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Industry Perspective – Key Considerations in Study Design for Glucose and Beyond

FDA-Industry IVD Roundtable Meeting

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Outline

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- Background
- Key Topics—IVD wide implications
  - Method of bias calculation
  - Acceptance criteria and inherent variability of reference analyzers
  - Appropriate role of QSR
- Recommendations & Looking Ahead

Background

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- FDA issued two draft guidances related to blood glucose monitoring (1/7/14)
  - Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use (SMBG)
  - Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use (POCT)

- Industry is committed to design and manufacture of BGMs that meet patient needs.

- Ongoing dialogue with FDA regarding ways to address concerns of harming access to BGM innovation and optimal scientific study design.

Key Topics

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- Among issues, key issues of larger relevance to IVD study design and submissions
  - Method of bias calculation used for the evaluation of potentially interfering substances and hematocrit
  - Acceptance criteria that do not take into account the inherent variability of reference analyzers
  - Appropriate role of QSR & distinction from premarket submission

Method of Bias Calculation – Interfering Substances: FDA Draft Guidances and CLSI EP7-A2

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- As currently proposed, in order to determine the influence of a potentially interfering substance:
  - A sample containing the interfering substance of interest should be tested on both the reference method and the BGM device.
  - The bias due to the interfering substance is determined by ***comparing the BGM results to those of the reference method.***

- Fundamental discrepancy with CLSI EP7-A2, *Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition*, which states that, in order to determine the influence of a potentially interfering substance:
  - A test sample, containing the interfering substance of interest, and a control sample, having a composition identical to that of the test sample minus the interfering substance, should both be tested on the BGM device.
  - The bias due to the interfering substance is then determined by ***comparing the BGM results obtained with the test sample relative to the results obtained with the control sample.***

- Departure from recognized method of bias calculation and numerous other FDA guidances—needs to be addressed

Method of Bias Calculation – Interfering Substances: CLSI EP7-A2 "Paired-Difference Testing"

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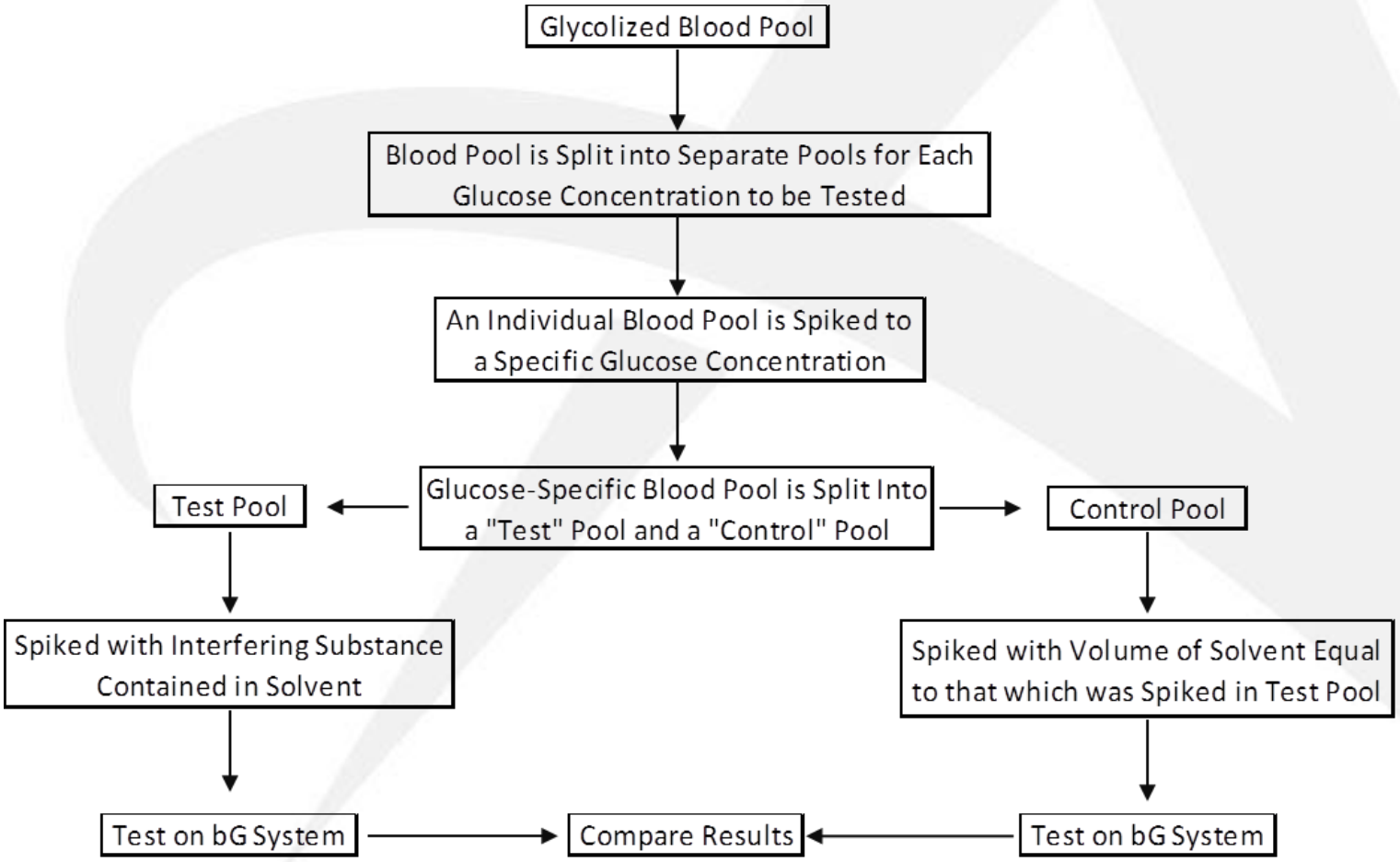
Interference is calculated relative to the measurement of the analyte in a control or base pool.



Method of Bias Calculation – Interfering Substances: The Importance of the Control Sample

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- The use of a control sample in interference studies is critical for ***isolating the effect*** of the potentially interfering substance under investigation;
  - The control sample eliminates systematic bias that can occur due to pre-analytical effects associated with contrived samples.

Control Sample – Bias Factors
~~Sample bias (due to donor, glycolysis, matrix effects, etc.)~~
~~Bias due to the solvent~~
~~Reference analyzer bias~~

Test Sample – Bias Factors
~~Sample bias (due to donor, glycolysis, matrix effects, etc.)~~
~~Bias due to the solvent~~
~~Reference analyzer bias~~
Bias due to interfering substance

When the control sample is used, the bias due to the potentially interfering substance is isolated.

Method of Bias Calculation – Interfering Substances: FDA Draft Guidance Procedure

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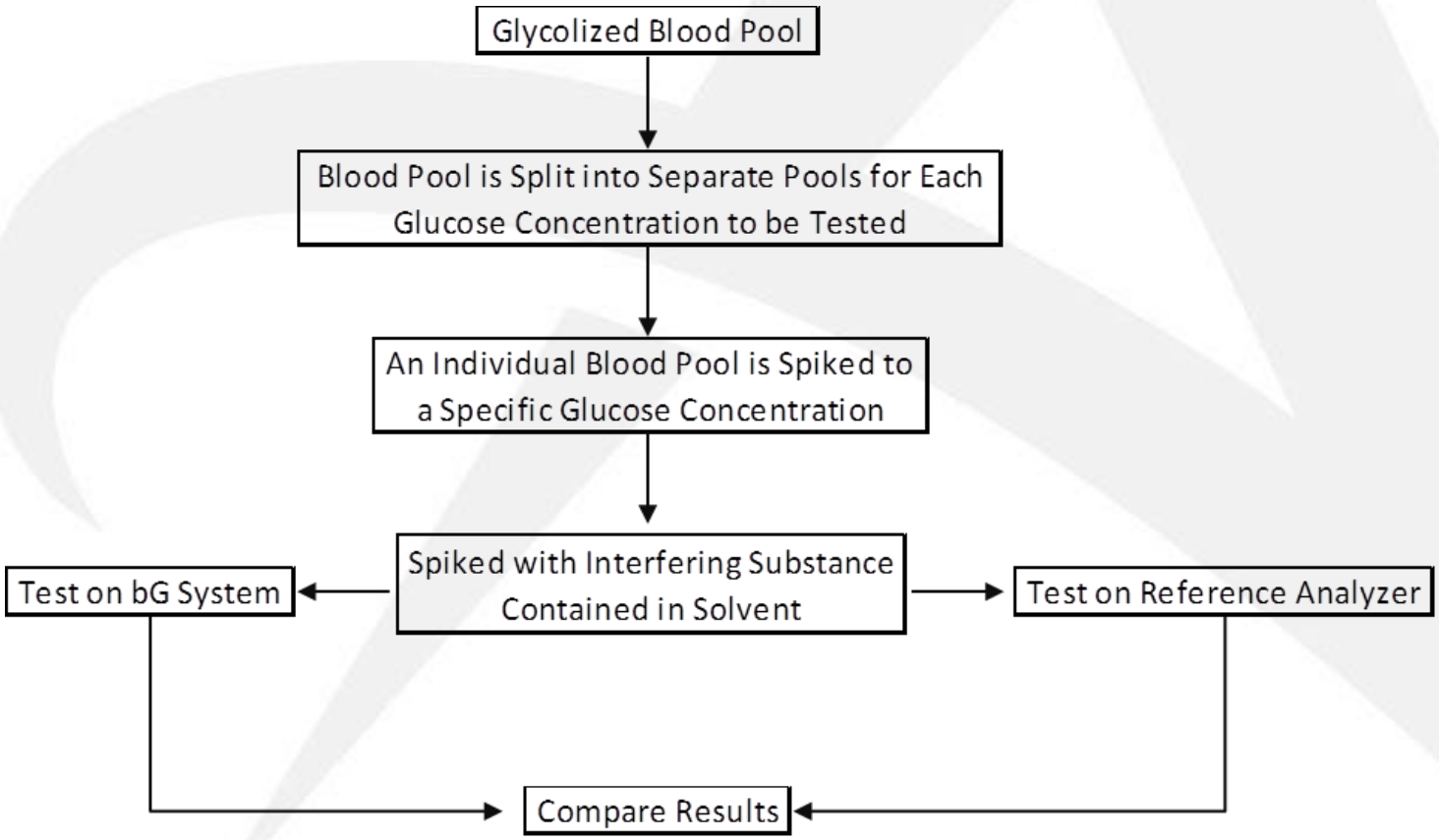
Interference is calculated relative to the reference analyzer, with no control sample used.



Method of Bias Calculation – Interfering Substances: Direct Comparison to the Reference Analyzer

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- By comparing the test results directly to the reference analyzer, the study design is susceptible to systematic bias that is unrelated to the substance under investigation;
  - No control sample is present to account for any pre-analytical effects.

Test Sample – Bias Factors
• Sample bias (due to donor, glycolysis, matrix effects, etc.) • Bias due to the solvent • Reference analyzer bias • Bias due to interfering substance

When this study design is used, it is not possible to isolate the effect of the interfering substance, and the effect may be over- or under-represented by the results.

Method of Bias Calculation – Interfering Substances: The Importance of the Control Sample – CLSI EP7-A2

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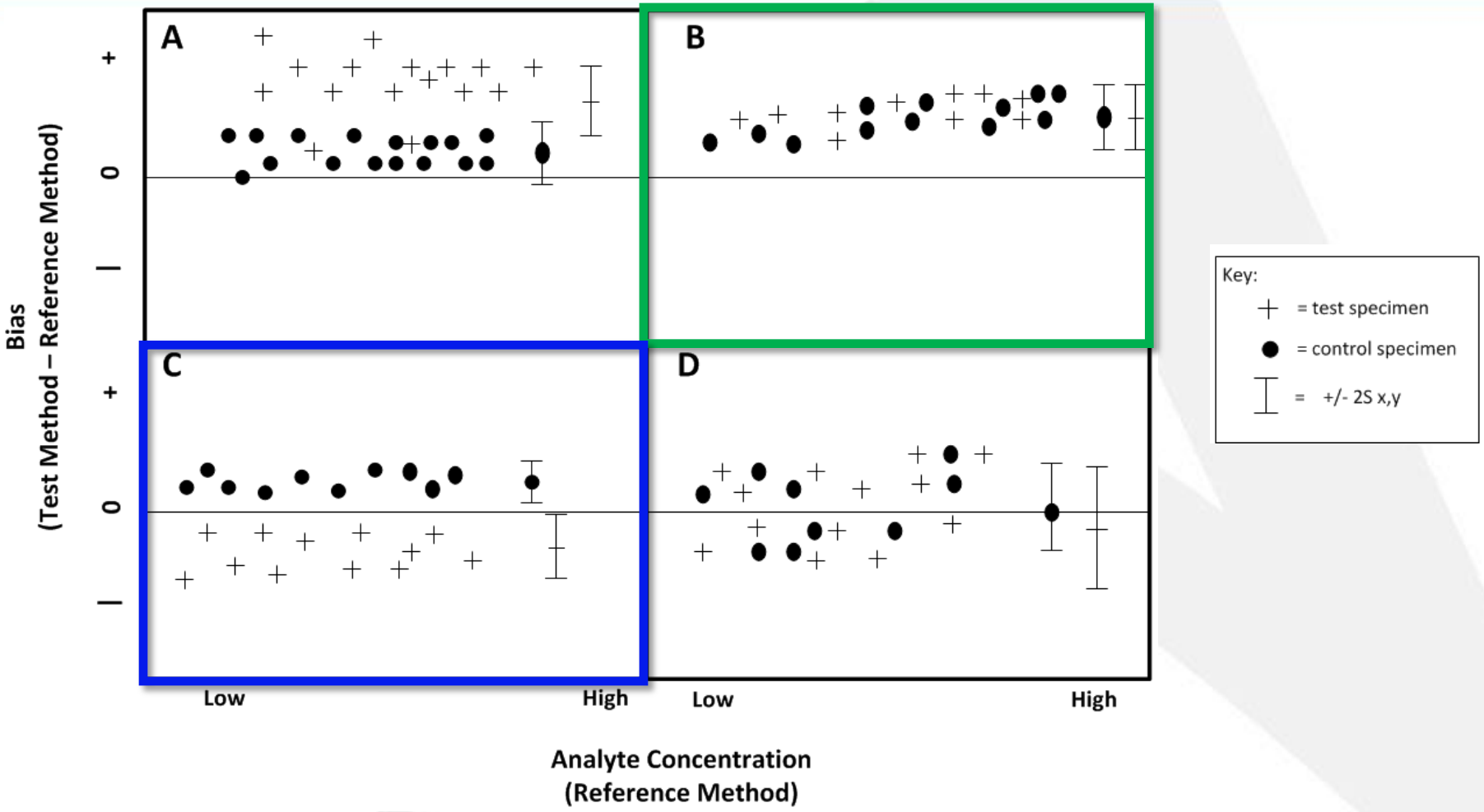

A control sample is necessary to correct for systematic bias that is unrelated to the potentially interfering substance of interest. This applies not only to BGM systems but to IVDs in general.

FDA BG Guidance Hematocrit Evaluation: Overview of Acceptance Criteria

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- For the evaluation of hematocrit, currently proposed that specify that:
  - For Self-Monitoring BGM Systems (SMBG), the bias should be less than 8% on average when compared to the reference value.
  - For Point-of-Care BGM Systems (POCT), the bias should be less than 5% on average when compared to the reference value.

- For the evaluation of hematocrit, both draft guidances set forth testing a blood sample having a glucose concentration targeted in the range of 30 – 50 mg/dL.

- For the evaluation of hematocrit, the maximum allowable error when testing a blood sample having a glucose concentration of 50 mg/dL would be:
  - For Self-Monitoring BGM Systems: ±4 mg/dL;
  - For Point-of-Care BGM Systems: ±2.5 mg/dL.

Inherent Variability of Reference Analyzers: Relation to BG Guidance Acceptance Criteria

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- Bias requirements of ±4 mg/dL (SMBG) and ±2.5 mg/dL (POCT) challenge the performance capabilities of even reference analyzers.
- The User Manual for a commonly used reference instrument for BG systems states that the precision of the system is "*±2% of the reading, or 2.5 mg/dL, whichever is larger.*"
- This means that, due to the imprecision of the reference analyzer alone, the entire or a large portion of the allowable BGM error budget for hematocrit would be consumed:

	Total Error Budget	=	*BGM Error Due to Hematocrit*	+	*Reference Analyzer Precision Error*
(SMBG)	*4.0 mg/dL*	=	*1.5 mg/dL*	+	*2.5 mg/dL*
(POCT)	*2.5 mg/dL*	=	*0.0 mg/dL*	+	*2.5 mg/dL*

With these criteria, 63% (SMBG) and 100% (POCT) of the entire allowable error budget is consumed by a factor that is not related to the performance of the BG systems.

Inherent Variability of Reference Analyzers: Additional Considerations

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- Recognition that reference analyzers will exhibit variability.
  - ***ISO 15197:2013*** (*In vitro diagnostic test systems – Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus)*
  - ***CLSI POCT12-A3*** (*Point-of-Care Blood Glucose Testing in Acute and Chronic Care Facilities)*
  - ***In accuracy studies per above, duplicate reference measurements must agree within ±4 mg/dL or 4% of one another***, whichever is greater
    - Necessary in order for reference result to be valid.
    - Reflects recognition by field that reference analyzers will exhibit variability.
- Notably, Dr. William Clark (Johns Hopkins University) showed that one reference analyzer would not even meet the accuracy criteria required in the POCT draft guidance when its results were compared to those of another reference analyzer—DTS Hospital Diabetes Meeting, 5/13/14

Need for acceptance criteria to take into account the inherent variability of reference analyzers.

Appropriate Role of QSR

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- Section VII of both draft guidances specifies that a description of the test strip lot release procedure and criteria must be included within the 510(k).
- Lot-release testing of finished products
  - conducted under good manufacturing practices to assure that manufacturing specifications have been met
- Lot release criteria
  - required by QSR to have lot release criteria to assure meeting of specifications of their products in the market
- Lot-release testing is not part of 510(k) submission.
  - post-market, not pre-market function
  - inclusion of lot-release testing in 510(k)s will not prevent non-compliant manufacturers from releasing poorly performing lots

Recognize postmarket, not premarket issue and support critical role of FDA to monitor adherence and enforce violations through postmarket inspection.

Overall Implications Beyond BGMs—Recommendations Moving Forward

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- Consider scientific rationale and longstanding recognized IVD study designs.
- Work together to support future innovation for patients.
  - Concepts described in CLSI EP7-A2 apply not only to the assessment of potentially interfering substances for BGM systems, but to all IVDs
    - Change to this well recognized methodology will have a significant impact across multiple industries that have long integrated and adopted this well grounded scientific approach.
  - Reference analyzer variability should be taken into account when developing acceptance criteria and this concept applies across the entire IVD industry.
  - Recognize the appropriate role of QSR as distinct from the review process (postmarket, not premarket issue). Support FDA's critical role in postmarket inspection and compliance to ensure access to safe and effective medical products.

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