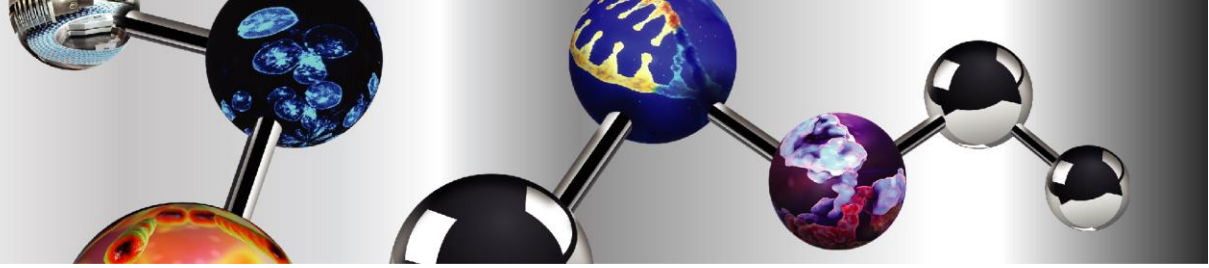
aaps PharmSci360 OCT 17-20 2021



Whole Blood Bioanalysis for Biologics- What Analyses Do You Need?

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BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

Session Description and Objectives

Microsampling for biologics has been somewhat hindered by the complexity of the whole blood matrix relative to the typical serum matrix. This talk will present a conceptual statistical plan using data from fully matched whole blood and serum samples. The goal is to identify additional analyses suggested by attendees that the field would appreciate to help facilitate movement towards whole blood bioanalysis as a viable alternative.

Upon completion, participants will be able to

- describe the importance of whole blood bioanalysis to microsampling.
- identify key questions before they would be comfortable implementing whole blood bioanalysis
- design a bridging study for whole blood and serum

Biography and Contact Information

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- Bioassay Development Lead at Bill & Melinda Gates Medical Research Institute (Gates MRI)
- Oversees all bioassay activities supporting primary and secondary objectives for selected programs in the global health program: e.g. malaria, respiratory syncytial virus, and maternal, neonatal, and child health
- Ph.D. in Biochemistry from The Scripps Research Institute
- Prior positions across bioanalytical, biomarker, and immunogenicity methodology and interpretation at EMD Serono, Biogen, Bristol-Myers Squibb, and BioMarin Pharmaceutical Inc.

Historical Microsampling (Dried Blood Spot) Rationale

Nonclinical

- 3R considerations:
  - Smaller samples
  - Reduce animal numbers
  - Refinement of bleed technique by reducing or eliminating rodent warming
- Data considerations
  - Serial PK profiles from same animal rather than composite
  - Directly correlating TK exposures with toxicology end points in the same animals rather than satellite
- Indirect cost savings
  - Animal husbandry
  - Reduced drug substance

Clinical

- Clinical considerations:
  - Obtain samples from children
  - Sampling of vulnerable subjects
- Data considerations
  - Collection of samples in a closer timeframe to a clinical event, e.g. suspected malaria infection
  - Freeing-up blood volume to collect additional samples (e.g. biomarkers)
- Patient experience:
  - Sample collection in settings more convenient to the patient (local practice, home, remote geographical locations)
  - Limiting disruption to normal life for clinical study subjects
  - Less invasive than venipuncture
- Direct cost savings:
  - Ambient temperature sample shipments (pending demonstrated analyte stability),
  - Shipping is major component of central lab cost
- Indirect cost savings:
  - Reduced requirements for clinical staff to collect blood samples, e.g. phlebotomist not required
  - Improved clinical trial recruitment and retention through more convenient blood collection procedures
- Process simplicity:
  - Reduced/eliminated on-site processing: requirement to separate serum fraction, store and ship frozen samples, defrost samples, subaliquot – among others

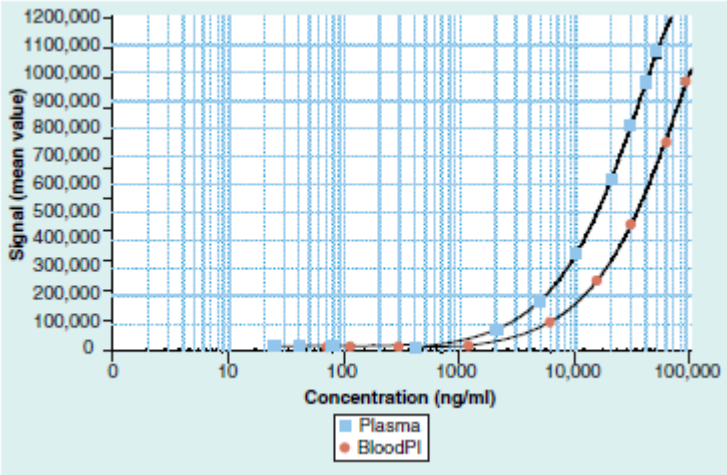
Spooner et al (2019)

Opportunity in Low and Middle Income Countries (LMIC) and Globally

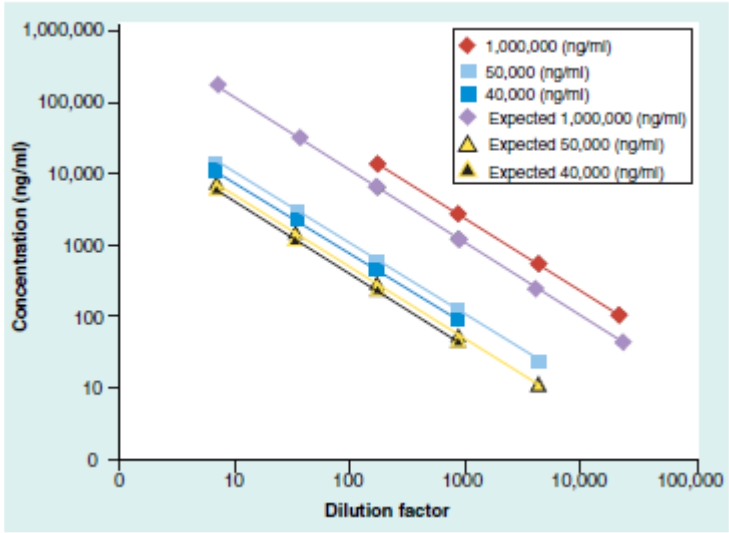
- Use whole blood volume absorptive microsampling (VAMS) as the primary matrix rather than serum
  - Other programs have bridged to VAMS for selected studies
  - Gates MRI target populations are the selected studies that others have pursued using VAMS
- Build upon the body of literature that has advanced volumetric microsampling for pharmacokinetics
- Begin building evidence to support home or community sampling in LMIC and globally (long-term goal)

Early Example of Monoclonal Antibody Analytical Comparison

Recovery



Dilution Linearity



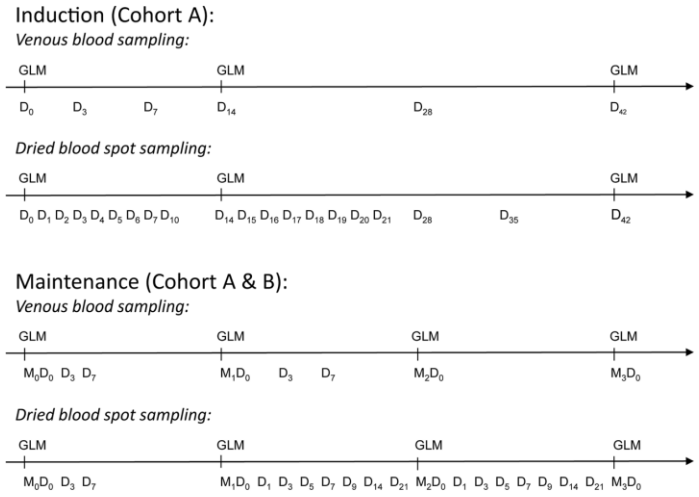
2010 Future Perspectives

- Further investment over the next 5 years to
  - advance the technique
  - develop user confidence in DBS technology for quantitating Ab
- Within 10 years the DBS sampling technology could be a standard

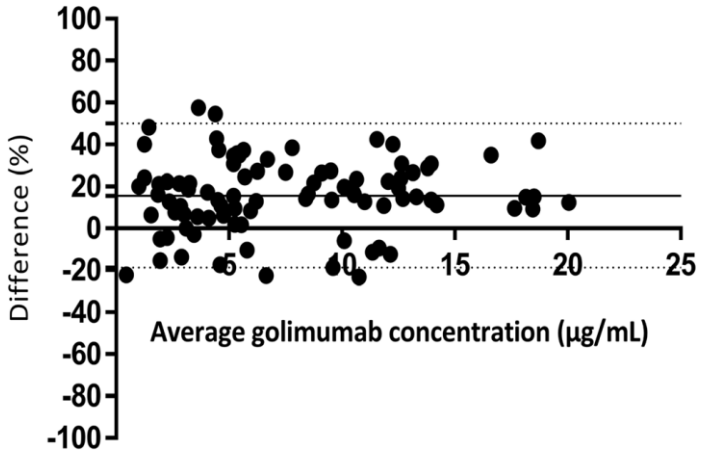
Prince et al (2010)

Example of Monoclonal Antibody Pharmacokinetic Bridging Study

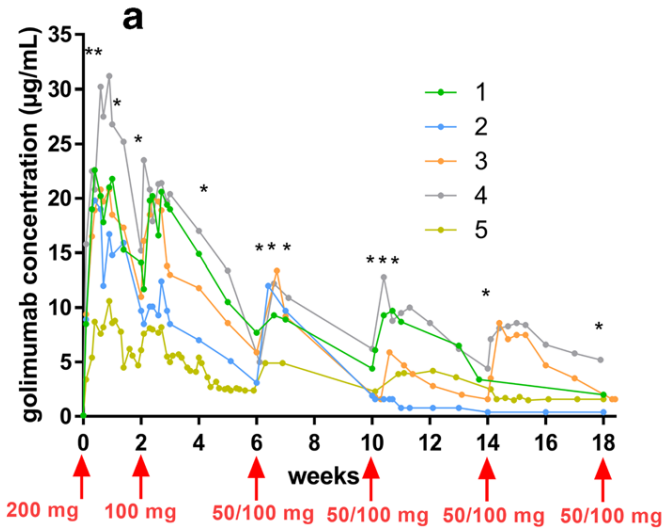
Study Design



Correlation Bland-Altman



Pharmacokinetic Profiles



Detrez et al (2019)

Diluted Whole Blood on Gyros – Preclinical Application in Mouse

Study Design

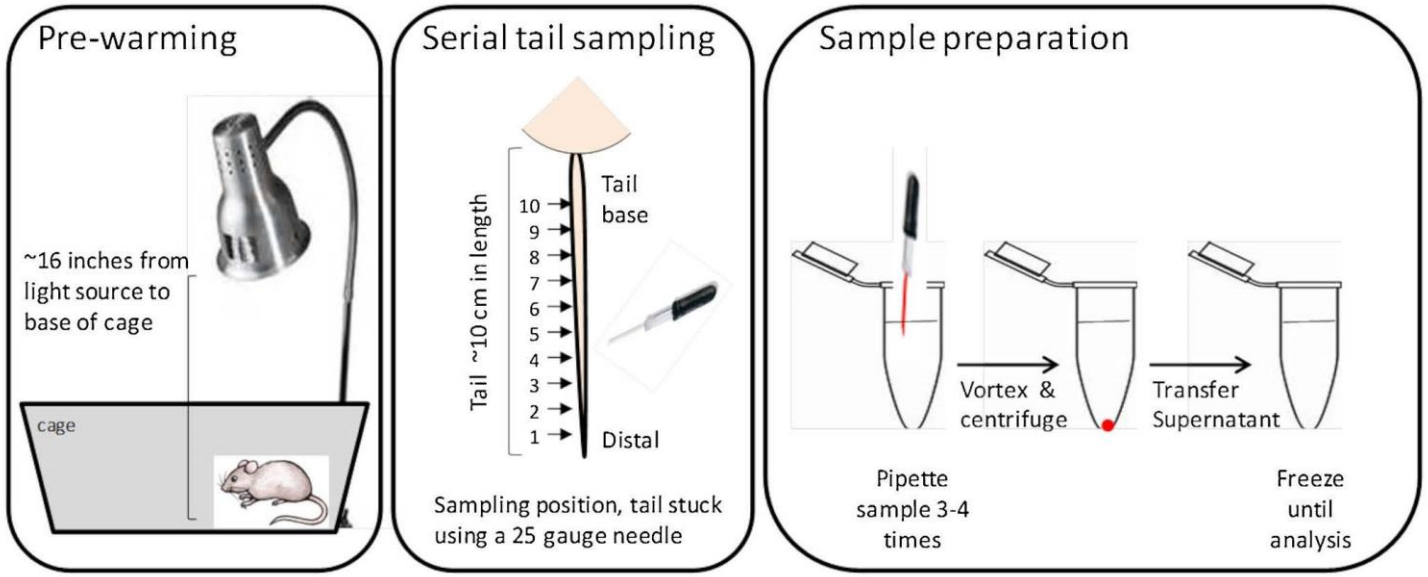
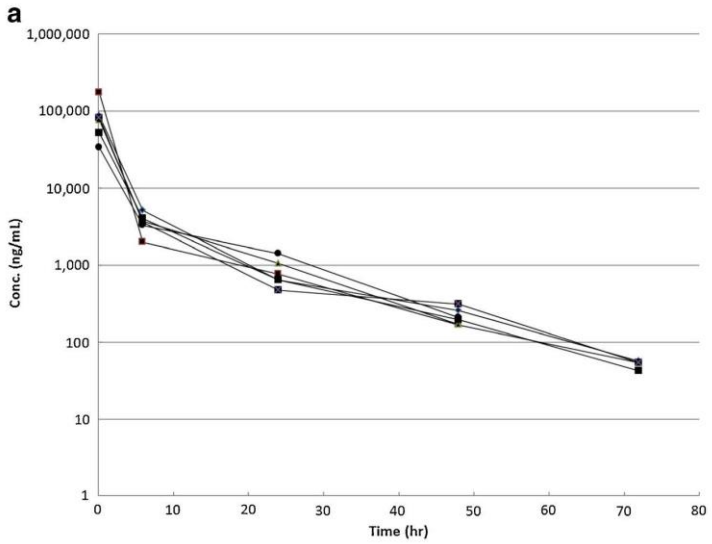


Fig. 1 Cartoon of serial sampling process. Cartoon depicts stages as pre-warming, serial tail sampling and sample preparation. Objects are not drawn to scale.

Individual PK Profiles



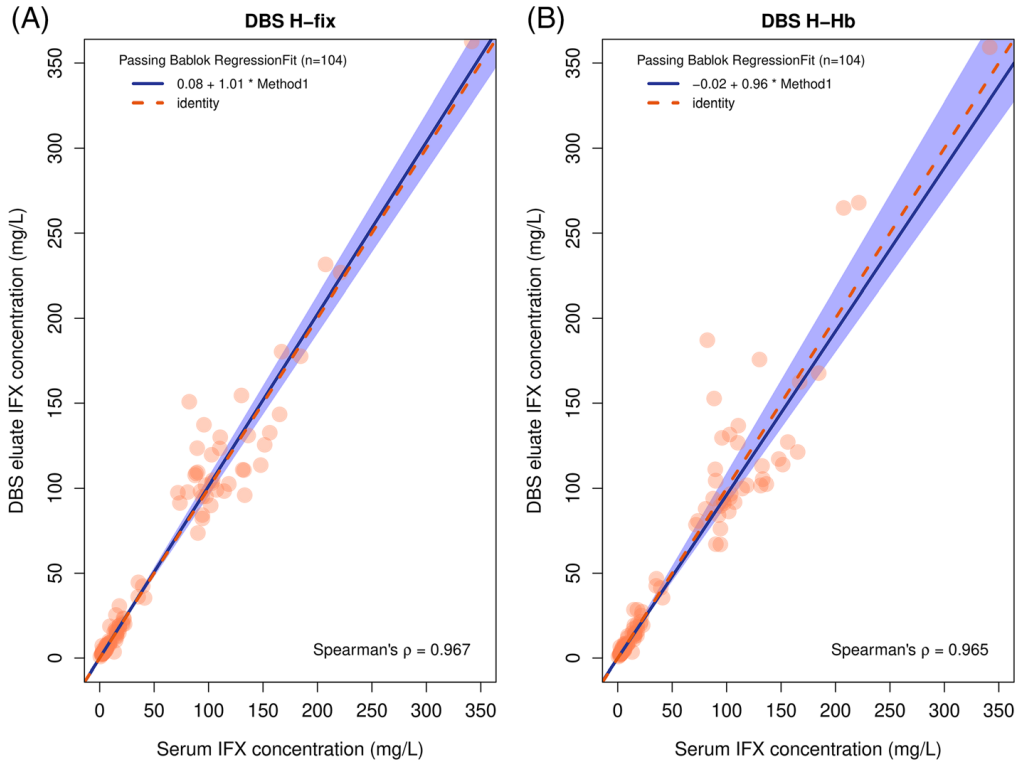
Joyce et al (2014)

Integrated Approach to Proactively Address VAMS Implementation

- Support whole blood as the **primary** matrix for mAb in clinical development
  - Support implementation starting in nonclinical stage for subsequent mAb portfolio
- Analytical Method Development
  - Use volume absorptive microsampling (VAMS) with plastic substrate
  - 100% recovery versus whole blood
- Clinical bridging study
  - Enable modeling to include nonclinical and historical comparator serum data
  - Fully matched profiles for venous serum vs capillary blood VAMS
    - Fully matched design provides unique opportunity for comparisons
- **Following slides present subset of options under consideration**

Planned Analyses: Sample Correlation

Correlations



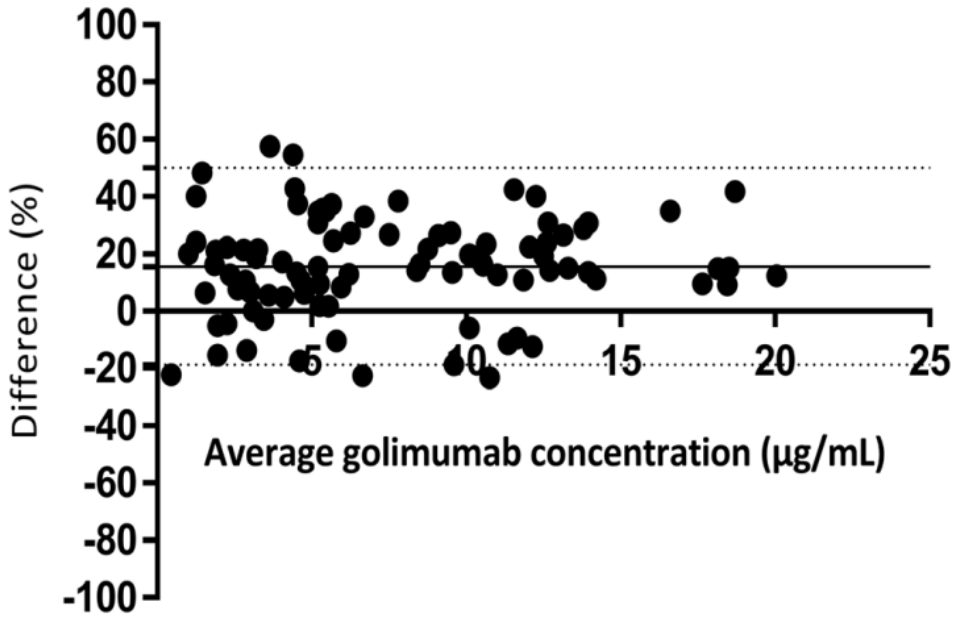
Variables

- Direct serum to whole blood not expected to be slope=1
  - mAb excluded from cellular fraction
- When slope=1 desired for visual purposes
  - Mean hematocrit (L)
  - Individual sample hematocrit (R)

Berends et al (2019)

Planned Analyses: Sample Bland Altman Correlation

Correlations



Variables

- Evaluate different factors on X-axis for visual trends
  - Average between serum and VAMS
  - VAMS concentration (primary matrix)
  - Individual sample hematocrit
  - Storage time (incurred stability)
- Potential for multi-factorial analysis to evaluate variable interactions

Planned Analyses: Patient Non-Compartmental Analysis (NCA)

Parameters to Compare?

- C_{max}
- T_{max}
- AUC
- $T_{1/2}$

Conclusions that Agree/Differ?

- Dose proportionality
- Bioavailability
- Gender effect

What would you do with an extensive data set with fully matched PK samples in both serum and VAMS?

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  - https://www.pcsig.org/
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  - Micha Levi
  - Jorg Thommes
  - Jeroen Medema
  - Jintanat Ananworanich
  - Jared Silverman
  - Product Development Team

Questions

- What would you do with an extensive data set with fully matched PK samples in both serum and whole blood?
- What information from this study would help you assess the possibility to use whole blood in your own clinical studies?
- Which analyses most interest you?

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