Population Modeling Is a Critical Element of Bridging Pharmacokinetic Data From Dried Blood Spot and Plasma Across Clinical Programs

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Abstract

Purpose: To demonstrate through two case studies how population pharmacokinetic (PK) modeling should be leveraged for bridging plasma and dried blood spot (DBS) PK data across clinical development programs.

Methods: In two case studies (MK-X and MK-Y), population PK models initially developed from Ph1 plasma data were updated to include plasma and DBS data from healthy subjects (Phase 1 setting) and patient (late-stage trials) plasma-DBS bridging studies. DBS samples were collected via in-clinic venipuncture (MK-X and MK-Y) and in-clinic and at-home fingerstick (MK-Y). An estimated population slope converted between DBS and plasma concentrations. Separate residual errors for plasma and DBS data were estimated. For MK-Y, residual error was further partitioned based on in-clinic vs at-home DBS sampling. Models were qualified through standard diagnostics and qualification approaches. Interchangeability of matrices was evaluated through various approaches including a comparison of post-hoc predicted exposures from plasma vs DBS data alone (using slope as a conversion factor).

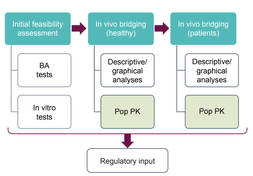
Results: In both cases, two-compartment population PK models were developed. Population PK parameter estimates were similar with and without DBS data. The slope parameters were well estimated and consistent with the DBS-plasma linear regression slopes and in vitro blood:plasma ratio data. Residual error for in-clinic DBS was low and generally comparable to that for plasma; however, high residual error (113% CV) was observed for at-home DBS (MK-Y). For MK-X, DBS and plasma based post-hoc estimates of plasma exposures were interchangeable and lacked bias. Phase 1 results were used to inform Phase 2 analysis plans and development of a DBS Go/No Go decision tree for later phase implementation.

Conclusion: The literature cites simplified approaches with generally arbitrary cut-offs (ISR criteria, regressions, Bland-Altman plots, etc) to bridge plasma and DBS concentrations. We have shown that pop PK modeling with prospective model-informed analysis plans should be a critical element of plasma-DBS bridging strategies. These approaches directly address the development question of whether DBS sampling supports pharmacometric aspects of regulatory submissions if incorporated in larger-scale patient studies.

Introduction

- DBS has continued to gain application across the industry as a viable alternative to plasma for PK evaluations due to several advantages[1,2]
- A critical component to using DBS in clinical programs is demonstrating interchangeability of plasma and DBS to enable bridging across the drug's development history
- To date, most published literature has applied statistical approaches of Phase 1 studies to enable bridging
- Merck has developed and gained regulatory feedback on an integrated strategy (**Figure 1**) that includes population PK analyses of Phase 1/1b and 2 studies to establish this bridge
- Two case studies of successful application of this strategy are presented
  - MK-X: DBS was considered an attractive option due to a targeted indication in a likely aging population
  - MK-Y: DBS was considered an attractive option due to the potential of collecting at-home PK samples proximal to use of MK-Y during episodic events

Figure 1. Merck's strategy for DBS



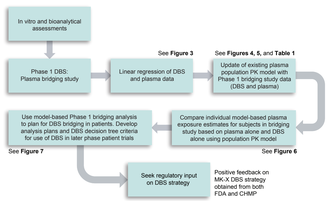
Purpose

To demonstrate through two case studies how population PK modeling should be leveraged for bridging plasma and DBS PK data across clinical development programs.

Methods: Case Study 1 (MK-X)

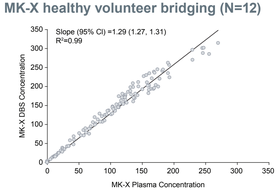
- A clinical strategy was developed to incorporate DBS in a staged manner in select clinical studies (**Figure 2**) and facilitate DBS-plasma bridging
- The existing plasma-based population PK model (developed in NONMEM) was updated with plasma and DBS data (venous sampling) from a Phase 1 DBS plasma-bridging study in healthy volunteers
- The Phase 1 model was used to develop prospective model-based analysis plans and Go/No Go DBS criteria for later phases of MK-X development

Figure 2. MK-X DBS clinical implementation roadmap



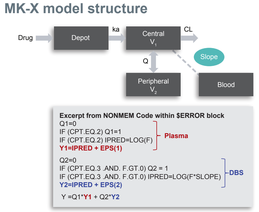
Results: Case Study 1 (MK-X)

Figure 3. MK-X healthy volunteer bridging (N=12)



11 concurrent DBS and plasma samples collected in healthy volunteer study (N=12). Based on linear regression, the whole blood concentrations from DBS samples correlated well with plasma concentrations ($R^2 = 0.99$). The regression model-estimated ratio (95% CI) between DBS and plasma concentrations was 1.29 (1.27, 1.31), in close agreement to the in vitro estimated blood:plasma (B:P) ratio for MK-X in humans of 1.22.

Figure 4. MK-X model structure



- The previously developed MK-X 2 compartment plasma PK model was updated with plasma and DBS data from a Phase 1 bridging study in healthy volunteers
- DBS concentrations were treated as a separate "blood" compartment with a "slope" parameter correlating plasma and blood concentrations
- Separate residual variability estimates were obtained for plasma and DBS data

Results: Case Study 1 (MK-X) (continued)

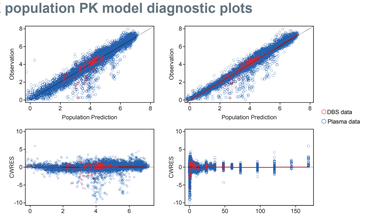
Table 1. Phase 1 MK-X population PK model parameter estimates (% residual standard error) for relevant parameters

Parameter	Parameter Description	Plasma-Only Model† Estimate (% RSE)	Plasma + DBS Model‡ 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)

†Model developed using Phase 1 plasma data; ‡Model developed using Phase 1 plasma data as well as DBS data from a healthy volunteer bridging study.

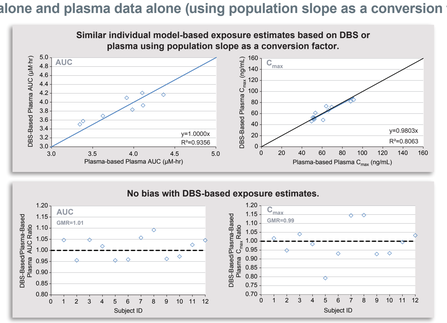
- The population PK model-based population slope estimate of 1.27 was similar to the regression-based slope (**Figure 3**) and the in vitro B:P estimate and was well estimated (4.61% RSE)
- Interindividual variability on the population slope was explored and found not to be significant
- All model parameters were well estimated and comparable between the plasma and plasma + DBS model

Figure 5. MK-X population PK model diagnostic plots



Goodness of fit plots for the plasma + DBS population PK model did not indicate any bias in DBS vs plasma data.

Figure 6. Model-based individual MK-X plasma exposure estimates based on DBS data alone and plasma data alone (using population slope as a conversion factor)



Individual plasma $AUC_{0-\infty}$ and C_{max} for each of the 12 healthy volunteers in the MK-X DBS-plasma bridging study were estimated based on (1) the plasma model and plasma data from the bridging study and (2) the plasma + DBS model and DBS data from the bridging study (using the population slope as a conversion factor). The comparison of DBS and plasma-based MK-X plasma exposure estimates are shown above. These exposure estimates were similar, and the DBS-based estimated did not show any over- or underprediction bias compared to the plasma-based estimates.

Figure 7a. MK-X decision tree #1 (linear regression analysis based on patient data only)

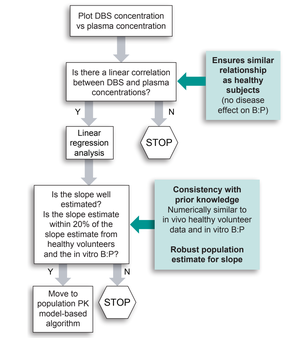
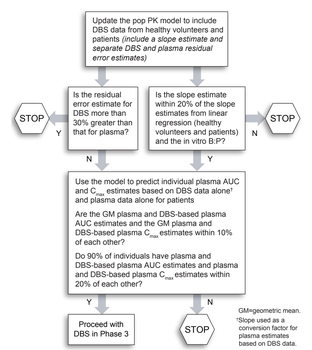


Figure 7b. MK-X decision tree #2 (pop PK model-based analysis based on healthy volunteer and patient data)



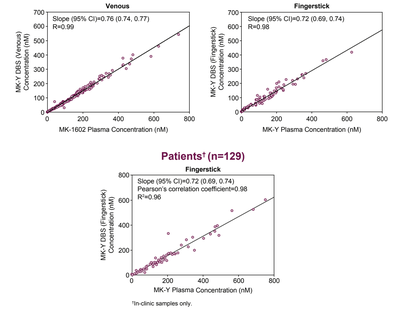
The MK-X Phase 1 DBS-plasma population PK analysis was used to define analysis plans and DBS Go/No Go decision trees for later phases of development (shown above) based (a) solely on patient DBS and plasma data from a later phase patient trial (linear regression analysis) and (b) on patient DBS and plasma data from a later phase patient trial as well as DBS and plasma data from Phase 1 (population PK model-based analysis). Regulatory concurrence was gained on this approach. Note that the decision tree and cut-off values shown were tailored to MK-X and could be different for other compounds.

Methods: Case Study 2 (MK-Y)

- DBS samples were collected in both a healthy volunteer study (venipuncture and fingerstick sampling) and a study in patients (fingerstick sampling). The patient study included at-home DBS sampling at 3 timepoints following treatment on the day of patients experiencing an episodic event in addition to 1 in-clinic sample
- Linear regression and population PK model-based analyses were conducted in a similar manner to MK-X
- In the population PK model, four separate residual errors by matrix (i.e., blood and plasma) and subject population (i.e., healthy volunteers and patients) were estimated

Results: Case Study 2 (MK-Y)

Figure 8. MK-Y bridging study results



†In-clinic samples only.

- Healthy volunteer study demonstrated strong correlations between venous and fingerstick DBS vs plasma
- Patient trial demonstrated strong correlations between fingerstick and plasma data collected in-clinic
- The regression model-estimated slopes were consistent with the in vitro-estimated B:P ratio for MK-Y in humans of 0.8
- Similar to MK-X, a population PK model-based bridging analysis was also conducted, and the estimated B:P ratio from this analysis was 0.732 (SE 0.0162), consistent with linear regression results

Table 2. MK-Y population model residual error estimates from select models

	Plasma		Blood		
	Healthy	Patient	Healthy (Clinic)	Patient (Clinic)	Patient (Home)
Model X	0.41	0.55	0.27	0.96	
Model Y	0.41	0.53	0.27	0.37	1.13
Model Z	0.41	0.52	0.283†		1.13

†Combined res error term for healthy and patient clinic based DBS.

MK-Y Pop PK model-estimated residual variability serves as a useful diagnostic tool for understanding source of variability

- Blood concentration data were less variable than plasma concentrations in healthy subjects (i.e., 27% for blood and 41% for plasma), supporting the adequacy of use of DBS sampling and assay methods for characterization of MK-Y concentration
- High variability (96%) in blood concentrations in patients compared with healthy subjects (27%) suggests that other factors may be contributing to the increased residual variability rather than the blood assay itself
- Further partitioning of the residual variability of blood data in patients (Model Y) revealed that high variability was associated with DBS samples self collected by patients in an outpatient setting (113%), and the blood residual variability in patients remains reasonable (37%) when DBS samples were collected during a clinical visit
- The residual variability appeared to be similar irrespective of patient populations, and the primary driver for variability differences appeared to be whether a DBS sample is collected in clinic vs in an outpatient setting (Model Z), suggesting problematic data/sample collection by outpatients

Discussion

- The case studies presented herein represent two examples of incorporation of DBS PK data into existing plasma population PK models
- In Case Study 1, incorporation of Phase 1 MK-X DBS data into the existing plasma population PK model facilitated healthy volunteer bridging and informed model-based analysis plans for patient data and DBS Go/No Go criteria for later phases of development. MK-X exposure estimates based on DBS data were similar to those based on plasma data, supporting that similar PK and PK/PD conclusions could be derived using either matrix
- In Case Study 2, population PK modeling facilitated the evaluation of the sources of variability between the plasma and DBS assays and elucidated that the major source was due to at-home versus in-clinic sampling, rather than any inherent differences between the plasma and DBS assays. As only sparse DBS PK samples were collected, both in-clinic and at-home, it would not have been feasible to partition these sources of variability without the use of the population PK model. Possible reasons for the increased variability observed for the at-home samples include (but are not limited to) imprecise diary entry or improper collection of DBS samples in an outpatient setting

Conclusions

- Population PK modeling is an important aspect of DBS:plasma PK bridging strategies to ensure that pharmacokinetic conclusions may be seamlessly derived across the two matrices
- The literature cites simplified approaches with generally arbitrary cut-offs (ISR criteria, regressions, Bland-Altman plots, etc) to bridge plasma and DBS concentrations. We have shown that pop PK modeling with prospective model-informed analysis plans should be a critical element of plasma-DBS bridging strategies. Model-based approaches directly address the development question of whether incorporation of DBS sampling into larger-scale patient studies would support pharmacometric aspects of regulatory submissions

References

1. Emmons G, Rowland M. Pharmacokinetic considerations as to when to use dried blood spot sampling. *Bioanalysis.* 2010;2(11):1791-1796.
2. Malcolm R, Shepard T. Interpretation of microsampling data during drug development and regulatory considerations. In: Zane P, Emmons GT, eds. *Microsampling in pharmaceutical bioanalysis.* London: Future Science Ltd, 2013:121-133.