Editorial

Implementing Dried Blood Spot Sampling for Clinical Pharmacokinetic Determinations: Considerations from the IQ Consortium Microsampling Working Group

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INTRODUCTION

This paper was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science-based and scientifically driven standards and regulations for pharmaceutical and biotechnology products worldwide. Within the IQ, various working groups (WG) have been formed, where the

microsampling WG is committed to providing a scientific forum for the advancement of both wet and dry microsampling techniques within the pharmaceutical industry. This first output from the microsampling WG is to summarize and reflect on the current knowledge and opinions on DBS sampling, to stimulate discussion, and to encourage future creative applications of DBS sampling.

Dried blood spot (DBS) sampling has established itself as an innovative sampling technique where wet blood is spotted onto absorbent paper or other paper materials and allowed to dry (1–4). DBS offers several potential benefits inherent to the technique, namely a low blood volume, simplified blood sample collection (5), and convenient sample storage and transfer. In certain applications, DBS sampling has been shown to stabilize certain analytes or metabolites without the addition of chemical modifiers (6–9). DBS has been routinely applied for decades in neonatal screening for phenylketonuria and other congenital metabolic disorders (10). The utility of DBS sampling has also been demonstrated for therapeutic drug monitoring (11) and for epidemiological studies (e.g., HIV and HBV detection/monitoring) (12) due to the practical advantages along with simplified sample collection and handling procedures. Finally, DBS can also be used for quantitative biomarker (PD) assessment from blood, where appropriate.

However, the technique is relatively new to the pharmaceutical industry and to government regulators overseeing new drug applications. Nevertheless, over the past 5 to 7 years, the technique has been extensively evaluated for quantifying drug exposure in nonclinical and/or clinical studies in various stages of drug discovery and development. The ease to collect, transfer, store, and process small volumes of blood samples has generated considerable interest in providing utility in volume-limited situations (e.g., small rodent, human pediatric studies) for toxicokinetic (TK), pharmacokinetic (PK), or pharmacodynamic (PD) sampling.

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Discovery and nonclinical studies. Rodent animal models are typically employed in these studies. The reduced blood volumes required for DBS can enable serial bleeding and, consequently, elimination of satellite animal groups and reduction of compound use. The ability to eliminate the satellite animal groups enables the assessment of exposure and toxic effects within the same animal. Studies involving expensive animal models (i.e., transgenic mice, knock-out mice, humanized mice, etc.) further highlight a persuasive scientific and economic case for DBS sampling since a complete pharmacokinetic profile can be obtained from a single study animal without the need for extra rodents merely for generating exposure data. These are perfectly in line with the principles of the 3Rs: reduction, refinement, and replacement of humane animal research (13–15). With greater emphasis from the regulatory authorities to study new drugs for infants, neonates, and pediatric populations, the requirement to conduct associated nonclinical juvenile rodent toxicity studies serves as an ideal scenario where the advantage of low blood volume in DBS sampling is undeniable. Although the advantages of DBS heavily favor rodent studies, it can also be used to refine non-rodent studies.

Clinical studies. The true value of DBS sampling may lie in its inherent ability to fill voids in drug clinical development paradigms and to collect data that otherwise would be very difficult or impossible to obtain via traditional PK sampling techniques. These values include, but are not limited to (1) PK sample collection in developing countries/areas, where traditional PK sample collection is not feasible due to the lack of basic facility requirements, e.g., a phlebotomist, centrifuges, freezers, and dry ice, and/or electricity; (2) PK sample collection from infants, neonates, pediatrics and other special patient populations, where minimizing collection volumes is of critical importance (16) and DBS samples can be collected by trained nurse or patient guardians, and (3) post-approval therapeutic monitoring, where PK sample collection more or less serve as compliance indicator for the patients participating in the study, or to ensure sufficient washout after drug treatment cessation.

The utilization of DBS sampling in non-regulated environments has received positive encouragement (17, 18). However, it has faced some concerns from health authorities as to whether it is acceptable for the current practices in regulated bioanalysis (19), and this uncertainty may have dissuaded some users from continuing to employ and/or explore the technique. Recent years have witnessed an increased and active participation of pharmaceutical companies, contract research organizations (CROs), instrument and technology vendors, academic laboratories, and health providers studying DBS. As more scientists became involved, and additional data disclosed on a variety of compounds, the bioanalytical community recognized that significant challenges and scientific issues were associated with the implementation of the technique. Industry sponsored scientific consortia have been formed and numerous symposia, meetings, and sessions have been dedicated to the topic (20–22). The potential advantages and opportunities of DBS sampling for compound specific or study specific drug research and development activities have been well discussed.

The focus of this manuscript is to take a fresh look at the value proposition associated with DBS sampling during clinical development; and provide general advice on the study design associated with DBS implementation. This paper is not intended to serve as a guidance document, but rather to summarize and reflect on the current knowledge and opinions on DBS sampling, to stimulate discussion, and to encourage future creative applications of DBS sampling. Clearly, as one of the many available tools in support of drug research and development and post-approval monitoring, the implementation of DBS sampling must be scientifically justified with full demonstration of ethical, practical and/or economic benefits. The majority of research and information around the implementation of DBS has been around small molecules; there has been limited application to the development of biopharmaceuticals (23). However, many of the same practices and principles discussed herein apply to development of virtually any modality.

PRACTICAL BIOANALYTICAL CONSIDERATIONS FOR IMPLEMENTING DBS

The potential bioanalytical issues and challenges associated with DBS sampling have been highlighted in recent publications (24, 25). From a bioanalytical perspective, feasibility assessments should first be conducted to determine if DBS sampling is suitable for an intended study. Table 1 provides several bioanalytical parameters that need to be assessed to determine DBS bioanalytical suitability. Typically, the volume of blood used to create a spot ranges from 5 to 20 μ L, and punch diameters are between 3 and 8 mm. The most common practice is to make a punch with a diameter smaller than that of the entire spot for subsequent extraction and bioanalysis; this technical approach is intended to minimize assay influence due to deviations in blood spot volume and reduce the requirement for spots of accurate volumes to be prepared. A primary consideration is that the analyte of interest must be quantifiable at the designated lower limit of quantification (LLOQ) using an intended bioanalytical method with the very limited sample volume of one or more DBS punch(es). Equally important, the analyte in the spot must be stable during the period between sample collection and analysis, and evenly distributed within the spot where the punched sample is taken. While hematocrit effects have been recently highlighted as an analytical concern for DBS (26–28), such concerns are not necessarily an impediment to successful implementation of the technique. In general, within a study population, except in some severe disease situations (e.g., renal impairment, hepatic impairment, oncology patients, etc.), hematocrit impact on quantitative analysis of DBS samples are minimal. Furthermore, strategies aimed at consistently collecting and analyzing a precise volume of blood to mitigate this impact have been evolving and appear to be quite promising (29–31).

While the remainder of this manuscript focuses on clinical applications/considerations of DBS, similar consideration should be given to nonclinical applications, particularly around comparisons between plasma and blood matrices, as well as venous and peripheral sampling comparisons.

Table 1. Suggested feasibility assessment of DBS bioanalytical assays

Parameter	Preliminary assessment
Specificity and sensitivity	Range, LLOQ, etc. Targeted LLOQ: 1 ng/mL (this should be a stress test to see if a very low LLOQ is achievable)
Stability	Room temperature for 1 month Frozen ($\sim -20^{\circ}\text{C}$) for 1 month Extreme temperature variations (-80°C , 37°C) for 1 day to mimic potential transportation times and potential conditions
Intra-day variability	To include LLOQ, LQC, MQC and HQC
Timing	Transition zone of late discovery preclinical development
Spot	Evaluation of spot volume and punch size; additionally evaluated whole spots in order to overcome hematocrit effects
Blood	Human with EDTA anticoagulant
Use non-treated DBS cards (preferred, but not mandatory)	Explore various cards (Alstrom, Whatman 903, DMPK-C (GE), equivalent untreated card)

IMPLEMENTATION OF DBS INTO CLINICAL PROGRAMS

Two strategies have evolved within the pharmaceutical industry for the inclusion of DBS sampling into clinical programs. In the first strategy, DBS is used exclusively as the TK/PK matrix starting from an early stage of development, such that DBS data is the only data type collected for TK/PK assessment in non-clinical development and later in clinical development, allowing results from any phase of the program to be readily correlated. In the second strategy, liquid matrix (i.e., blood, plasma, or serum) may have been chosen as the TK/PK matrix early in non-clinical and clinical development, but DBS is implemented at later stages of the program to address the needs of specific patient populations or study logistics, for which traditional wet matrix (blood, plasma, or serum) collection is unethical or impractical. Considerations for both strategies are described below:

1. Implementation of DBS for Continuous Development (from First-In-Human)

Implementation of DBS sampling as the only approach of PK sample collection in clinical development relies on fully informed decisions made by the program teams based on the knowledge of (1) intended patient population, (2) blood-to-plasma (B2P) partitioning, (3) plasma protein binding, and (4) bioanalytical feasibility (primarily adequate analyte stability and bioanalytical sensitivity). The data from pharmacology, non-clinical development, and bioanalysis should be generated in parallel to assist decision making before or at candidate nomination, where various strategies and decision trees have evolved (32). With this knowledge, the determination of the preferred matrix for PK assessments (blood, plasma, or serum) can be made. This topic has been covered in depth by Emmons and Rowland (33, 34). Briefly, when there is an indication that B2P partitioning for a given new chemical entity (NCE) is neither time- nor concentration-dependent, blood becomes a suitable matrix for assessment of PK

parameters, thus making DBS a desirable technique. To a collective experience of the participating companies, time- or concentration-dependence B2P partitioning of NCEs are rare. When it occurs, the dependency is typically associated with compounds that are directed at the red blood cells (e.g., antimalarial drugs and immunosuppressants).

While DBS can be selected as the sole PK matrix, bridging between liquid samples (plasma, blood, or serum) and DBS at relevant dose/exposure levels (pharmacologic and/or toxicological) in at least one species should be assessed quantitatively for the analyte of interest in order to understand the relationship between the two matrices. Necessary statistical/regression analysis will be helpful in describing this relationship, especially in non-clinical situations where plasma/blood data may have to be compared with DBS data across different studies (35).

The combination of *in vivo* animal B2P data along with the *in vitro* B2P human data gives confidence in making the decision to use DBS as the sole matrix in the FIH studies. However, in situations where there is insufficient animal B2P or *in vitro* human B2P data or in situations where there are contrasting differences between the animal species and the *in vitro* human B2P data, a more cautious approach to the use of DBS as the sole matrix in the FIH study is warranted.

Once the relationship between DBS and the corresponding wet matrix is fully characterized and bioanalytical feasibility criteria have been met for the DBS assay, the correlation between *in vivo* and *in vitro* B2P ratios should be examined. This can be carried out in the first-in-human (FIH) study, where venous blood samples and associated DBS samples can be collected in parallel with traditional plasma samples for quantitative analysis. The *in vivo* B2P is considered predictive for all human studies, allowing the estimation of exposure using either DBS or plasma.

During FIH studies, comparability between venous and peripheral (finger prick) sampling could also be

assessed. Peripheral sampling is different from venous sampling in that no anticoagulant is required for sample collection/deposition. In these situations, the comparison of venous to peripheral sampling also assesses both variables (sampling site and anticoagulant). Once the relationship between the two sampling sites is established, the alternate sampling site can be employed for ease of patient sample collection in phase II/III studies and data from all sites can be pooled for use in population PK modeling.

2. Integration of DBS for Specific Programs into Plasma/Serum-Based On-Going Clinical Development

Under this paradigm, DBS is used primarily for studies in which traditional liquid matrix sampling is simply not feasible or not ethical for the intended patient population. Alternative to the implementation of DBS from early drug discovery and development program as discussed above, this approach is to selectively incorporate DBS sample collection into a traditional liquid plasma/serum-based clinical PK program. Examples of such studies include ones where the clinical sites are not equipped for the collection/storage of liquid samples (no centrifuges, freezers, etc.), home-based or self-sampling is required (therapeutic drug monitoring applications), or frozen shipment of samples is logistically impossible. In such a situation, little to no exposure data could be collected without DBS sampling. The main advantage of DBS sampling in these scenarios is to augment the existing data set of a liquid sampling-based program by providing information that would otherwise be unavailable. However, development of a mathematical correlation of DBS concentrations to those of the previously used matrix (plasma or serum) is generally necessary.

PRACTICAL ASPECTS FOR INCORPORATING DBS INTO CLINICAL PROGRAMS

Data to assess the relationship of analyte concentrations between traditional wet sample (plasma or blood) and DBS is typically obtained from a cohort in the clinical study where both sample types are simultaneously collected for analysis (i.e., bridging data). The appropriate population in which to conduct bridging studies is currently a subject of discussion. From a logistical/practical point of view, it would be the most effective for a bridging study to be conducted in a data rich environment, preferably during the First-in-Human (FIH) study, so that confidence in DBS data can be established early in clinical development. Furthermore, the logistics of such a study are typically simpler in healthy subjects compared to those in phase II or III. For those late phase studies, if the physiology of the patient population is anticipated to be different from that of healthy subjects, bridging data from the patients will be necessary; and such data has already been requested by regulatory agencies. Regardless of the population chosen, it is recommended that bridging data be obtained at clinically relevant dose, ideally using final marketing dose.

While it is necessary to perform representative sampling, this dual sampling exercise is not always needed for every

patient or at every PK time point. However, consideration should be made to ensure dual samples (liquid plasma or blood vs. DBS) are collected from appropriate size of subjects/patients. The data from this exercise can serve as an indicator of acceptability of DBS sampling. The dual sampling can be made either via serial or sparse sampling. It is important that a prior discussion with regulatory agency should be taken in place early and on a case-by-case basis.

METHODOLOGIES/APPROACHES TO INTEGRATE DATA FROM DIFFERENT MATRICES

Correlation of analyte concentrations between DBS and blood (wet) is expected to be simple as both blood and DBS are basically the different forms of the same matrix. However, integration of DBS data into a clinical program where data is dominantly based on plasma does require a model to relate the concentration data obtained from the two matrices of the same samples.

Under ideal conditions where analyte B2P ratio is not subjected to the time and/or concentration dependency as discussed above, the relationship between plasma to DBS (or blood) concentrations is linear according to the following equation (24):

$$(\text{DBS}[\text{analyte}]/[1-\text{Hematocrit}])(1-f_{\text{BC}}) = \text{Plasma}[\text{analyte}]$$

where f_{BC} is the fraction of analyte bound to blood cells, which could be obtained by an *in vitro* or *ex vivo* test. Other approaches employ nonlinear mixed effect modeling for the assessment of DBS vs. plasma concentration relationship. One modeling approach is provided in the NONMEM® software, which is capable of performing regression analysis. The software can handle data from various matrices as part of a compartmental model. The mathematical relationship between plasma and DBS can be directly estimated as the slope in the case of a linear model.

Several graphical approaches have been proposed to a rapid assessment of the relationship between DBS and plasma or blood concentrations:

Plotting DBS concentration vs plasma (or blood) concentration. As noted above, when dealing with an analyte where f_{BC} is neither concentration nor time dependent, a plot of the plasma to DBS concentrations should be linearly related. Hence, a simple plot of DBS versus plasma concentrations obtained in bridging studies is recommended as an initial evaluation. As shown in Fig. 1 for compound A in a bridging study, a linear relationship between DBS and plasma concentrations is observed over the concentration range assessed. Data are distributed symmetrically along the regression line. The slope of 0.68 from the linear regression is in good agreement with the blood to plasma partition ratio of 0.70 determined for the compound *in vitro*. Apparently, this direct plotting approach can help unveil any nonlinear correlation between DBS and plasma data. As shown in Fig. 2 for compound B, the lack of a linear relationship is easily visualized mainly for high concentrations.

Different from the DBS/plasma concentration relationship, for which the correlation slope is linked to f_{BC} , a 1:1

Fig. 1. Linear relationship obtained from plotting plasma and DBS data from a bridging study

correlation (or a slope of 1) is expected when comparing wet vs. dry formats of the same matrix. Fig. 3 shows data collected from an oral dose escalation study where both wet blood and DBS samples for compound C were collected at each time point. An excellent concordance between wet and dry blood sampling was observed (Pearson's r , 0.9964 ($p < 0.001$) and Lin's concordance coefficient, 0.9964); furthermore, a good concordance in PK parameters between the matrices was calculated and shown in Table 2. In contrast, a non 1:1 correlation could be indicative of issues with the analytical method (i.e., poor recovery from the DBS spot) or analyte stability. In this case, further investigation is most likely warranted.

Plotting difference (%) between the predicted plasma concentrations based on DBS values vs actual plasma concentration. By this approach, the DBS and plasma data are first subjected to linear regression analysis. The resulting slope is used to calculate predicted plasma concentrations based on the DBS concentrations (DBS concentration/slope =

Fig. 3. Plot showing DBS versus wet blood concentrations following oral administration of a well-absorbed compound (C) in a dose escalation study

predicted plasma concentration). The differences (%) between the actual and predicted concentrations are then calculated. These calculated differences (%) are then plotted versus the actual measured plasma concentration for assessment of the correlation and associated diagnosis. As shown in Fig. 4 for compound D, the diagnostic plot shows that for the majority of points at low concentrations, the difference between the predicted and actual plasma concentrations is greater than 20%. This indicates that such a relationship is not appropriate for relating DBS and plasma data for this compound over the full range of observed concentrations, and a nonlinear model may be necessary to relate DBS and plasma concentrations. Once such a model is developed, new predicted plasma concentrations can be calculated, and the diagnostic plot regenerated to see if the differences between actual and predicted plasma concentrations are lessened.

Plotting ratio of DBS to plasma concentrations vs actual plasma concentration. An alternative diagnostic plot consists of plotting the ratio of the DBS to plasma concentrations

Fig. 2. Example of a non-linear relationship observed during a bridging study

Table 2. Comparison of pharmacokinetic parameters obtained using whole blood and dried blood spots for compound C in human subjects

Parameter	Whole blood			Dried blood spots		
	<i>n/N</i>	Median	CV%	<i>n/N</i>	Median	CV%
α -half-life (h)	26/28	1.7	37	27/28	1.8	39
β -half-life (h)	20/28	6.2	50	18/28	7.1	42
Fasting T _{max} (h)	20/20	1.0	–	20/20	1.0	–
AUC % Extrapolated	20/28	4.4	117	18/28	4.9	98
Apparent oral clearance (L/h)	20/28	42.2	30	18/28	39.7	33
Fasting C _{max} at 240 mg (ng/mL)	4/4	2779	11	4/4	2614	10
Fasting AUC(0- ∞) at 240 mg (ng*h/mL)	4/4	7095	15	4/4	6825	16

All parameters are pooled across fasted and fed treatment groups except where noted
n subjects included in the analysis, *N* total available subjects

from a bridging study versus the plasma concentrations. A consistent linear relationship between the DBS and plasma data will result in a plot tightly centered on a horizontal line corresponding to the B2P. An example of such a plot is shown in Fig. 5 for compound E, where data is taken from a study in which both venous and peripheral (finger prick) DBS data was compared to plasma data.

Bland-Altman Plot. The Bland-Altman plot is a useful graphical approach to assess agreement between two measurement techniques that are anticipated to generate similar results, such as wet versus dry blood or venous blood sampling compared to peripheral blood sampling. In a Bland-Altman plot, the difference between the two measurements is plotted versus the mean of the two measurements. When the difference is anticipated to be dependent upon the magnitude of the measurements, it is appropriate to use log transformed data. Figure 6 shows a Bland-Altman plot for a study for compound F, for which finger stick and venous sampling for blood collection is compared. When comparing peripheral versus venous sampling sites, there are potential differences in the composition of the blood drawn from these two sites, especially with regard to the concentration of red blood cells. Reports have shown varying degrees of difference

in drug concentrations when venous blood was compared to finger-prick blood (36); however, it seems there is no consistent trend. Similar to bridging studies between matrices, the assessment of bridging between sampling sites should also be conducted in a data-rich study at relevant clinical doses. The relationship between analyte concentrations determined in venous versus peripheral blood could be instrumental in decision making to move DBS sampling from a standard clinic setting into a home setting for therapeutic drug monitoring or for dosing compliance assessment.

SPECIFIC CONSIDERATIONS FOR INTENDED PATIENT POPULATIONS

As highlighted previously, thoughts need to be given on the possible difference in blood properties between the healthy subjects enrolled in data-rich environment (e.g., FIH) and the intended patients, from whom DBS sampling is to be conducted, prior to initiating or committing to using DBS sampling for clinical development. The example shown

Fig. 4. Diagnostic plot comparing venous and fingerstick DBS concentrations with plasma concentrations

Fig. 5. A diagnostic plot showing no significant difference between DBS and plasma concentrations at low concentrations. *Black circle* Venous/Plasma GMR (90% CI): 1.03 (1.01, 1.05), *White circle* Fingerstick/Plasma GMR (90% CI): 1.00 (0.98, 1.04)

Fig. 6. Bland–Altman plot comparing results obtained from fingertip and venous sampling

in Fig. 7 for compound G highlights the importance of collecting correlative data in the intended patient population. In the first study, the compound was administered to healthy volunteers, and both wet plasma and DBS samples were collected over the course of 14 days. The analysis of the resulting data showed a linear correlation between the matrices and a dose-proportional PK (open circles). In a second study, the same compound was administered to the patients under intensive care, and both wet plasma and DBS samples were collected and the analysis of the resulting data also showed a linear correlation between the matrices and a dose-proportional PK (stars). However, the measured plasma analyte concentrations in this patient population appeared to be higher than the measured DBS concentrations, compared to those measured from the healthy volunteers. Thus, the correlation generated using healthy human subjects would have affected the discussion and conclusion on the DBS results in the intended patient population if the second bridging study was not conducted. Once the relationship between liquid samples (blood or plasma) and DBS is understood and established in relevant patient populations, there is no need for continued dual-sampling of both liquid and dry matrices, and a well-validated DBS bioanalytical method can be used to support clinical studies, particularly if the data are to be considered primary or decision making.

Fig 7. Plot showing DBS versus plasma concentrations following oral administration of a well-absorbed BCS Class I compound to healthy subjects and ICU patients [$y=0.6695x+80.46$ (healthy) and $y=0.4957x+86.48$ (ICU)]

FUTURE DIRECTIONS AND CONCLUSIONS

In many ways, DBS as a sampling technique for the pharmaceutical industry has graduated from a research and evaluation phase. The technique is now actively employed in a growing number of drug discovery and development programs across the pharmaceutical industry, for which several examples were cited in this opinion paper. DBS sampling, like any other novel bioanalytical approach, does have technical limitations and challenges. Concern has been directed at some well-studied aspects related to DBS, such as the impact of extremes of hematocrit, uncertainty about long term stability, and lack of sample homogeneity, etc. However, should these limitations mean that the great potential of DBS be disregarded and abandoned at this point of time? The answer is “No”. As an industry, we should be mindful not to propose DBS as a panacea nor abandon it due to an overabundance of caution. The potential limitations of DBS need to be placed within the context of its benefits and opportunities that it can provide. The bioanalytical community should build a scientific rationale of the appropriate acceptability of DBS data. This would not only facilitate the industry but also help the regulators to better understand the value of the technique and, consequently, make quality decisions based on the quality data.

One should also consider integrating a tiered approach(s) into regulated bioanalysis, asking how we can accept or reject data in bioanalysis in general (37). As an industry, we are currently accepting or rejecting bioanalytical data based on the “4-6-15” rule, i.e., back calculated values of calibration standards and independently prepared QC samples. Perhaps, the focus should be more on what these data will be used for; in connection with key stakeholders, can quality decisions be made with the data? What would this mean for DBS? At the time when technology was new in regulated bioanalysis, several potential challenges have been identified, e.g., impact of hematocrit, long-term stability, or lack of spot homogeneity. We as an industry should be mindful not to propose DBS as a one-size-fits-all and insufficiently recognize the impact of imperfection but build a scientific rationale of why DBS data are acceptable as an alternative to plasma data. It would facilitate end users and regulators to better understand what the value of the data, and associated decisions.

Other microsampling techniques are currently on the horizon which may be free of some DBS-specific issues (hematocrit impact, sample inhomogeneity and B2P correlation, etc.). These techniques utilize either a novel blood collection substrate (38), or utilize small volume blood collections (30–70 μ L), but then prepare plasma for bioanalysis. Plasma microsampling provides low blood volume benefits similar to DBS, but it may minimize potential regulatory concerns by virtue of the plasma matrix. Several collection and processing methods are currently being used; briefly, the blood sample is collected in a 30–70 μ L in a microsampling capillary or plasticware device which is then centrifuged and the resulting plasma saved for bioanalysis. While these methods have the volume advantages of DBS, they are inherently more complex than traditional plasma collection methods, requiring specialized supplies. They also require a centrifugation step and samples to be stored and

shipped frozen. A recent perspective article reviews some current industry trends in microsampling and lists various techniques (39). Therefore, plasma microsampling may provide the most practical benefits to preclinical studies. Wet plasma microsampling does not provide the additional logistical benefits of DBS for those late stage clinical studies where access to facilities such as centrifuges and freezers is limited. However, a novel device has recently become available, which utilizes a rapid plasma extraction technology capable of collecting and drying a 2.5- μ L aliquot of plasma within 3 min from a finger-stick and does not require centrifuges and freezers (40).

From FIH through late phase clinical trials, the value of DBS sampling as a bioanalytical or PK strategy becomes dependent on specific aspects of the drug candidate and associated development programs. The physiochemical properties of the drug itself, blood to plasma partitioning, the intended PK sampling population, and the point of DBS implementation in the development program all need to be considered. The current opinion paper has navigated through the key decisions that are open to the bioanalytical scientist and end-user of the data to enable a scientifically defensible approach to the use of DBS throughout the clinical development, and represents a growing trend to bring sampling closer to the patient. At present, data associated with DBS technology is sparse compared to other matrices, therefore, as our collective experience grows with its use around refinement of these considerations may be necessary for its acceptance.

One of the key learnings from this collection of researchers is that any strategic approaches for implementing DBS sampling in the clinic should proactively be discussed with regulatory agencies at the beginning of the intended clinical program.

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