QA perspective on DBS analysis

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BARQA

The Research Quality Association

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- Standards / norms
- Quality requirements
- Metrics & CAPA

BARQA's Mission

1. To develop and promote quality standards in scientific research and development.
2. To facilitate knowledge sharing and transfer through:
   - Discussion
   - Training
   - Seminars
   - Conferences
   - Publications
   - Partnership
3. To liaise with regulatory agencies in the development & interpretation of regulations & guidance.

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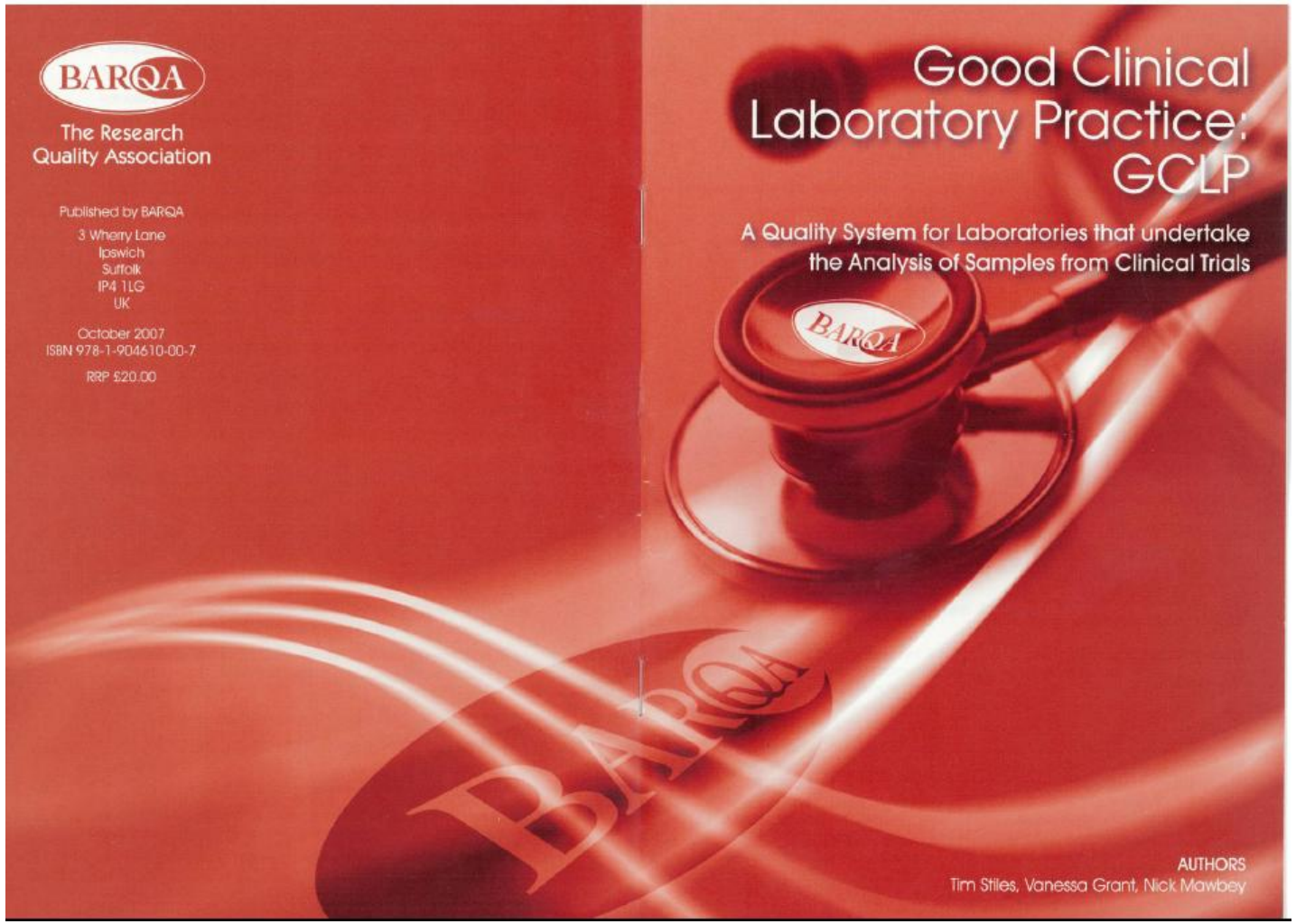
Standards / Norms (1)

- ISO 17025:2005 General requirements for the competence of testing and calibration laboratories
- ISO 15189:2003 Medical laboratories -- Particular requirements for quality and competence
- GCLP
- GLP

Standards / Norms (2)

- CPA – Clinical Pathology Accreditation (UK) Ltd
- GBEA – Guide de Bonne Exécution des Analyses de Biologie Médicale (France 1994, Mali)
- Gute Analysen und Laborpraxis (Austria)
- Directive pratique pour la mise en place d'un système qualité dans les laboratoires agréés dans le cadre de l'INAMI (Belgium)
- Accreditation of medical/diagnostical laboratories (Germany)
- CCKL guide of practice (Holland)
- Nordkem project for a model of quality manual for medical laboratories (Scandanavia)
- Critères de fonctionnement des laboratoires d'analyses médicales (Switzerland)
- CLIA - Clinical Laboratory Improvement Amendments (FDA)
- CAP - Standards for Laboratory Accreditation (College of American Pathologists – 2000).
- Consultation on Technical & Operational Recommendations for Clinical Lab Testing Harmonization & Standardization (Mozambique 2008)

Seminal texts (1)



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Good Clinical Laboratory Practice

Organisation and Personnel
Trial Facility Management Responsibilities
Analytical Project Manager Responsibilities
Trial Staff Responsibilities
Facilities
Trial Facilities
Archive Facilities
Waste Disposal
Equipment, Materials and Reagents
SOPs
General
Application
Planning of the work
Content of the Analytical Plan
Sub-Contracting

Trial Materials
Receipt
Chain of Custody
Logistics
Conduct of the Work
General
Computer Systems
Method Validation
Processing trial materials
Reporting Results
General
Analytical Report
Analytical results
Quality Control
Quality Audit
Storage and Retention of Records
Confidentiality

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ISO 17025 - Competence of Testing & Calibration Labs

Management Requirements

- Organization
- Quality system
- Document control
- Review of requests, tenders and contracts
- Subcontracting of tests and calibrations
- Purchasing services and supplies
- Service to client
- Complaints
- Control of nonconforming testing and/or calibration work
- Corrective action
- Preventive action
- Control of records
- Internal audits
- Management reviews

Technical Requirements

- General
- Personnel - Accommodation & environmental conditions
- Test and calibration methods & method validation
- Equipment
- Measurement traceability
- Sampling
- Handling of test and calibration items
- Assuring the quality of test and calibration results
- Reporting the results

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Seminal texts (2)

Guidance for Industry reference paper for bioanalytical method validation

Shah, VP *et al* (2001)

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf

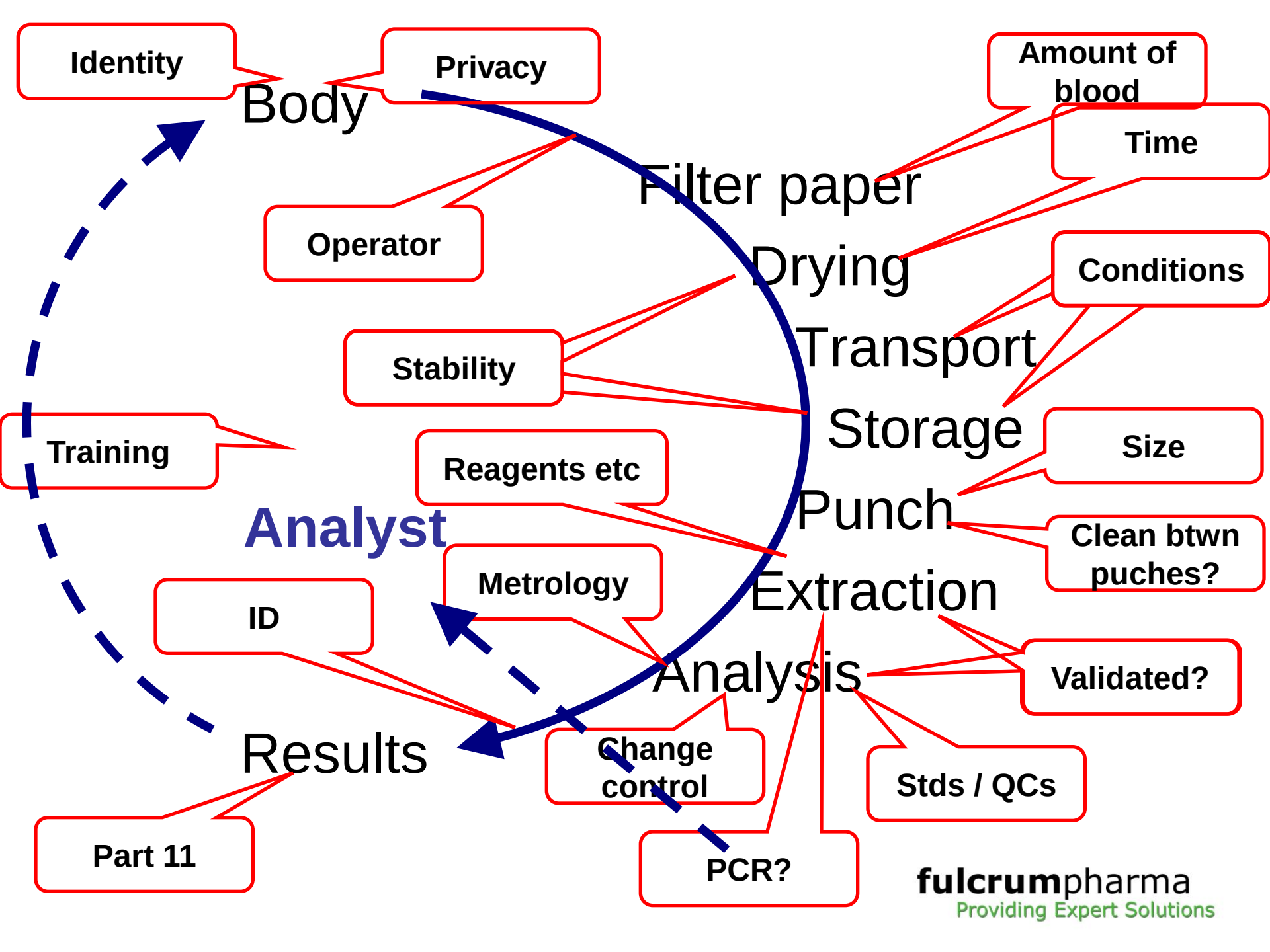
Based on Shah

- Usual assay validity criteria

  precision, accuracy, linearity, sensitivity, selectivity, recovery, FREEZE / THAW, within-assay variation, between assay variation, inter-operator variation

- Other criteria

  stability of the analyte and metabolites
  effect of the volume of blood spotted,
  device used to spot the blood,
  temperature of blood spotted.


Identity
Privacy
Body
Amount of blood
Time
Filter paper
Operator
Drying
Conditions
Transport
Stability
Storage
Training
Size
Reagents etc
Punch
Analyst
Clean btwn puches?
Metrology
Extraction
ID
Validated?
Analysis
Change control
Stds / QCs
Results
Part 11
PCR?
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QA / QC Challenges

In a GXP or ISO environment, DBS provides the same QA/QC challenges as does any other clinical pathology or drug levels analysis.

Or does it?

Essentially these are:- traceability from test subject to report, stability of the specimen, storage through to destruction, method transfer, method validation, incurred samples, contamination and data management (LIMS?) / reporting.

Collection by non-medical persons

Quality of blood spots collected
by non-medical field interviewers (2006?)
>90%

- 1370 filter paper cards
- Between 0 & 9 usable spots of varying size per card.
- 93% of cards contain at least four usable blood spots.

1/14th ?

Evaluation of Dried Blood Spots Collected by Non-medically Trained Interviewers: Number, Size and Quality of Spots.
Sharon R. Williams,
Center on Aging, University of Chicago and Department of Anthropology
http://paa2006.princeton.edu/download.aspx?submissionId=60733

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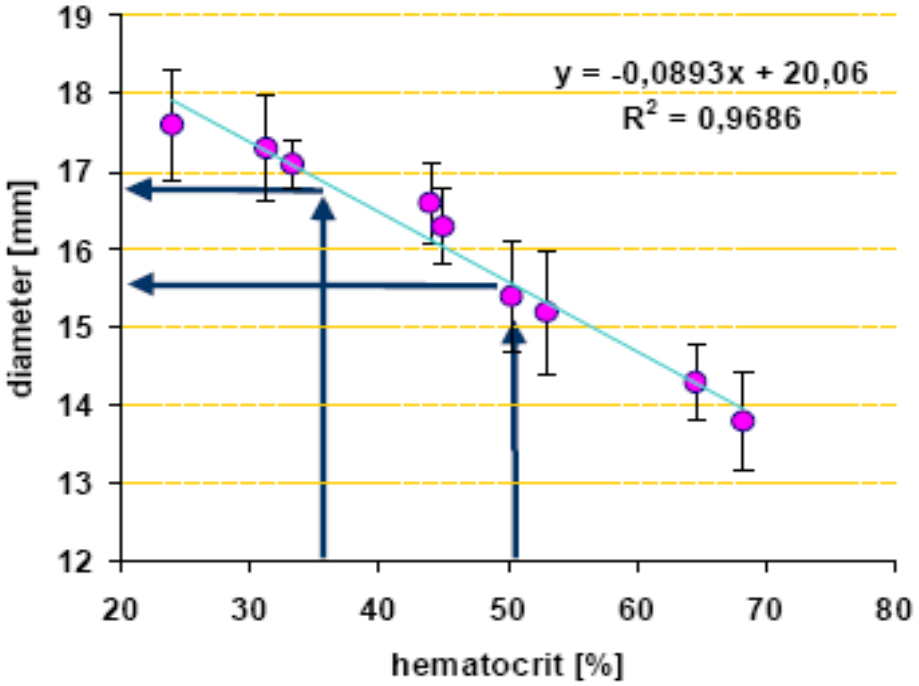
Spot diameter & hematocrit value



Dependence of the spot diameter [mm] on the hematocrit value [%], the variation within the physiological range is indicated by the arrows.

Blood Spot Analysis, G Skopp (2004?)
Institute of Legal Medicine and Traffic Medicine, RuprechtKarls University, Heidelberg,
http://www.icadts2007.org/print/128bloodspotanalysis.pdf

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Differences

- Calibration Standards
  - Wet standard and/or QC samples by spiking fresh whole blood.
  - DBS standards on analogous filter paper
- Risk estimation
  - Blood volume / unit area
  - Chromatographic behaviour
  - Is analyte is stable to drying

Metrics

- Number unacceptable results
- Normal values of hemaglobin / hematocrit

Method transfer

If you already have a validated method for traditional plasma sampling, then you would need to revalidate to demonstrate acceptable precision, accuracy etc for the extraction from the dried blood spot. And although there should be fewer issues, you would still need to demonstrate stability of the sample because the matrix and storage conditions have changed.

Cost : benefit

So whilst DBS may be attractive for new molecules, the cost:benefit is less clear if you already have a validated method for conventional sampling and especially from the scientific perspective if the conventional matrix has already been used on the molecule.