0</td>
</tr>
<tr>
<td></td>
<td>%CV</td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>X₂</td>
<td>Mean</td>
<td>0.5</td>
<td>30.0</td>
<td>100.0</td>
<td>1000.0</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.1</td>
<td>1.5</td>
<td>5.0</td>
<td>60.0</td>
</tr>
<tr>
<td></td>
<td>%CV</td>
<td>20%</td>
<td>5%</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Within-laboratory precision profile for $X_1$

<table>
<thead>
<tr>
<th>$X_1$</th>
<th>Mean</th>
<th>5.0</th>
<th>20.0</th>
<th>200.0</th>
<th>2000.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>1.0</td>
<td>2.0</td>
<td>20.0</td>
<td>300.0</td>
<td></td>
</tr>
<tr>
<td>%CV</td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
<td>15%</td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing %CV values for different $X_1$ values with linear interpolation.](image-url)
Within-laboratory precision profile for $X_2$

<table>
<thead>
<tr>
<th>$X_2$</th>
<th>Mean</th>
<th>0.5</th>
<th>30.0</th>
<th>100.0</th>
<th>1000.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>0.1</td>
<td>1.5</td>
<td>5.0</td>
<td>60.0</td>
<td></td>
</tr>
<tr>
<td>%CV</td>
<td>20%</td>
<td>5%</td>
<td>5%</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

Linear interpolation
Example: Score = $f(X_1, X_2) = 5 \times X_1 + 3 \times X_2$
- Investigate the distribution of random measurement error of the Score at different values of the Score.

Example: Score is a linear function of $X_1$ and $X_2$

\[ f(X_1, X_2) = 5* X_1 + 3* X_2 \]

Distribution of the measurement error of the Score in this example is normal.

- Consider precision profiles for individual analytes using precision data of 3-5 concentrations.

Using precision profiles for individual analytes, calculate precision profile for the Score using Monte Carlo simulation.
Example: Score = f(X₁, X₂) = 5* X₁ + 3* X₂ = 150
<table>
<thead>
<tr>
<th>Score</th>
<th>Point</th>
<th>$X_1$</th>
<th>SD</th>
<th>$X_2$</th>
<th>SD</th>
<th>SD of Score</th>
<th>%CV of Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>(1)</td>
<td>5.0</td>
<td>1.0</td>
<td>41.7</td>
<td>2.1</td>
<td>8.0</td>
<td>5.4%</td>
</tr>
<tr>
<td>150</td>
<td>(2)</td>
<td>10.0</td>
<td>1.6</td>
<td>33.3</td>
<td>1.7</td>
<td>9.9</td>
<td>6.6%</td>
</tr>
<tr>
<td>150</td>
<td>(3)</td>
<td>29.7</td>
<td>3.0</td>
<td>0.5</td>
<td>0.1</td>
<td>15.0</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

![Graph showing the relationship between $X_1$ and $X_2$ with different points and precision profiles.](image-url)
Basic Steps

STEP 1

Consider a sample with a combination of two analytes with values:
Analyte 1 $X_1 = U$ (mean value of analyte 1) and
Analyte 2 $X_2 = V$ (mean value of analyte 2).

Using within-laboratory precision profiles, obtain $SD_1(U)$ for $X_1 = U$ and
$SD_2(V)$ for $X_2 = V$. 
Basic Steps (cont.)

STEP 2

Monte Carlo simulation of error propagation

random number generator

Generate $X_1^*$ using normal distribution with mean value of $U$ and standard deviation of $SD_1(U)$ and generate $X_2^*$ using normal distribution with mean value of $V$ and standard deviation of $SD_2(V)$. Calculate $Score^* = F(X_1^*, X_2^*)$.

After performing $T$ times (for example, 1000), calculate the mean value of score of $T$ measurements $Score_{mean}^*$ (mean value of the score for $X_1=U$ and $X_2=V$) and standard deviation $SD$ and $%CV$ of the $T$ score measurements.
Basic Steps (cont.)

STEP 3

Provide within-lab precision profile for the Score: values of the mean score \( \text{Score}^*_{\text{mean}} \) with the SD and %CV from the previous step for all possible combinations of U and V for which precision profiles are available.
Example: Score = \( f(X_1, X_2) = 5X_1 + 3X_2 \)

Within-Lab Precision Profile for Score Values 26.6 - 500.
Example: Score = f(\(X_1, X_2\)) = 5 \cdot X_1 + 3 \cdot X_2

Within-Lab Precision Profile for Score Values 26.6 -13,000.
Precision at Clinically Possible Score Values

If we have only one analyte -> precision profile -> consider analyte values for all patients in the clinical study (clinically possible analyte values) -> Assumption: one time measurement is close to the mean value of analyte

For Score:
- Consider all patients in the clinical study

- For each patient,
  - Consider Score and Values of $X_1$ and $X_2$;
  - Using precision profiles of individual analytes, evaluate the precision of the Score with values of $X_1$ and $X_2$ for this patient using Monte Carlo simulation;
  - Present this point on the Score precision profile graph.
Precision at Clinically Possible Score Values (cont.)

- Present list of patients for whom precision of their Score was not evaluated because of precision profile for their individual analyte values were not available => You may need precision study for individual analytes at additional concentrations

Precision Around the Cutoff

- Investigate precision of the Score around the Cutoff for the Score;
  Concentrations \((X_1, X_2)\) of individual analytes give a Score close to the Cutoff
  \[ f(X_1, X_2) = \text{Cutoff} \]
Summary

1) Precision profile for the Score based on precision profiles of individual analytes and Monte Carlo simulation of error propagation provides additional valuable information.

2) Percent subjects in the clinical study with Score values close to the cutoff provides information about clinical impact of Score random measurement error.

3) Further investigation is needed for different IVDMIA scenarios (as multiplex assay).
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Contact Information:
Marina.Kondratovich@fda.hhs.gov

Phone
(301) 796-6036