Microsampling – What it is and how it can influence drug development

1st February 2018

AAPS Webinar

Neil Spooner & Prajakti Kothare

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Session Description and Objectives

This session will provide a background to the use of microsampling for the quantitation of drugs, metabolites and biomarkers in preclinical and clinical development. Presentations will include techniques, benefits and challenges and will also provide an update on what's new with microsampling (novel techniques / devices). Further, there will be case studies demonstrating clinical applications and how bridging study data is used to demonstrate concordance between concentrations in DBS and plasma samples and gain regulatory approval.

Objectives

- What is microsampling and how / when can it be used
- Advances in microsampling - currently implemented and novel techniques/devices
- Implementing microsampling for clinical studies including bridging studies
- Future of microsampling, including home sampling

LIVE POLLING QUESTION #1

Myself or my company is currently using microsampling for:

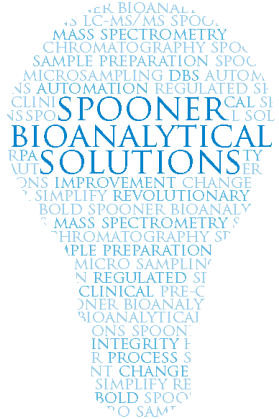
1. Discovery studies (PK, PD, Pharmacology etc.)
2. Preclinical toxicology
3. Clinical
4. Currently not using microsampling

Introduction to Microsampling

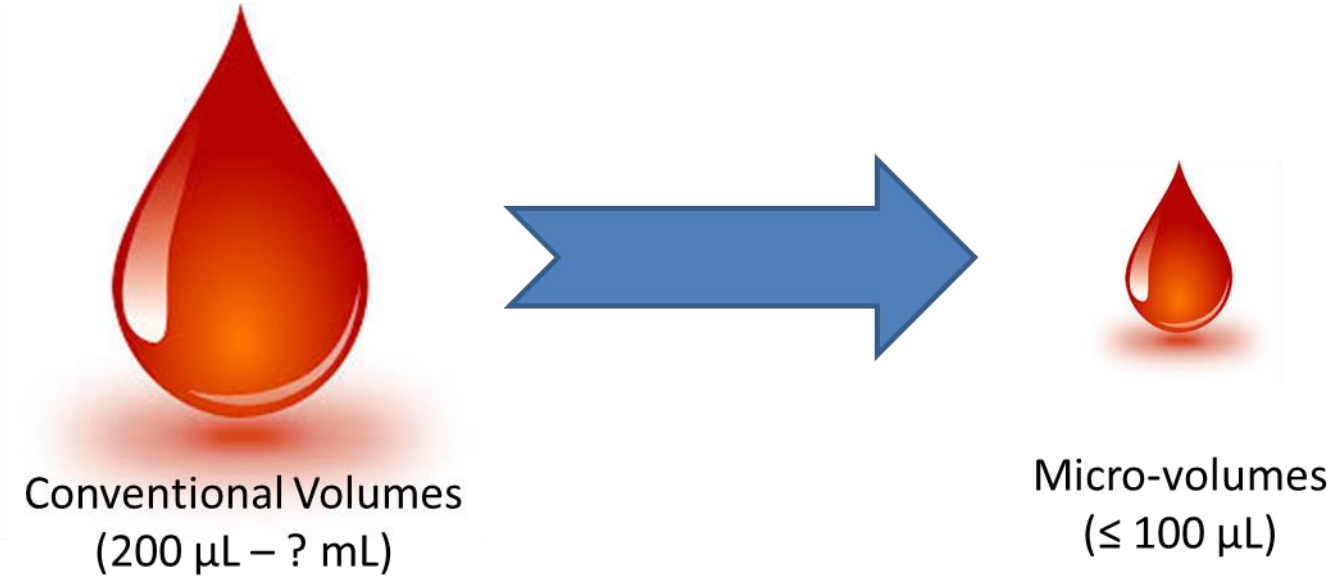
1st February 2018

AAPS Webinar

Neil Spooner

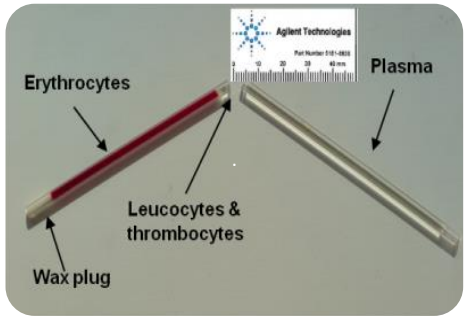


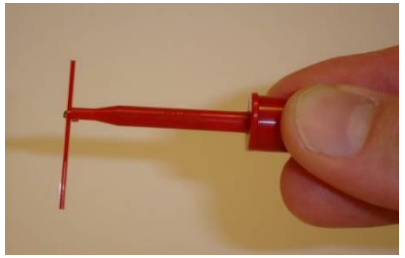
What is microsampling?

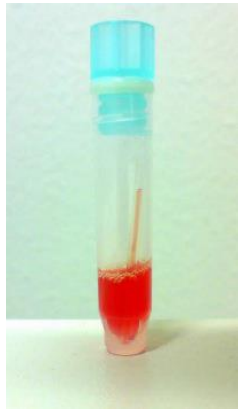


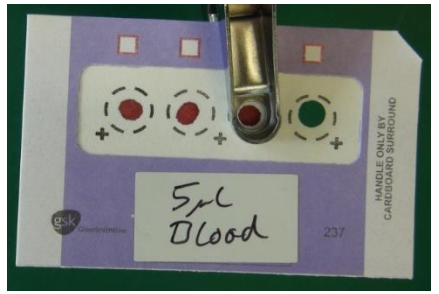
Technologies for collecting & analysing smaller blood and plasma / serum volumes for the accurate determination of circulating concentrations of therapeutic drugs, metabolites & biomarkers in pre-clinical & clinical studies

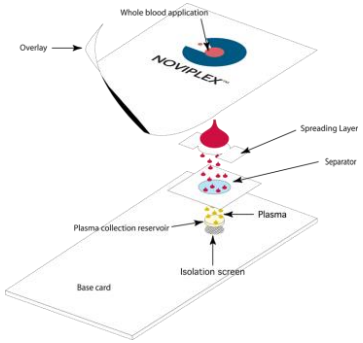
What techniques are available?











Drivers for implementation of microsampling

Pre-clinical

- Ethical - 3Rs
  - Reduction in rodent animal number requirements
    - Elimination of TK satellites reduces number of animals by 30-40%
      - » Effects primarily on reticulocytes; no affect in overt toxicity assessment, e.g., hepatotoxicity, renal toxicity*
    - Serial TK & PK sampling in mice
    - Discovery PK, mouse TK & PK & juvenile studies
  - Refinement of bleeding technique
    - Reduction, or elimination of rodent warming
    - Sampling from more convenient / less disruptive location

*Powles-Glover *et al* (2014) *Reg. Toxicol. Pharmacol*. **68**, 325

Drivers for implementation of microsampling

Pre-clinical Continued

- Improved data quality
  - Exposure data in main study animals, rather than additional satellites
  - Direct correlation of exposure with PD and toxicological outcomes
- Enables samples to be taken for other purposes
  - Additional PK/TK timepoints, biomarkers, metabolites, Clin. Path. determinations, etc.
- Cost
  - Reduced animal numbers, housing, drug substance
    - …..but, consumable costs are higher

However…… May be an issue for metabolites in safety testing!

Microsampling has been widely adopted by Pharma companies & CROs for pre-clinical work

Useful guidance on approaches on NC3Rs website microsampling pages

- Study designs, technique videos, bibliography, decision trees, benefits, *etc*

Drivers for implementation of microsampling

Clinical

- Potential for simplified sample collection – ‘finger prick’ approach
  - Improved recruitment?
- Ability to generate exposure data where otherwise difficult or not possible
  - Patient convenience – Home / pharmacy & self / assisted sampling
  - Sampling in geographically remote locations
  - Pediatrics
  - Therapeutic drug monitoring
  - Critically ill patients
  - Demonstration of patient compliance
  - Obtaining data related to a clinical episode
  - Application to popPK and trough sampling study designs

Drivers for implementation of microsampling

Clinical Continued

- Enables samples to be taken for other purposes
  - Biomarkers, metabonomics, co-medications
- Simplified workflows for dried blood approaches
  - No centrifugation, matrix transfer, aliquotting, etc. Facilitates automation
- Cost Savings
  - Particularly for dried blood – Ambient temperature shipment and storage
- Minimises blood “wastage”
  - Why are we sampling 2 mL blood when we are analyzing a 25 µL aliquot?

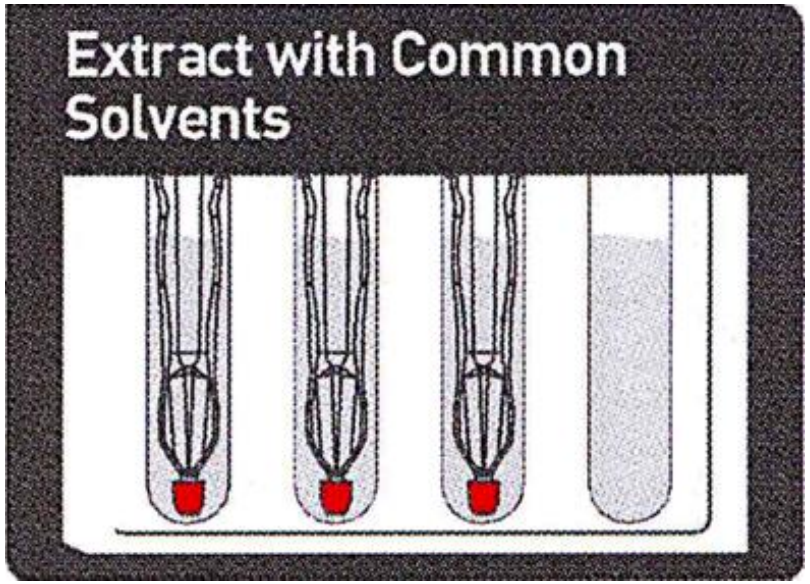
Facilitating patient driven healthcare…….

NB - these technologies all require a time stamp for sample collection

Drivers for Implementation of Microsampling

Bioanalysis

- Potential for increased automation of sample extraction……..
- Increased communication with sample originators, and those responsible for data processing & submission
- Increased consideration of the journey of the sample
- Staff involvement with new technology development & implementation



Dried Blood Spots

- Established for neonatal screening for 50+ years
- Delivers all the advantages of microsampling
- **PLUS** - Simpler process
  - Removes need for centrifugation or sub-aliquots
  - Dry ice and freezers not required
    - BIG cost savings on sample shipments

Barfield *et al* (2008) *J. Chrom. B* **870**, 32; Spooner *et al* (2009) *Anal. Chem.* **81**, 1557; Spooner *et al* (2010) *Bioanalysis* **2**, 1515; Pandya *et al* (2011) *Bioanalysis* **3**, 779; Stokes *et al* (2011) *Lab. Animals* **45**, 109

Automated analysis of DBS samples

ThermoFisher SCIENTIFIC

PerkinElmer For the Better

CAMAG

Spark HOLLAND

prolab Instruments GmbH

Hudson ROBOTICS, INC.

Advion

BSD ROBOTICS

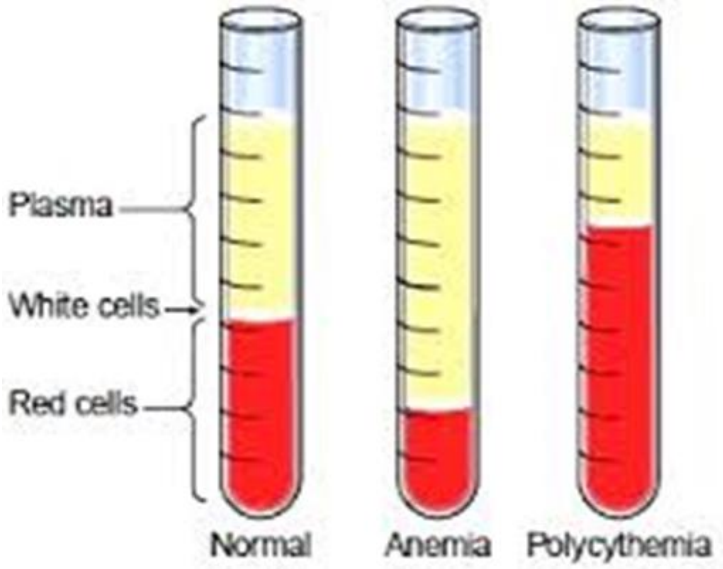
However…….

…..for quantitative analyses, an accurate volume needs to be spotted,

or punched from the sample

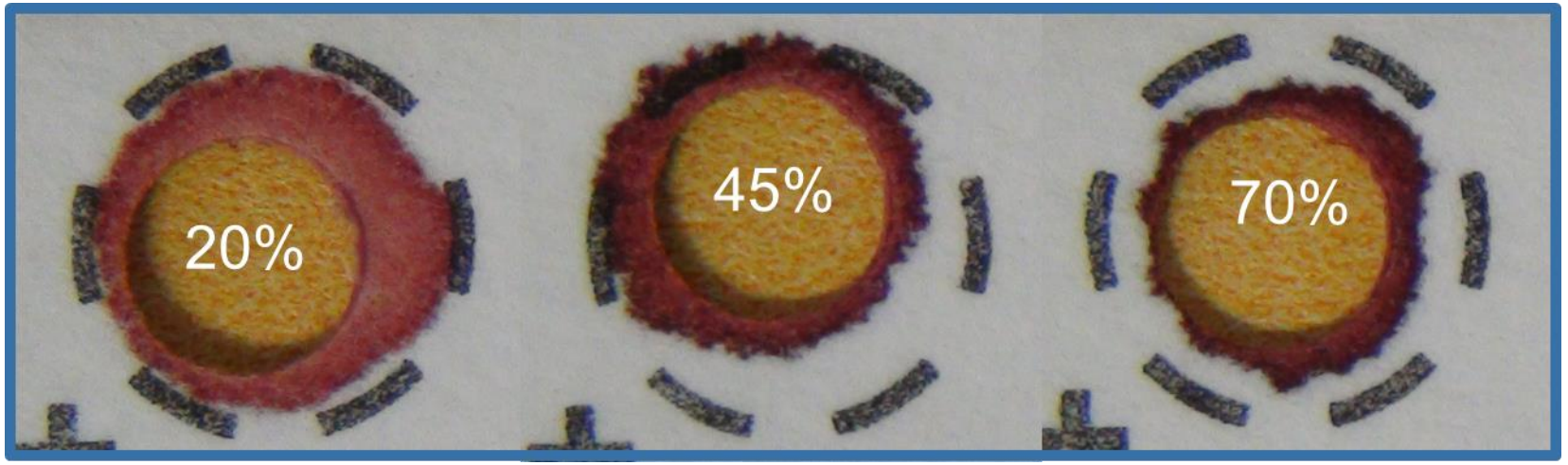
Problem!!!

Hematocrit



Woops!!!

Blood hematocrit affects the size of the derived blood spot



- Solved by spotting accurate volume & punching whole spot, or closely matching HCT of cal's & QC's to samples
- Wide range of HCTs not often a major issue for tox studies

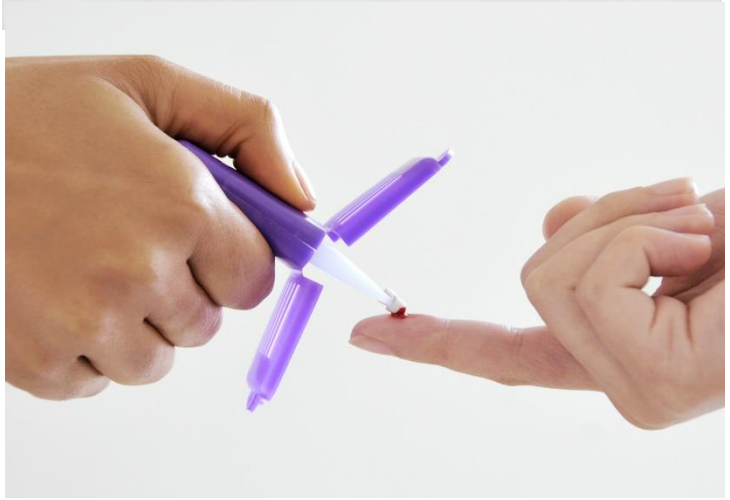
O'Mara *et al* (2011) *Bioanalysis* **3**, 2335; de Vries *et al* (2013) *Bioanalysis* **5**, 2147; Cobb *et al* (2013) *Bioanalysis* **5**, 2161

….but that didn’t stop the technology from progressing

Volumetric Absorptive Microsampling - Mitra

neoteryx™
The promise of microsampling, delivered

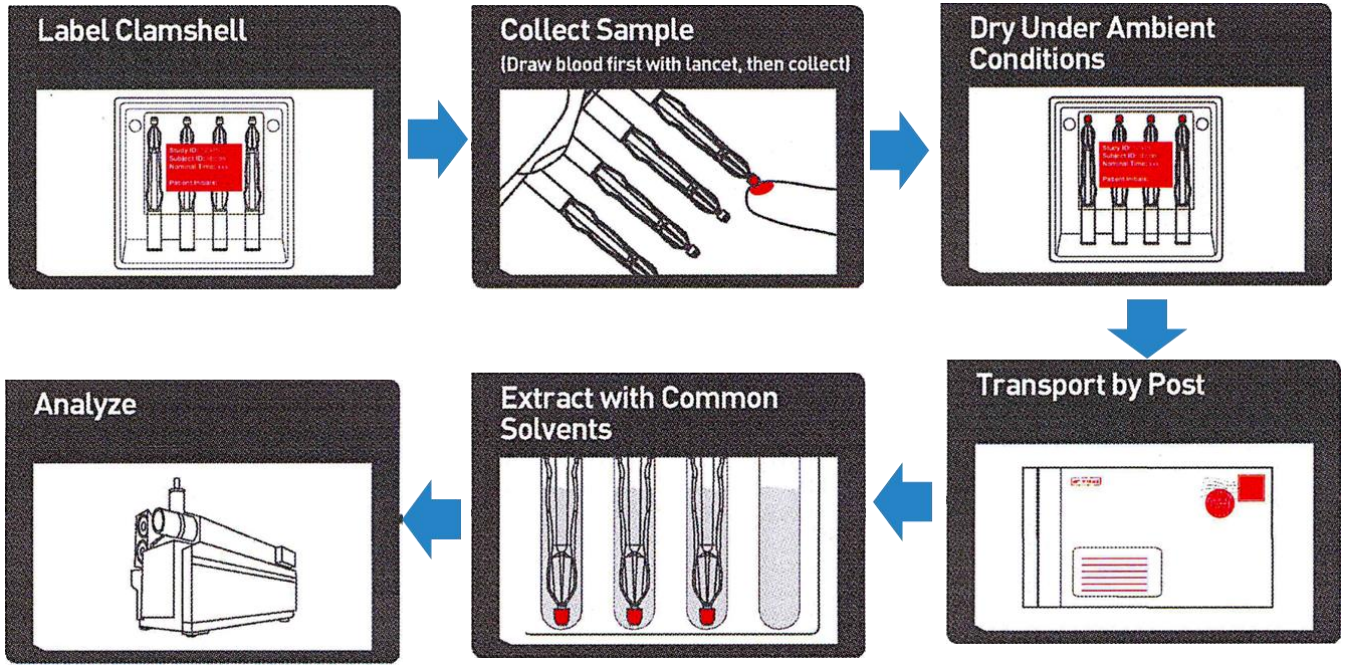
- Dried blood sample
- Hydrophilic porous material
- Each Tip has a fixed, highly reproducible internal porous volume
  - 10µL, 20µL & 30µL
- Rapid wicking
  - Under 6 seconds
- Simple to use

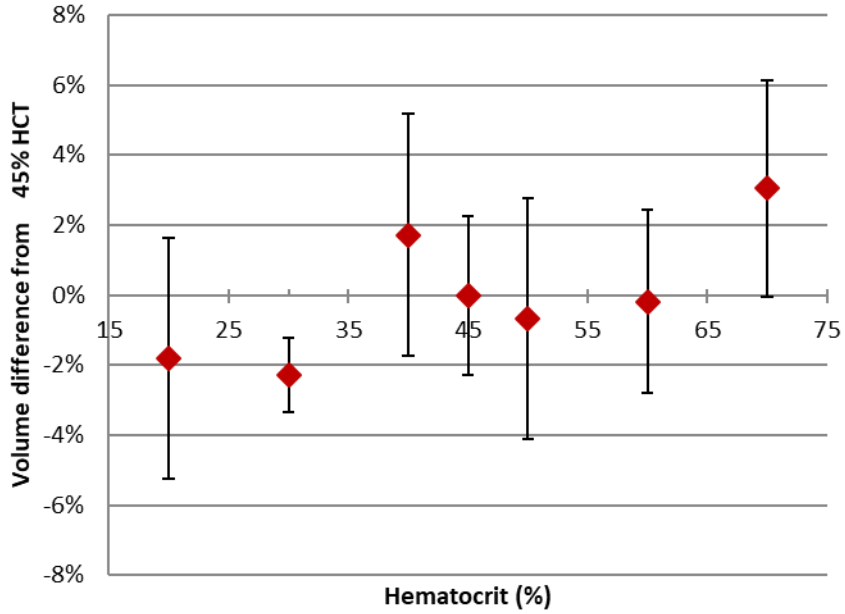


neoteryx™

The promise of microsampling, delivered

Mitra®



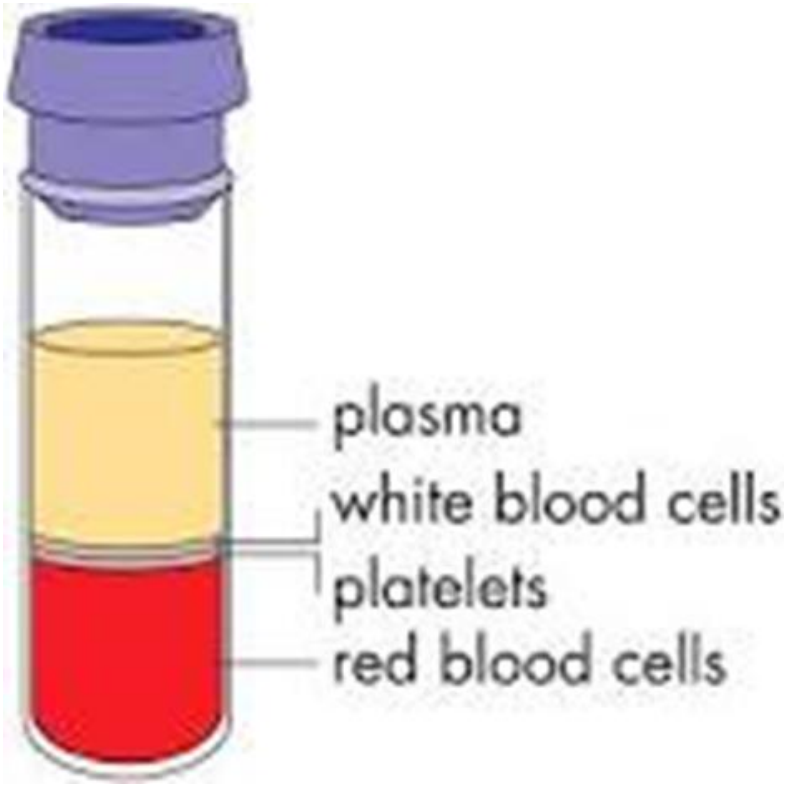


Human blood at different HCTs was spiked with ^{14}C caffeine

Tip oxidised to CO_2 and counted

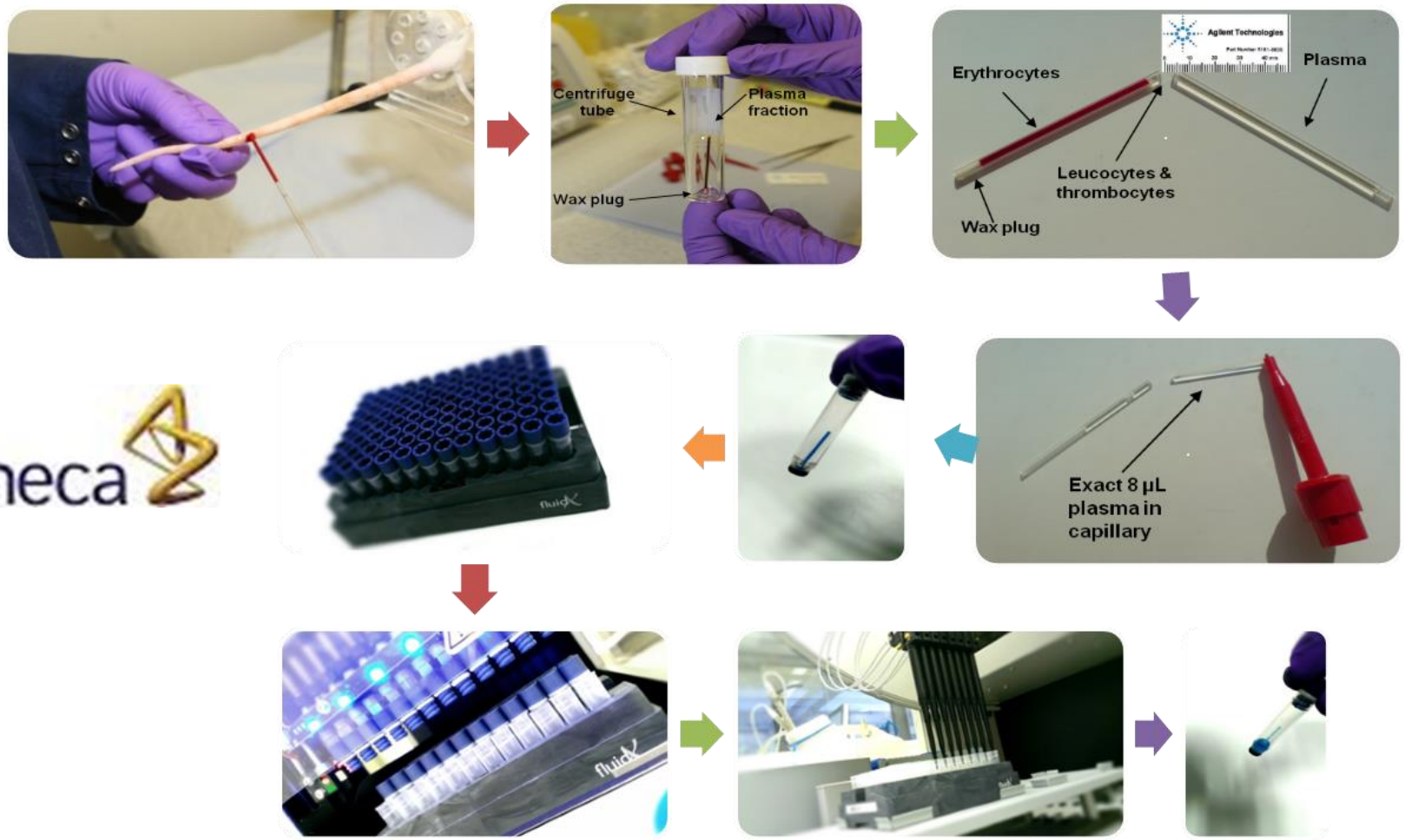
Denniff & Spooner (2014) *Anal. Chem.* **86**, 8489; Denniff *et al* (2015) *J. Pharm. Biomed. Anal.* **108**, 61; Spooner *et al* (2015) *Bioanalysis* **7**, 653

But what if you want plasma rather than whole blood??!!



Emmons & Rowland (2010) *Bioanalysis* **2,** 1791

Plasma sample collection & processing



AstraZeneca

Jonsson, *et al.* (2012) *Bioanalysis* **4,** 1989

SARSTEDT

Microvette®

Current Regulatory Landscape

Pre-Clinical

- Broad Regulatory support
  - Beharry (2010) *Bioanalysis* **2**, 1363
  - Viswanathan (2012) *Bioanalysis* **4**, 1417
- ICH Q&A on Microsampling as part of ICH S3A Guideline for TK
  - Finalised November 2017

Clinical

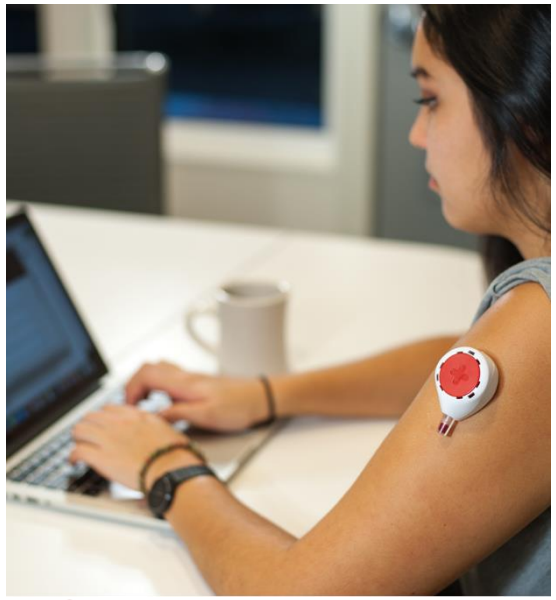
- FDA & EMA requirement to demonstrate concordance between wet and dry samples for each indication investigated
  - Evans, *et al* (2015) *AAPS J.* **17**, 292
  - Kothare, *et al* (2016) *AAPS J.* **18**, 519

Bioanalytical

- No specific guidance at this time
  - Follow current BA Guidance from EMA & FDA, plus consider:
    - HCT, recovery, spotting volume, stability during drying & different temperatures, homogeneity
      - Xu *et al* (2013) *Bioanalysis*, **5**, 341
      - Nilsson *et al* (2013) *Bioanalysis* **5**, 731
      - Timmerman *et al* (2013) *Bioanalysis* **5**, 2129
      - Jager *et al* (2014) *Bioanalysis* **6**, 2481
      - White *et al* (2014) *Bioanalysis* **6**, 2581
      - Wickremsinhe (2015) *Bioanalysis* **7**, 869

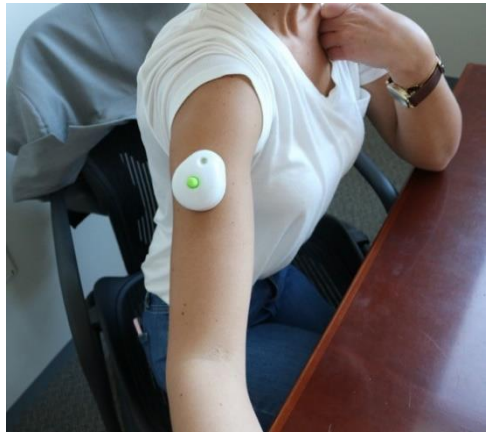
New Patient Centric Sampling technologies are on the way!

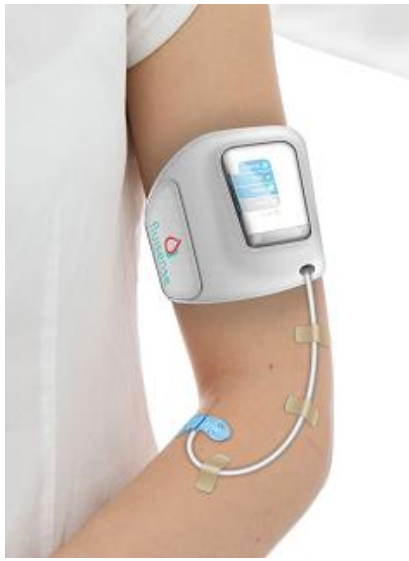
Patient Centric Technologies – Samplers



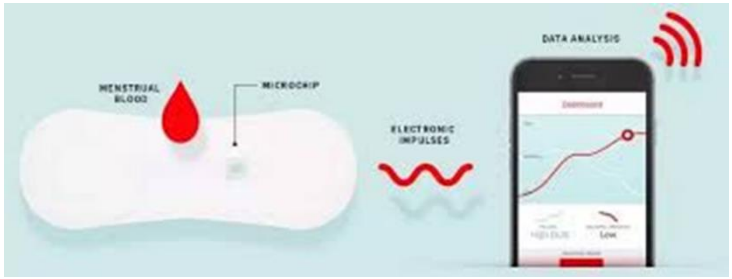
Tasso HemoLink™

SeventhSense BIOSYSTEMS TAP®





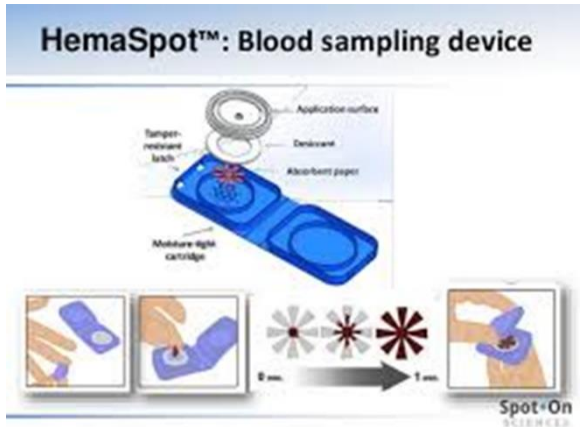
fluisense® Fluispotter®



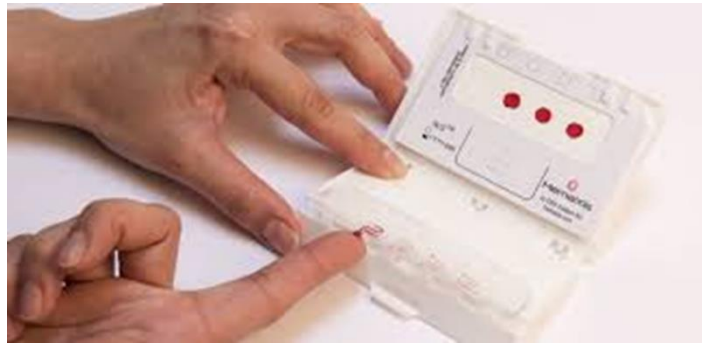
QURASENSE

Patient Centric Technologies – Blood Collection

bmf
Boston Microfluidics



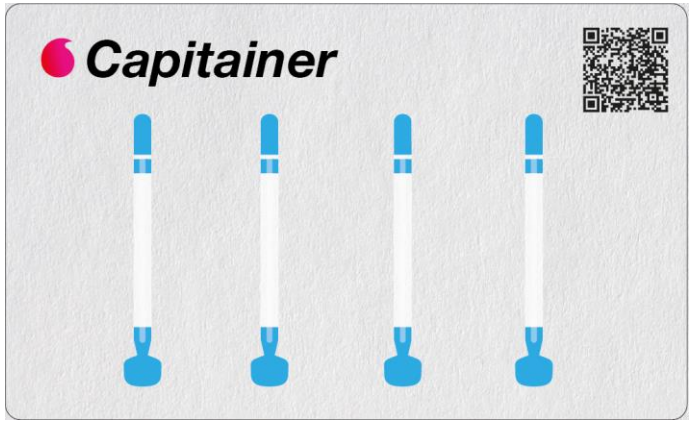
Spot*On SCIENCES



HemaXis

DBS System

Leuthold *et al*. (2015), *Anal. Chem.* **87**, 2068



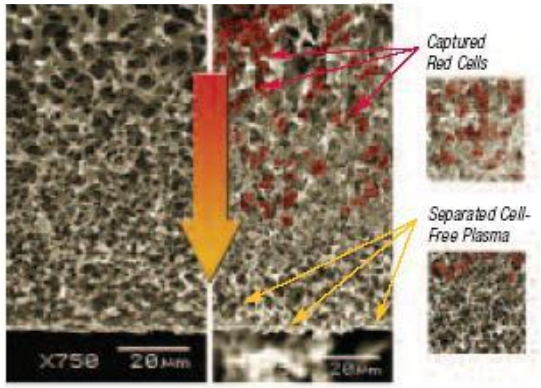
Capitainer

Lenk *et al* (2015) *Bioanalysis* **7**, 2085; Spooner *et al* (2018) *J. Pharm. Biomed. Anal.* **149**, 419

TRAJAN hemaPEN®

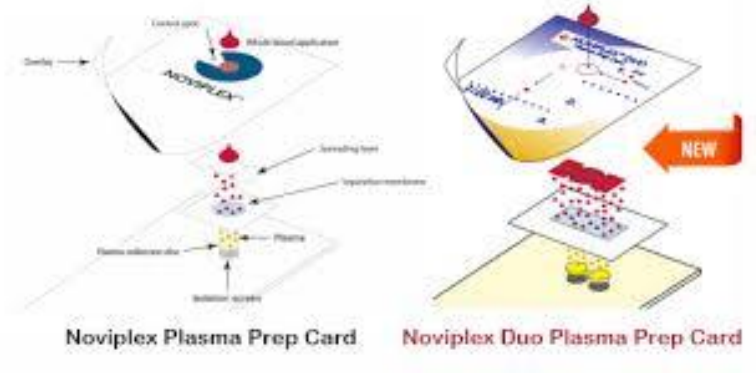
Patient Centric Technologies – “Plasma” Collection

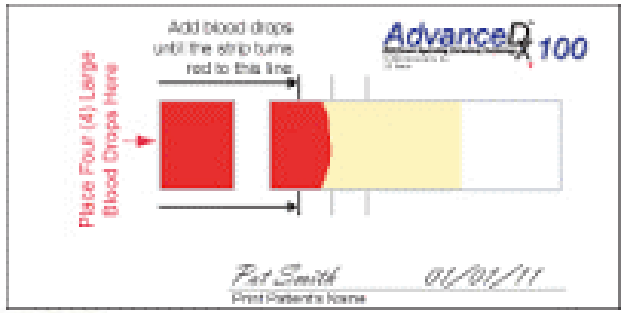
PALL Pall Corporation [Vivid™]



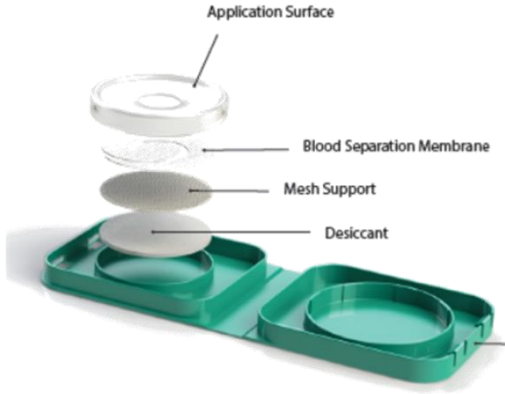
SHIMADZU NOVILYTIC INNOVATORS IN DIAGNOSTICS

[Noviplex™]





AdvanceDx 100



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[HemaSpot™-SE]

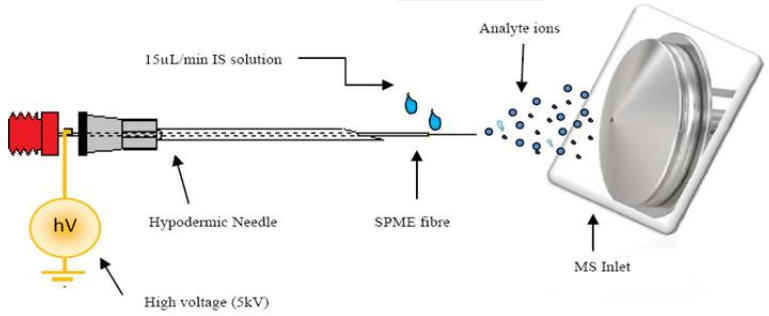
Patient Centric Technologies – Sample Analysis

NEW OBJECTIVE

PicoChip™

MilliporeSigma
MERCK

SPME

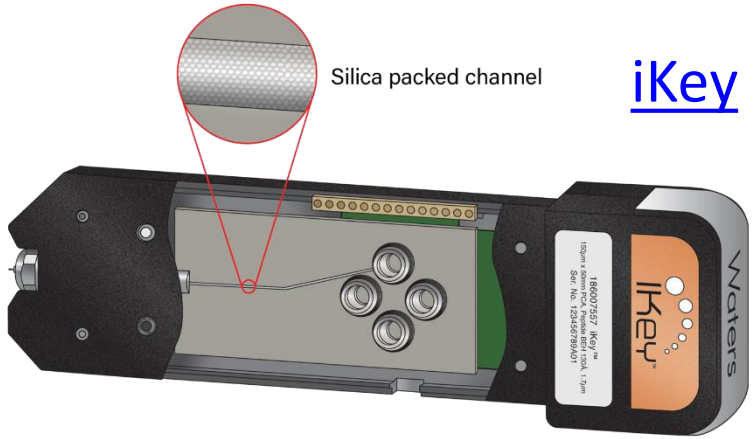


Courtesy Sheelan Ahmad, GlaxoSmithKline

Ahmad *et al* (2015) *Anal. Chem*. **87**, 754

Waters

THE SCIENCE OF WHAT'S POSSIBLE.®



iKey

Summary

- Numerous approaches to microsampling
  - Select the one that fits best with your organisational, experimental, quality and logistic requirements
  - Will require a lot of change control and training
  - Requires a lot of high quality site training, particularly for Clinical
- Microsampling not a solution for all situations
  - Useful tool to have available
- The field and technology is developing quickly
- You are not alone……
- Consider carefully the journey of the sample and the fate of the analyte(s) when validating / qualifying methods

Don’t forget the patient!

Contact Information

neil@spoonerbioanalytical.co.uk

https://www.spoonerbioanalytical.co.uk/

Microsampling: Clinical Perspectives

1st February 2018

AAPS Webinar

Prajakti Kothare

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Clinical Experience with Microsampling: Overview

- Clinical Applications of DBS in Late-Stage Clinical Trials are presented through two case studies
  - **Case Study # 1: MK8931**: Clinical and regulatory experience in gaining acceptance for DBS as the sole matrix for a large Phase 3 study
    Kothare, et al, The AAPS Journal, Vol. 18, No. 2, March 2016]
  - **Case Study #2: MK1602**: Experience from outpatient DBS sampling in a Phase 2 setting
    Li, et al, J Clin Pharmacol 2017
- Perspective:
  - Challenges and opportunities in establishing high-fidelity patient centric home sampling

Overview of Strategy and Case Study #1

The AAPS Journal, Vol. 18, No. 2, March 2016 (© 2016)
DOI: 10.1208/s12248-015-9860-3

Research Article

An Integrated Strategy for Implementation of Dried Blood Spots in Clinical Development Programs

Prajakti A. Kothare,[1,2] Kevin P. Bateman,[1,2] Marissa Dockendorf,[1] Julie Stone,[1] Yang Xu,[1] Eric Woolf,[1] and Lisa A. Shipley[1]

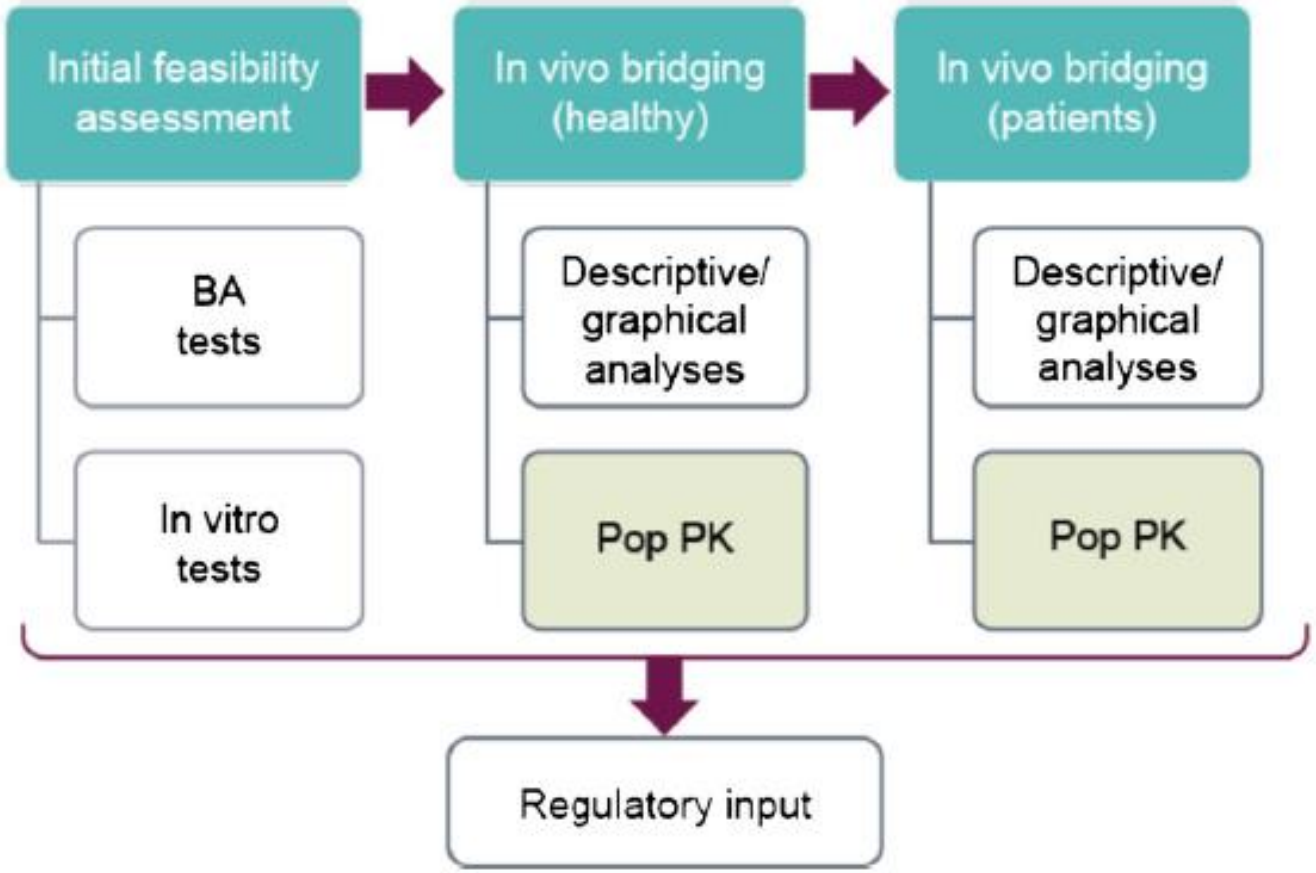
Clinical Perspective: Value Proposition

- Microsampling approaches such as DBS have the greatest potential for impact in late-stage clinical trials
  - ↓ patient burden (blood volume) in vulnerable populations (e.g. pediatric or elderly)
  - Opportunity for reduced logistical burden for sites (ambient temperature storage/shipping, etc) and associated cost savings
  - In an out-patient setting, enable access to data that would otherwise not be feasible

Additional Considerations

- Weigh pros/cons on a case-by-case basis v. traditional matrices
- Prospective, multi-disciplinary approach, integrated with clinical planning
- Robust quantitative bridging strategy: Plasma v. DBS
- Programmatic PKPD objectives should remain a core consideration and unaffected by choice of the matrix

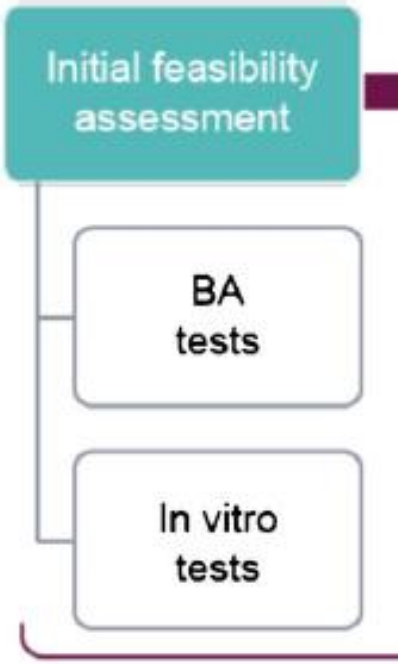
Strategy Overview



Case Study: MK8931

- Goal: Implement DBS as sole matrix in Phase 3
- Indication: Alzheimer's Disease
  - ↓ patient burden (blood volume)
  - ↓ site burden (enrollment)
- Phase 1 studies were conducted with plasma
- PK and exposure-response were important components for dose justification
- Bridging package needed to be robust

In vitro Assessments: Supported Suitability of DBS for Clinical Evaluations

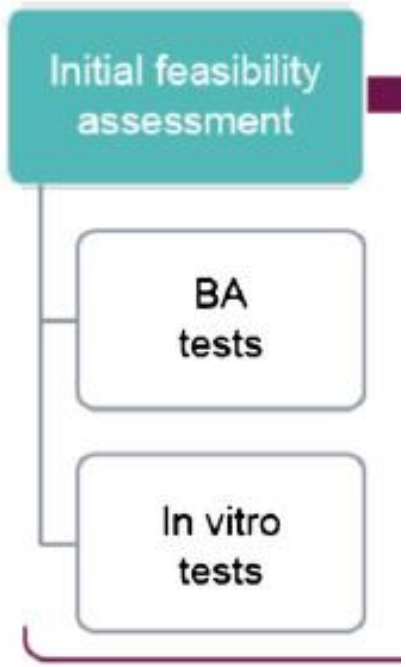


- Plasma protein binding, blood-cell to unbound plasma concentration ratio and hematocrit assessed over a clinically relevant range, are important determinants of suitability of DBS as a PK matrix

  Emmons G, Rowland M. Bioanalysis. 2010;2(11):1791–6

- **Blood: Plasma Ratio**
  - 1.22
  - Not concentration dependent
- **Protein Binding**
  - Modestly plasma bound (35%)
  - Not concentration-dependent
- **Hematocrit**
  - No significant impact over a clinically relevant range

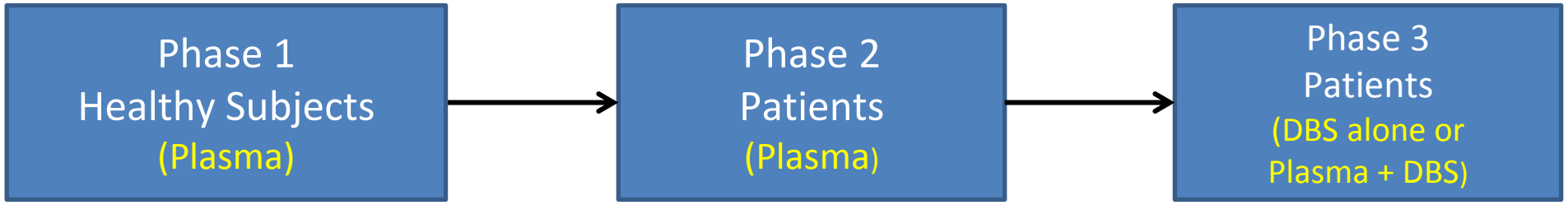
Bioanalytical Assessments: Supported Suitability of DBS for Clinical Evaluations



- No regulatory guidance specific to DBS
- Assay validation
- Additional studies included:
  - Hematocrit impact
  - Stability
  - Card type/extraction method
  - Spot volume/homogeneity
- ISR (Clinical samples)
- Bland-Altman analyses showed a lack of bias

Based on in vitro and BA evaluations, MK-8931 was deemed suitable for further evaluation in the clinic

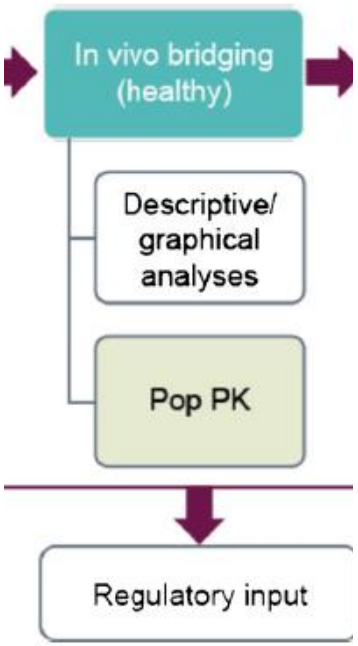
Integration of DBS into MK8931 Clinical Program

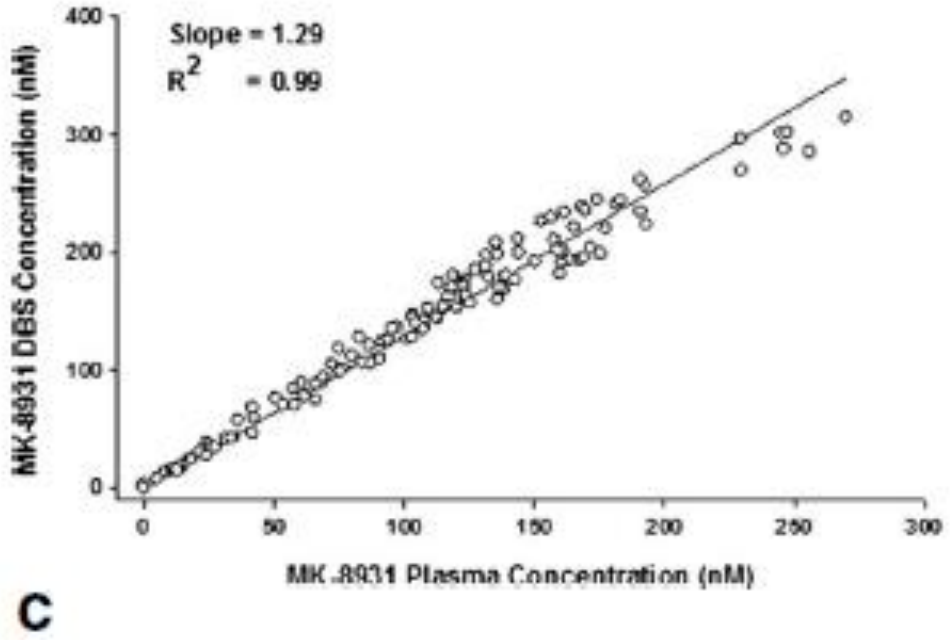


- Phase 1 studies (early PKPD, DDI, QTc, Special Pops) used plasma
- DBS was included with plasma, in one healthy subject study and one patient study to enable plasma-DBS bridging
- Once bridging demonstrated:
  - Aim was to utilize **DBS** as the **sole PK matrix** for the remainder of the **Phase 3 program**
  - **Plasma** would remain the **reference matrix** and continued for all Phase 1 studies (eg. special populations)

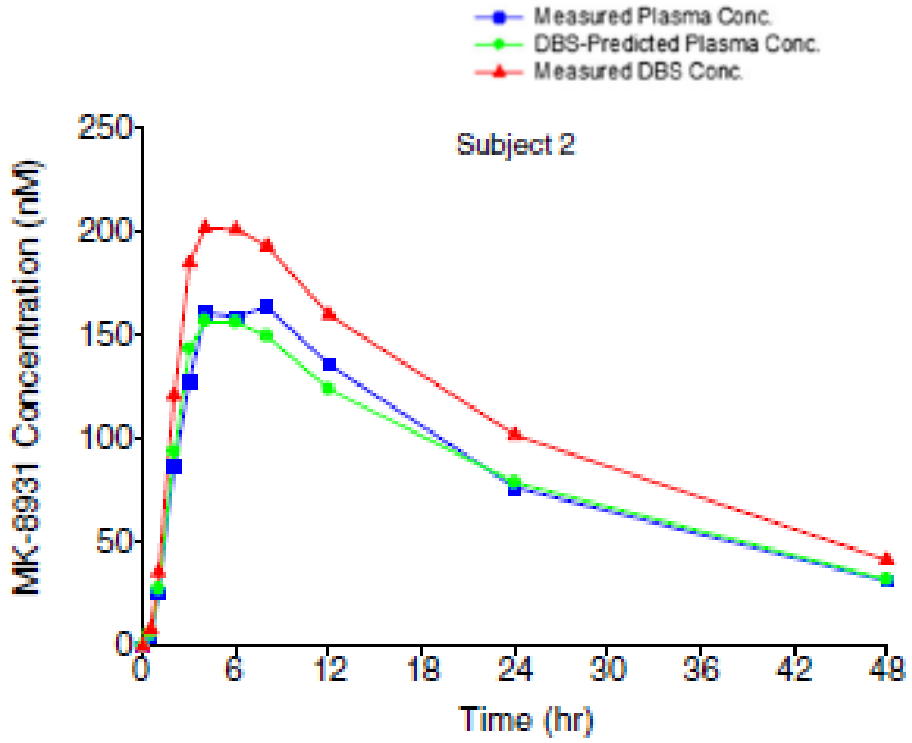
Graphical and Descriptive Analyses supported Interchangeability of Blood and Plasma Concentrations

- Focus: Exploring trends (i.e., no "acceptance" cut-offs)



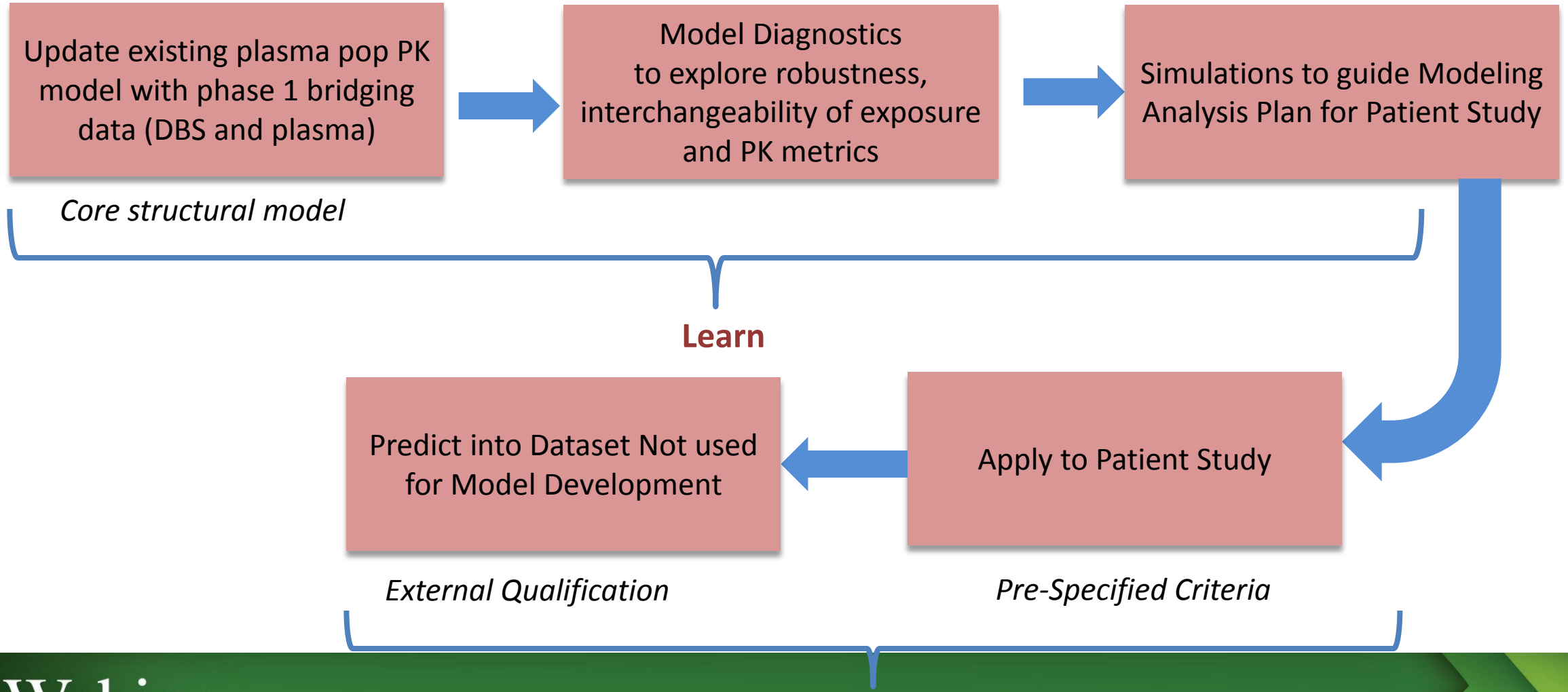


Close agreement of regression slope (1.29) with in vitro B:P (1.22)

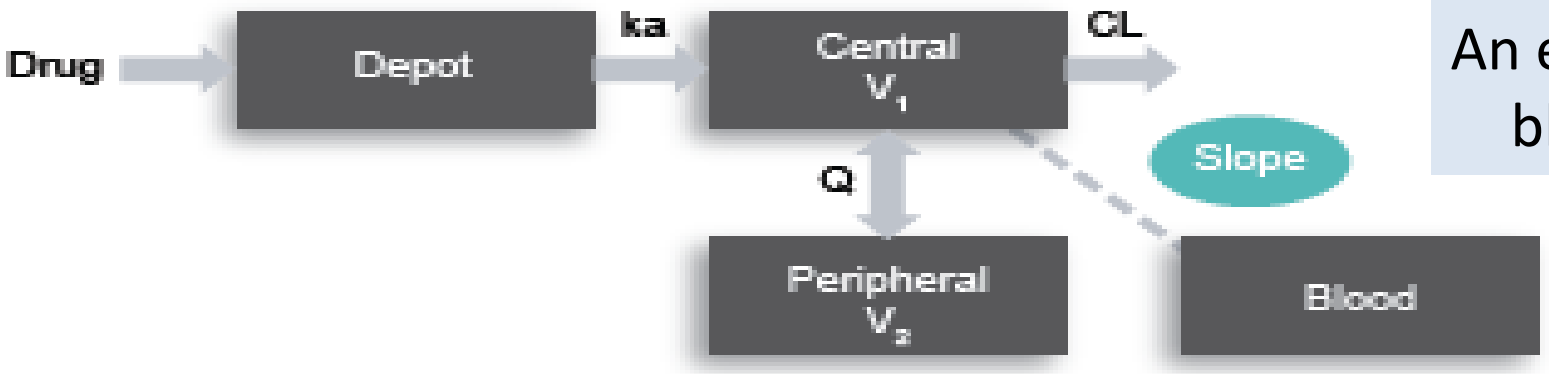


Measured plasma concentration (blue) ~ plasma concentration predicted from DBS (green)

Population PK: A Critical Component of Bridging Analysis



MK-8931 Base PK Model



An estimated "**Slope**" correlates blood and plasma

~ regression and in vitro B:P

Table III. Phase 1 MK-8931 Population PK Model Parameter Estimates (% Residual Standard Error) for Relevant Parameters

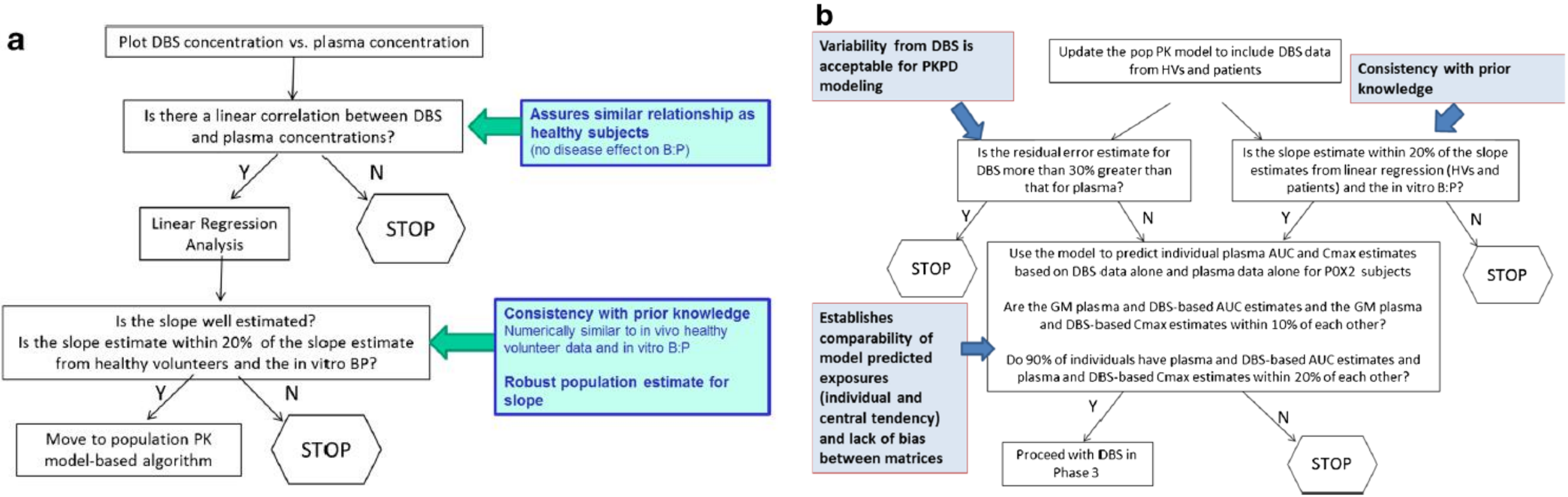
		Plasma-Only Model[a]	Plasma + DBS Model[b]
Parameter	Parameter Description	Estimate (%RSE)	Estimate (%RSE)
Slope	DBS/plasma ratio	–	1.27 (4.61)
σ^2plasma	Additive residual variability for plasma	0.142 (7)	0.144 (7.29)
σ^2DBS	Additive residual variability for DBS	–	0.186 (34.7)

[a] Model developed using phase 1 plasma data
[b] Model developed using Phase 1 plasma data as well as DBS data from a healthy volunteer bridging study

Similar variability for assay

Parameters well estimated and comparable between plasma and plasma + DBS model

MK-8931: Prospective modeling analysis plan with decision criteria and cut-off values evaluated appropriateness of DBS for pop PK



Regulatory Interactions for MK8931

- MK-8931 met all pre-specified criteria to proceed with DBS
- Given the lack of regulatory guidance on acceptance of DBS, a comprehensive background document (inclusive of bridging package) was submitted
  - FDA accepted the proposal for DBS as the sole matrix for Phase 3
  - Scientific Advice [CHMP]:
    - requested an Oral Hearing as they indicated this was their first regulatory experience of DBS and needed to understand the rationale for the proposed modeling decision criteria

MK-8931: Highlights of Oral Hearing

- Overall very positive meeting and productive discussion
  - Noted that DBS may be particularly useful for studying patient PK in the patient population and for Pop PK and PKPD analyses
- The MK-8931 package was regarded as robust
  - Questions on BA were mostly clarifying
  - Discussion on population slope; need for external qualification
- Concurrence on the proposed bridging patient strategy but stated that each program may need adjustments
- The qualification team recognized the value of home sampling, but refrained from stating a specific position

Case Study 2: MK1602

Population PK Analyses of Ubrogepant (MK-1602), a CGRP Receptor Antagonist: Enriching In-Clinic Plasma PK Sampling With Outpatient Dried Blood Spot Sampling

The Journal of Clinical Pharmacology
2017, 0(0) 1–10

DOI: 10.1002/jcph.1021

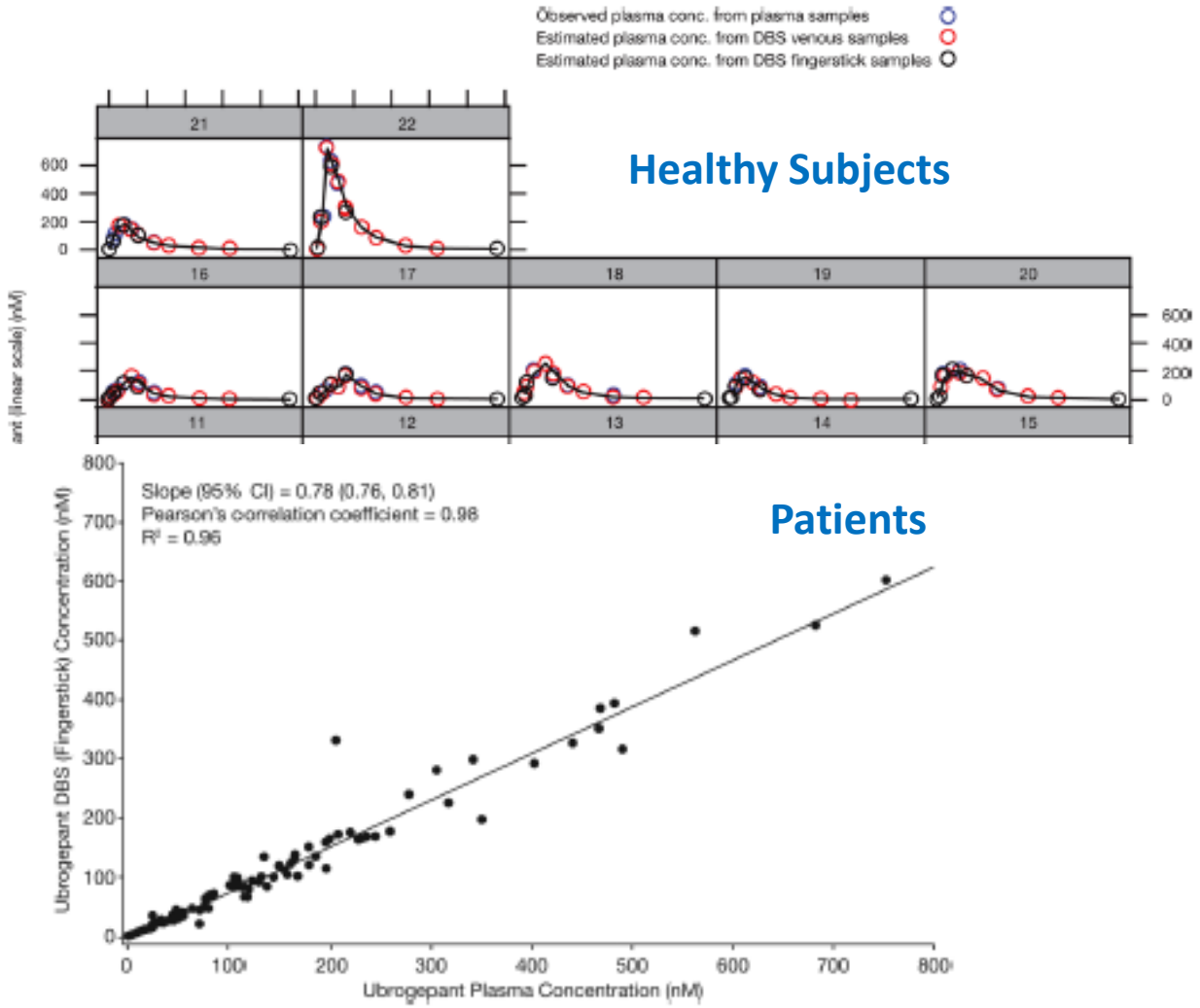
Chi-Chung Li, PhD[1,2], Marissa Dockendorf, PhD[1], Ken Kowalski, MS[3,4], Bei Yang, PhD[3], Yang Xu, PhD[1], Iris Xie, MS[1], Huub Jan Kleijn, MSc[1,5], Rolien Bosch, MSc[1,6], Christopher Jones, BA[7], Bob Thornton, MPH[7], Eugene E. Marcantonio, MD, PhD[8,9], Tiffini Voss, MD[8], Kevin P. Bateman, PhD[1], and Prajakti A. Kothare, PhD[1]

Case Study 2: MK1602

- MK1602: CGRP antagonist for treatment of acute migraine
- Similar strategy for DBS implementation
- Strategic value: Enrich datasets with PK information that would otherwise have been difficult to access in a Phase 2 setting (given nature of endpoint)
- Merck’s first experience with DBS in an outpatient setting

DBS: In-clinic v. Out Patient

In Clinic



Out Patient

- DBS ~ plasma variability in controlled clinical settings
- Substantially increased (113% v 28%) for outpatient DBS data
- The study used paper diaries for recording dosing/PK sampling times
- Potential for error ?

Subject Questionnaire Data: Keeping the Patient in Mind

MK1602 Study: Healthy Subjects

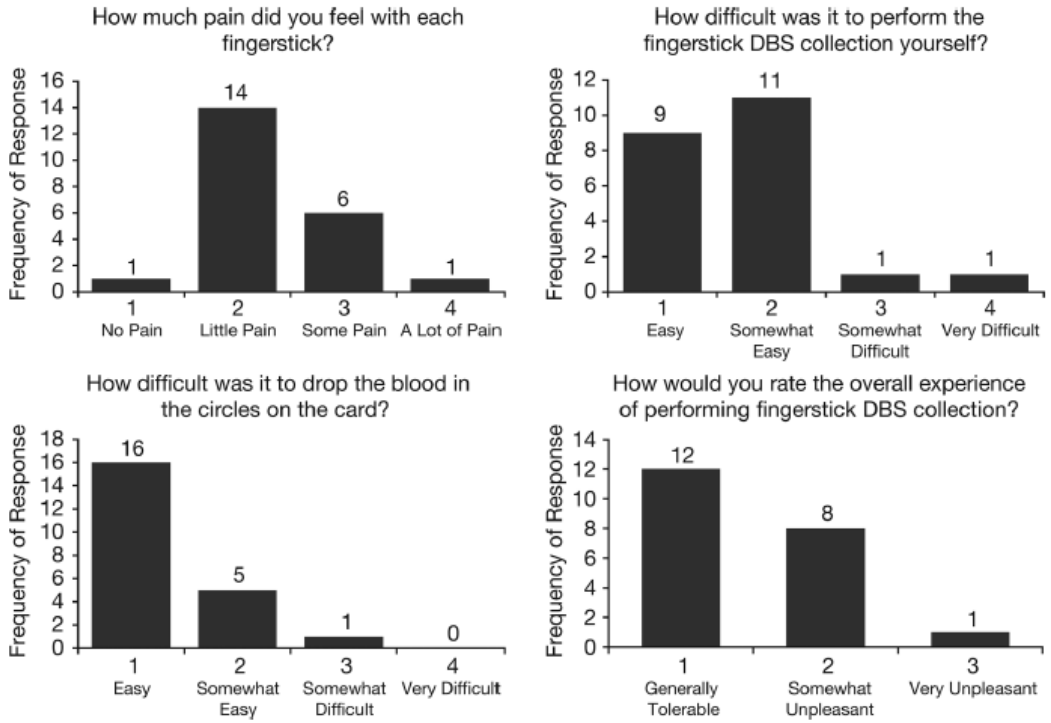
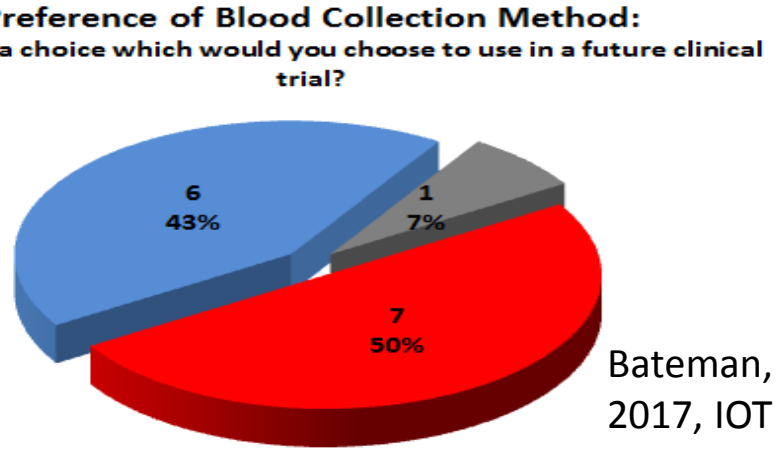


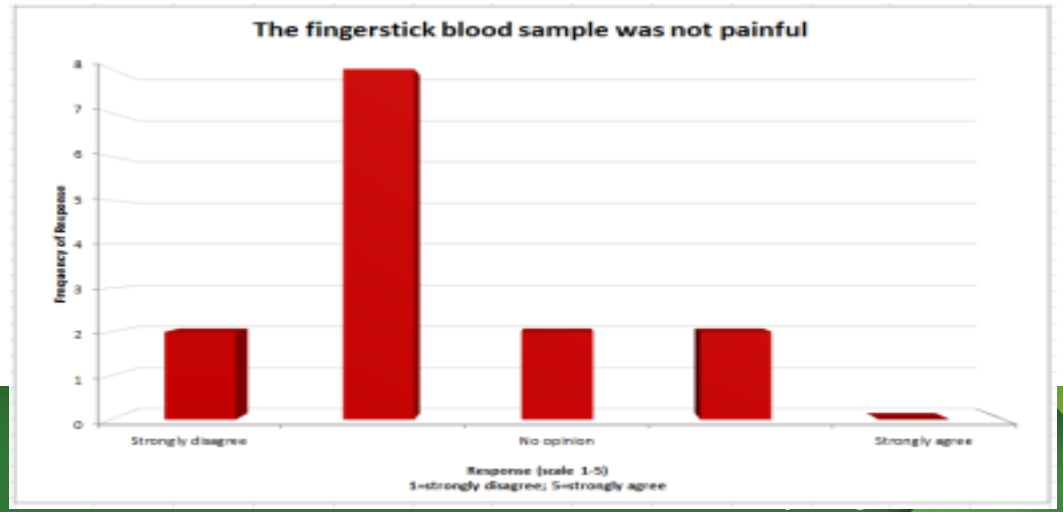
Figure 2. fingerstick DBS questionnaire results from study PN005 (n = 22). DBS, dried blood spot.

A separate study evaluating home sampling:

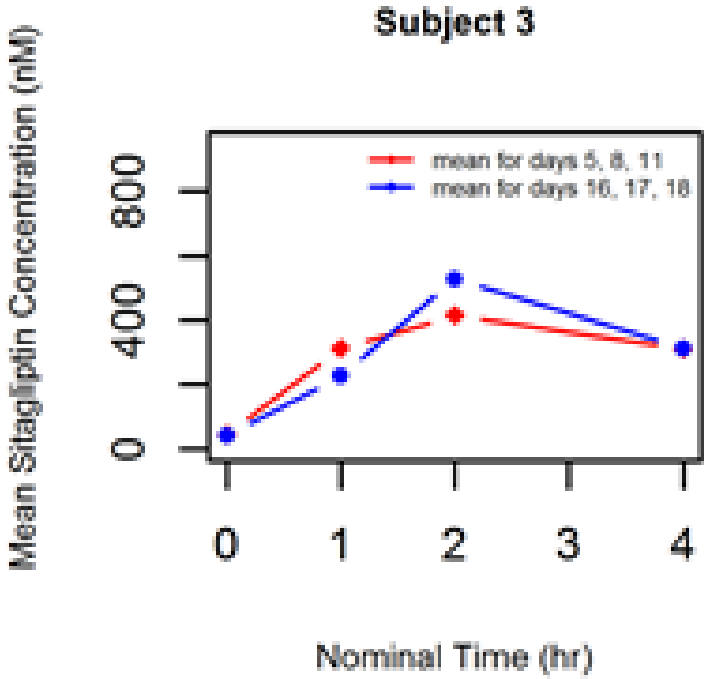
- no clear preference for at-home fingerstick vs. in-clinic venous blood draw
- Reported pain with fingersticks (4 samples per PK sampling day)



Bateman, 2017, IOT



Outpatient sampling: Where are we going?



Continued development of high-fidelity minimally invasive, outpatient sampling:

- Quality PK/PD/Biomarker data with adequate precision
- Minimally invasive: Blood, plasma or alternate matrices
- "Automated" date/time stamps

Red: at-home samples
Blue: in-clinic samples

Dockendorf et al, 2016, APA

Summary

- The choice of microsampling should be weighed on a case-by-case basis
- Current experience suggests rational, prospective and quantitative approaches for bridging are accepted by regulators for late-stage studies
- Continued investments in high-fidelity collection methods for blood/plasma collection with automated date/time records could significantly enhance PKPD datasets and foster patient centricity in trials

Back ups

MK-X: EMA Interaction

- Does the Agency agree with Merck's overall strategy for implementation of DBS in clinical programs exemplified by MK-X?
- Does the Agency agree with Merck's conclusion that DBS can be used as the sole matrix for the remainder of the MK-X Phase 3 program?

If time permits:

- Does the Agency agree with the Applicant's approach to ensure appropriate quality for in home-collected DBS samples for use in future developmental programs (not MK-X)?

Land O'Lakes, BA Conference 2015

EMA Meeting Summary: DBS as sole matrix for the Phase 3 Program of MK-X

- Overall the package was considered to be **robust and acceptable** to support the use of DBS as the **sole** source of PK data for the remainder of the **MK-X Phase 3 program** based on the presented data and assuming that the results of the PopPK model continued to demonstrate acceptance criteria are met
- ***BA/In vitro:***
  - BA and in vitro packages were acceptable; clarifying questions related to assurance that ISR was performed routinely and assay clinical study performance data were compliant with acceptance criteria
- ***Other:***
  - The acceptance for the current program would be limited to in-clinic venous sampling. If any changes to this were made (eg. finger prick capillary sampling), this would require a new validation

Land O'Lakes, BA Conference 2015

EMA Meeting Summary: DBS as sole matrix for the Phase 3 Program of MK-X

- ***Modeling:***
  - **The PK model-based criteria** were strict and could be **endorsed**
  - The use of a **population slope** as a scaling method for conversion between DBS and plasma resulted in extensive discussion
    - Utility for individual variability in PK parameters
    - Merck noted that intersubject variability in the slope parameter was explored in the Phase 2/3 dataset (P0X2) and found not to be significant
  - A proposal was endorsed that would demonstrate predictability for data not used in the original model build (**external qualification**)

Land O'Lakes, BA Conference 2015

EMA Interaction: Home Sampling

Pre-meeting Correspondence

In particular, the home based capillary sample raises the following practical concerns:

- The method of applying the blood to the paper can significantly alter the volume absorbed into a given area and thus the resulting concentration measurement.
- There is a considerable risk of sample contamination with the DBS technique due to transfer when handling both the drug and the sampling paper.
- It may add yet another level of uncertainty around time of sampling in relation to drug intake.

Oral Hearing

While the Agency acknowledged the potential future benefits of home sampling, they refrained from providing commentary as they considered it to be technology in early stages of development.

Land O'Lakes, BA Conference 2015

MK1602 Pop PK Residual Variability

Table 2. Ubrogepant Population Model Residual Error Estimates From Selected Models (% CV)

	Plasma		Blood		
Partitioning Method for Residual Error	Healthy	Migraine	Healthy (Clinic)	Migraine (Clinic)	Migraine (Home)
A	41	55	27	96[a]	
B	41	53	27	37	113
C	41	52	28[b]		113

In method A, residual variability was partitioned based on subject population and matrix. In methods B and C, the residual variability of blood data in individuals with migraine was further partitioned based on sampling context (ie, at home vs in the clinic). CV, coefficient of variation; DBS, dried blood spot.

[a]Combined residual error term for clinic-based and home-based DBS in individuals with migraine.

[b]Combined residual error term for clinic-based DBS in healthy subjects and individuals with migraine.

DBS sampling – Potential for cost savings…….

- Removal of the need for dry ice shipments and frozen storage of samples represents considerable savings
  - ~$40K for 1500 sample, multi-centre trial
    - See Neoteryx Clinical Trial Cost Calculator tool
- ~30% of the dry ice shipments reported to have issues such as incorrect packaging or incorrectly completed documentation
  - van Amsterdam & Waldrop (2010) *Bioanalysis* **2(11)** 1783-1786

Home Sampling – Potential for Cost Savings

- Obtained by removing the requirement for subjects to travel to a central clinic on study days where only PK samples are being collected

	Phase II	Phase III
Cost Saving	€93K	€310K

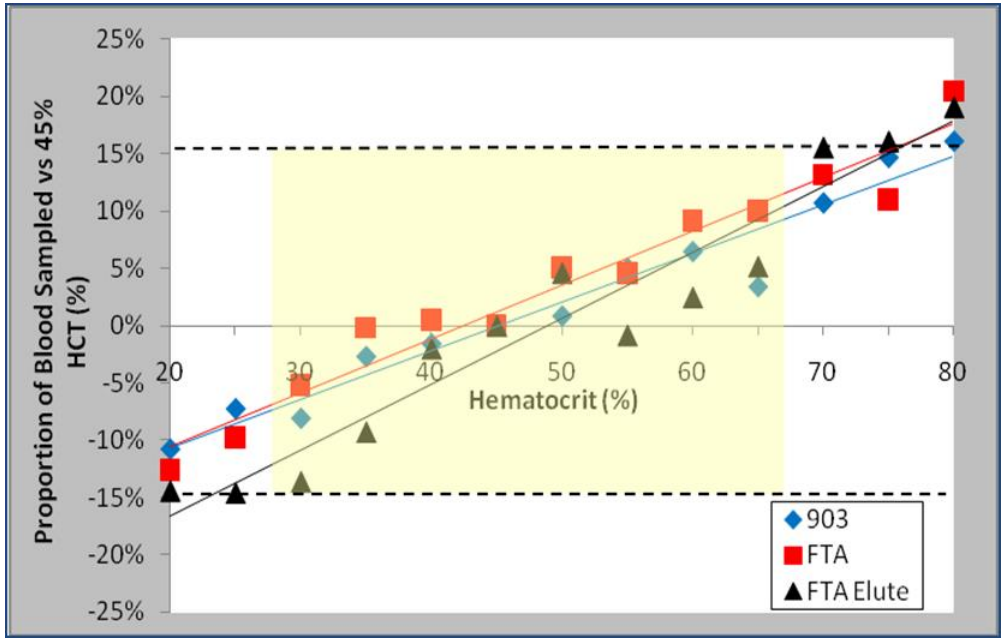
- Data is for an 'average' study defined as follows
  - Average number of patients = 300 for Phase II, 1000 for Phase III
  - Average number of sampling occasions per study where dosing is not occurring, or blood samples are not being collected for another purpose = 2
  - Average subject expenses cost per visit to the clinic = £120
- The following are not included in the cost savings
  - 2-4 hours of subject time per visit
  - Cost of the home sampling kit
  - Subject training
  - Staff costs associated with collection of these samples at the clinic

Cost savings for TDM

- DBS for TDM of renal transplant and hemato-oncology pediatric patients
- Total societal costs include healthcare costs provision, patient related costs and costs related to loss of productivity of the caregiver
- Cost reduction of 43% for hemato-oncology patients (€277 to €158) and 61% for nephrology patients (€259 to €102) per blood draw
- Healthcare only savings of 7% for hemato-oncology patients and 21% for nephrology patients

Martial *et al* (2016) *PLOS ONE* | DOI:10.1371/journal.pone.0167433

Effect of HCT on volume of blood sampled



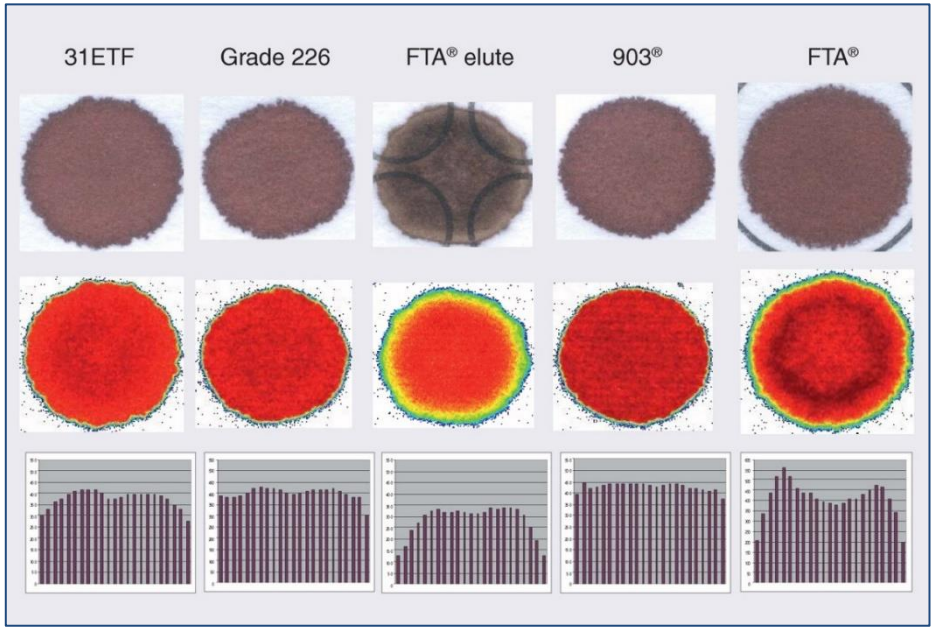
Fixed disc collected from spot with varying area

Denniff & Spooner (2010) *Bioanalysis* **2,** 1385

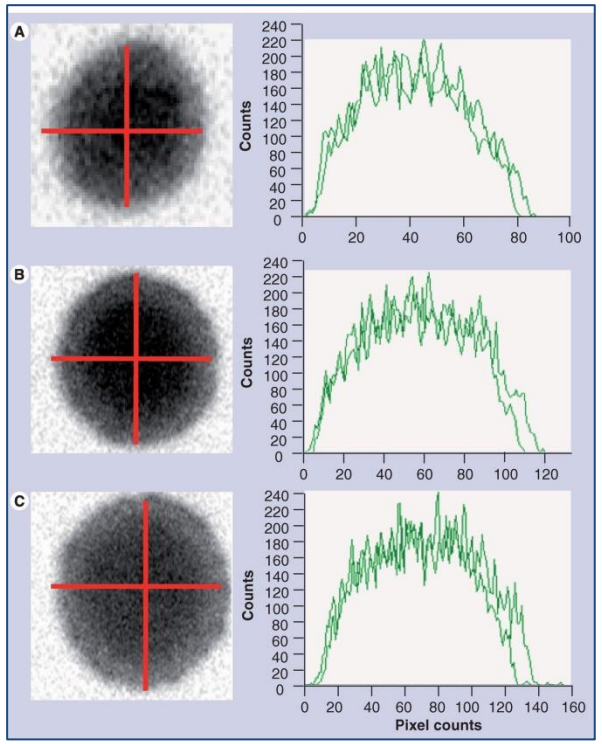
- Solved by spotting accurate volume & punching whole spot, or closely matching HCT of cal's & QC's to samples
- Wide range of HCTs not often a major issue for tox studies

O'Mara *et al* (2011) *Bioanalysis* **3**, 2335; de Vries *et al* (2013) *Bioanalysis* **5**, 2147; Cobb *et al* (2013) *Bioanalysis* **5**, 2161

Spot homogeneity



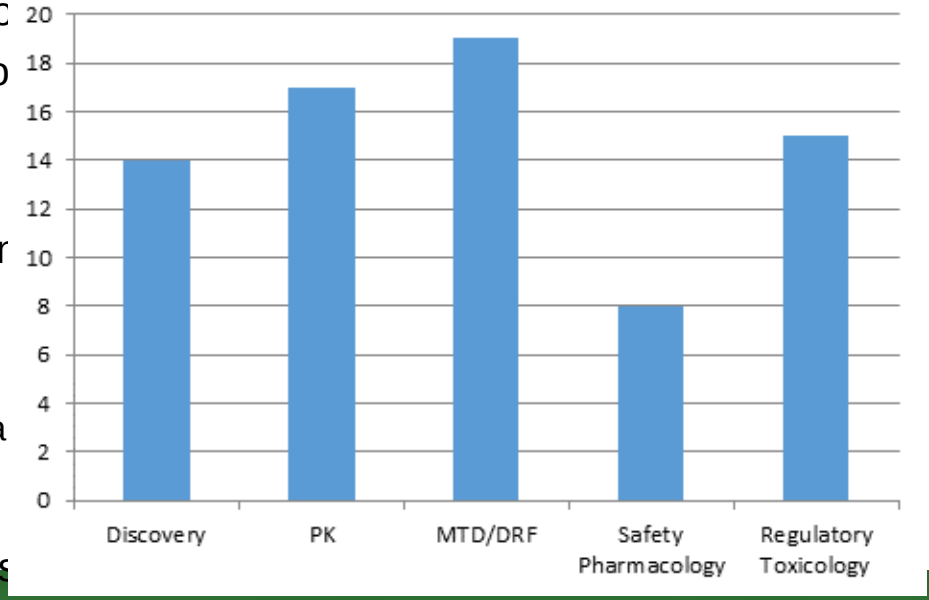
Ren *et al,* (2010) *Bioanalysis* **2,** 1469;
Clark *et al* (2010*) Bioanalysis* **2,** 1477



Example radio histograms of the (A) 15-, (B) 30- and (C) 45-µl blood spots spiked with 14C radiolabeled UK-414495

Competitive Landscape – Pre-Clinical

- Bioanalysis Zone Surveys – 2014 & 2016
  - Large increase in those using microsampling regularly (from 29% to 49%)
  - Use for clinical research has increased from 4% to 15%
  - 38% of respondents report >50% reduction in number of animals used
  - 17% of respondents report >70% reduction in number of animals used
  - >50% working with small mc
  - >20% working with large mo
- NC3Rs Microsampling User
  - 53 Individuals
  - 31 Companies / organisatior
    - 17 Pharma
    - 2 Biotech
    - 6 CROs, 2 Consultants
    - 1 Chemical / Agrochemica
    - 2 Regulatory Agencies
    - 1 Government
  - Website outlining techniques



Competitive Landscape – Clinical & Bioanalytical

- IQ Consortium Microsampling Working Group
  - Publications on how to show wet vs dry concordance
    - Evans *et al* (2014) *The AAPS Journal* **17(2)**, 292-300
  - Education of Regulators (FDA)
  - Now an AAPS Working Group
- European Bioanalysis Forum – Liquid Microsampling Consortium
  - Cross company execution of protocols to understand bioanalytical issues and subsequent publication of the results
    - Ability to aliquot small volumes
    - Sample homogeneity
    - White, *et al* (2014) *Bioanalysis* **6(19)**, 2581-2586