

FDA/CDRH perspectives on imaging biomarkers: technical performance and analytical validation

Dan Krainak, Ph.D.

Biomedical Engineer

U.S. Food and Drug Administration (FDA)

Center for Devices and Radiological Health (CDRH)

Office of In Vitro Diagnostics and Radiological Health (OIR)

Division of Radiological Health (DRH)

Magnetic Resonance and Electronic Products Branch (MREP)

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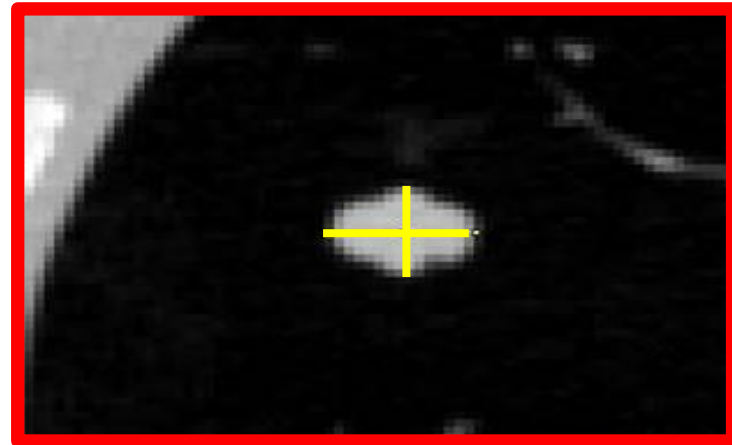
Analytical validation expectations

Establishing that the performance characteristics are acceptable in terms of relevant performance characteristics

- **Establish** = demonstrate through data
- **Acceptable** = performance meets requirements or specifications
- **Relevant** = characteristics that have bearing on the matter at hand

Example 1 - Tool measures volume

- A 3D slicer measurement tool on a phantom data

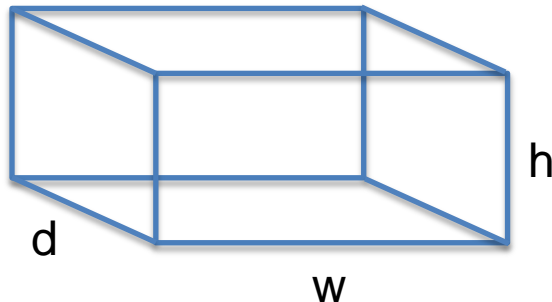


Example 1 - Tool measures volume

- Version A

Using the ruler, measure width (w), height (h), and depth (d) of the object

$$\text{Volume} = w * h * d$$

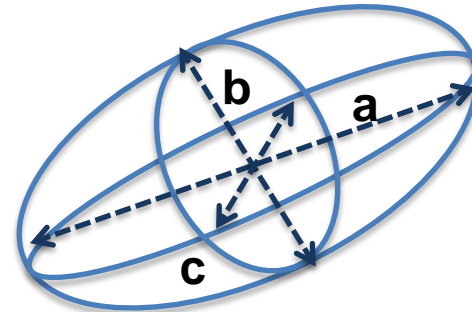


- Version B

Using the ruler, measure width (a), height (b), and depth (c) of the object

$$\text{Volume} = \frac{\pi}{6} abc$$

$$\begin{aligned} w &= a \\ h &= b \\ d &= c \end{aligned}$$



Example 1 – Tool measures volume

What analytical validation is needed?

- **Establish** = verify tool provides volume based on three linear, orthogonal measurements, and verify the calculation is implemented correctly
- **Acceptable** = requirement is to measure volume, both tools measure volume
- **Relevant performance characteristics** = “this device provides tools for measuring volume”

Example 2 – Tumor volume change

This device may be used to measure changes in tumor volume greater than 25 mm³ from CT images in patients with lung cancer



Example 2 – Tumor volume change

Analytical validation

- **Establish** = phantom data and/or clinical data to support performance
- **Acceptable** = requirement to measure changes in tumor volume greater than 25 mm³ on CT across all factors that affect performance
 - Reproducibility:
 - 95% Limits of agreement within (-___mm³, ___ mm³)
 - Mean bias: $\bar{d} < \text{___ mm}^3$
- **Relevant performance characteristics**
 - **Accuracy:** bias, linearity, ...
 - **Precision:** repeatability, reproducibility, ...

Key Analytical Parameters

- Accuracy (relative)
- Measurement Range
- Parallelism
- Reproducibility
- Selectivity
- Specificity
- Stability

From *Draft Points to Consider Document: Scientific and Regulatory Considerations for the Analytical Validation of Assays Used in the Qualification of Biomarkers in Biological Matrices* <https://healthpolicy.duke.edu/events/public-workshop-scientific-and-regulatory-considerations-analytical-validation-assays-used>

Analytical Performance Characteristics

- **What are the relevant characteristics for the research or clinical question?**
- Some common attributes (bias and imprecision)
 - Bias (Accuracy)
 - Linearity
 - Reproducibility
 - Repeatability
 - Measurement range (limits of detection/quantitation)



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