Analytical validation and IDEs- ID Case Study

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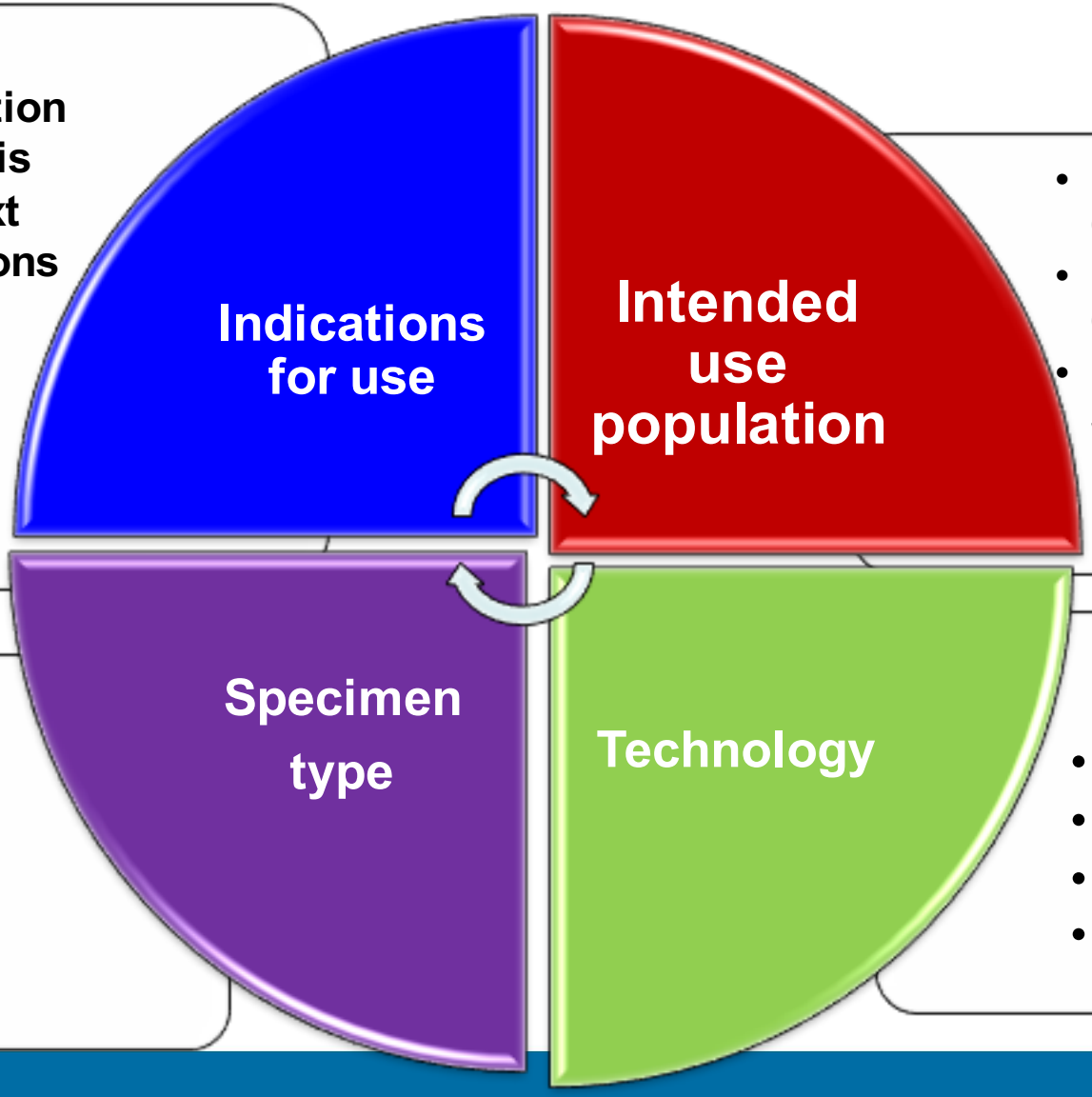
Presentation Outline

- Principals of IDE submission for viral IVD
- Analytical Study Requirements
- Conclusions
- Additional Resources

For a Successful IDE Submission to FDA

- Clear & precise “intended use” (IU)
- Complete device description
- Scientific evidence supporting the IU
- Analytical Performance
- Labeling

Indication for Use



- Examples:
- Risk Stratification
- Aid in Diagnosis
- Clinical Context
- Contraindications

- Inclusion Criteria
- Exclusion Criteria
- Represented in Study Population

- Blood, Plasma, Nasopharyngeal

- Measurand
- Quantitative
- Qualitative
- Instrument

Device Description

- Principle of the Test from Sample to Result
- Description of Reagents
- Target Selection
- Instrumentation
- Quality Control and Procedural Limitations

Interpretation of Results

- List the possible result categories and recommended interpretation.
- For quantitative tests, define the different levels of quantitation and their clinical significance.
- For qualitative tests, describe how a positive/negative result will be used for patient management.
- Define any other clinical information required for the result interpretation and patient management.

Analytical Performance I

- Precision/Reproducibility
- Analytical Sensitivity
- LoB, LoD, LoQ as applicable
- Linearity
- Traceability

Analytical Performance II

- Sample Stability and Matrix effects
- Reagent Stability
- Cross Reactivity
- Interference

Traceability & Commutability

Metrological Traceability

VIM (2008), 2.41

property of a measurement result whereby the result can be related to a stated reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty. Metrological traceability requires an established Calibration Hierarchy.

- Primary standard
- Secondary standard
- Reference standard
- Working standard

ISO 17511 (2003)

In-vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials

"For measurements of quantities in laboratory medicine, it is essential that the quantity is adequately defined and the results reported to the physicians … are adequately accurate (true and precise) to allow correct medical interpretation and comparability over time and space."

ISO 17511, Introduction

ISO 17511 (2003)

According to ISO 17511, for **calibrators:**

- ❑ Design a traceable calibrator
- ❑ Demonstrate that the entire value assignment process works
- ❑ Document the transfer process
- ❑ Determine the uncertainty of the transfer process
- ❑ Demonstrate the commutability (when a reference procedure exists)
- ❑ Provide to users information about traceability of calibrators upon request

Linearity

CLSI EP06-A
the ability (within a given range) to provide results that are directly proportional to the concentration {amount} of the analyte in the test sample

ISO 18113-1 (2009)
A.3.21
ability to provide measured quantity values that are directly proportional to the value of the measurand in the sample

ISO 17511 (2003)

Commutability of a Material

closeness of agreement between the mathematical relationship of the measurement results obtained by two measurement procedures for a stated quantity in a given material, and the mathematical relationship obtained for the quantity in routine samples

Commutability

is a property of a reference material whereby the same numeric relationship (within clinically meaningful limits) can be demonstrated between 2 or more measurement procedures for both the reference material and a panel of representative individual patient samples.

Measurand

VIM (1993): quantity **subject** to measurement
VIM (2008): quantity **intended** to be measured

- The term measurand includes multiple molecular forms when the clinically important component may not be fully understood.
- Results for a given measurand should be numerically equivalent (within clinically meaningful limits) among different laboratories using ***different procedures.***

Standardization

When results for a measurand are equivalent and, in addition, the results are traceable to the International System of Units (SI) through a higher-order primary (pure substance) reference material and/or reference measurement procedure.

Harmonization

When results for a measurand are equivalent either by being traceable to a reference material or based on consensus approach (such as agreement to all-methods mean) but neither higher-order primary reference material nor an reference measurement procedure exists.

Standard Materials

- Calibration Hierarchy
- Sample type
- Well characterized panels

Pre-submission

- Obtain Feedback on classification, analytical and clinical study design and more
- FDA guidance: Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff; http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf

Conclusions

- Principals of IDE submission for viral IVD
- Analytical Study Requirements

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Thank you!

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Additional Resources

FDA Definition of In-vitro Diagnostic Devices

"Reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. … for use in the collection, preparation, and examination of specimens from the human body."
[21 CFR 809.3]

Benefit-Risk Analysis

False Results

- Identify the risks of false positive and false negative results
- Specific for intended use population & indication
- Indicate the available mitigations

Misinterpretation of Results

- Identify potential risks
- Specific for intended use population & indication
- Indicate the available mitigations

IDE- premarket Submission

- The Agency recognizes that some IDE sponsors may wish to determine whether their IDE study design may support a marketing application if it is successfully executed and meets its stated endpoints without raising unforeseen safety concerns.
- FDA Decisions for Investigational Device Exemption Clinical Investigations http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf

Standard Databases

- Medical Devices Standards Database http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm

- Clinical Laboratory Standards Institute (CLSI) develops global consensus standards and guidelines for healthcare testing (industry, government, professional) Evaluation Protocols (EP) for study design/analysis www.clsi.org

- ISO (International Standards Organization) Standards for estimating bias and imprecision of test methods

Standard Documents I

- C28-A3c. Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory
- EP05-A3. Evaluation of Precision of Quantitative Measurement Procedures
- EP06-A. Evaluation of the Linearity of Quantitative Measurement Procedures
- EP09-A3. Measurement Procedure Comparison and Bias Estimation Using Patient Samples
- EP12-A2. User Protocol for Evaluation of Qualitative Test Performance
- EP17-A2. Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures
- EP21-A. Estimation of Total Analytical Error for Clinical Laboratory Methods
- EP24-A2. Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves;
- MM17-A. Verification and Validation of Multiplex Nucleic Acid Assays

Standard Documents II

- ISO 17511 (2003) is under revision (TC 212, WG2, January 2013)
- EP14-A3 (2014) “Evaluation of Commutability of Processed Samples”
- EP30-A (2010) (former C53-A) “Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine; Approved Guideline”
- EP32-R (2006) (former X05-R) “Metrological Traceability and Its Implementation; A Report” Under revision
- CLSI MM06: “Quantitative Molecular Methods for Infectious Diseases
- ISO N269 Guidance for the preparation of Secondary Reference Materials for NAT and Serological Infectious Disease Assays: Calibration to WHO International Standards

FDA Guidance Documents

- "In Vitro Diagnostic (IVD) Device Studies- Frequently Asked Questions" Published 10/25/07 http://www.fda.gov/cdrh/oivd/guidance/1536.pdf
- Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078384.htm
- Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm267829.htm
- FDA Decisions for Investigational Device Exemption Clinical Investigations http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf
- Highly Multiplexed Microbiological/Medical Countermeasure In Vitro
- Nucleic Acid Based Diagnostic Devices http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM327294.pdf