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Population PK modelling as an alternative route to bioequivalence

Parmesh Gajjar[a,b]*, Jake Dickinson[a], Harri Dickinson[a], Linette Ruston[a], Hitesh B. Mistry[a,c], Claire Patterson[a], Paul A. Dickinson[a]

[a] Seda Pharmaceutical Development Services, Unit D, Cheadle Royal Business Park, Oakfield Road, Stockport, SK8 3GX, UK, [b] Department of Materials, University of Manchester, Oxford Road, M13 9PL, UK, [c] Manchester Pharmacy School, University of Manchester, Oxford Road, M13 9PL, UK.

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*Corresponding author.
E-mail:
parmesh.gajjar@sedapds.com

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SUMMARY

Demonstrating bioequivalence (BE) is important for the development of lower cost generic products, and also for approving post-submission manufacturing changes. However, for many complex parenteral products, BE demonstration can be very challenging. For example, long-acting injectable products are engineered to have an extended release over several weeks or months, but this also means that a traditional BE study can take many months or years to perform. Here, we summarise how population PK modelling, which captures differences in PK profiles due to population variation, could be used explore hundreds of virtual formulations, and thus determine a range of products that are bioequivalent after both multiple and single dosing. This provides a guide for formulation development but also opens alternative, more streamlined routes to BE assessment.

INTRODUCTION

Bioequivalence (BE) assessment is important for developing lower cost generic products, since it demonstrates that there is no difference in the rate and extent of absorption between the test and reference products. Whilst there are reliable BE methods for oral products, BE assessment for complex parenterals such as long-acting injectables (LAI), can be very challenging (Sharan, et al. 2021).

Recently, model integrated evidence (MIE) is increasingly being used in BE demonstration, and the USA FDA recently held a public workshop to explore how MIE could be used in best practice for BE assessment of LAI products. Population PK (popPK) models predict the pharmacokinetic (PK) profiles for individuals, based on physiological parameters such as age, gender or BMI, and provide a powerful way to predict PK profiles similar to a clinical trial.

Here, we summarise results from the talk given by the authors of this manuscript at the aforementioned FDA workshop, with full results provided elsewhere (Gajjar, et al. 2022).

MATERIALS AND METHODS

The simulations use the popPK model for paliperidone (Samtani, Vermeulen and Stuyckens 2009) as an illustrative case study, with the reference product considered to the have the same values as the original model and virtual formulations created by varying the absorption rate k_a and dose-partition coefficient f_2 as a percentage of the reference product value. A virtual population of 25 individuals from the USA was created, with each individual taking part in three clinical studies for each virtual product and dosing regime (multiple doses of 150 mg on days 1, 8, 36, 64 & 92 or a single dose of 150 mg on day 1). A virtual BE study was performed using a different 50 individuals from the same population, and a PK model with the same structure as the reference

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product fitted. Full details are available in (Gajjar, et al. 2022).

RESULTS AND DISCUSSION

PK profiles for the 25 individuals when given a single 150 mg dose of the test product are shown in Fig 1. Similar simulations were performed for multiple dosing and for all virtual test formulations.

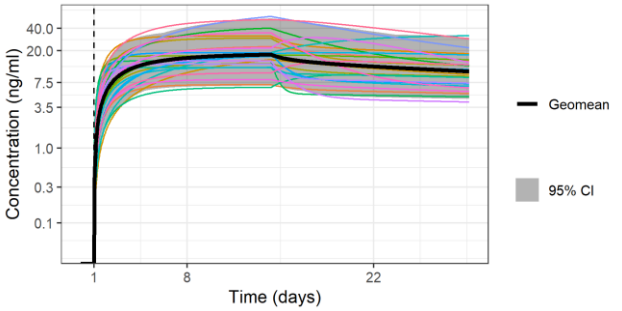

Fig. 1. *PK profiles for 25 individuals given a single dose of the test product. Figure adapted from (Gajjar, et al. 2022).*

The range of products which are BE depends on the metrics used in assessment. Fig. 2A shows that the addition of partial AUCs (pAUC) leads to a smaller range of BE products than simply using Cmax, Cmin and AUC. As shown in Fig. 2B, it is also possible to identify some products which are BE after a single dose, although this is a smaller subset of the full range of products that are BE after multiple dosing.

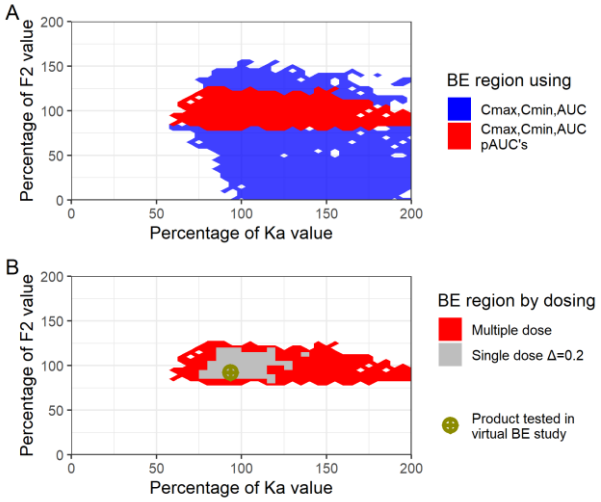

Fig. 2. *(A) Bioequivalent products after multiple dosing, when assessed using either Cmax, Cmin and AUC, or using partial AUC's in addition. (B) Comparison of all BE products after multiple dosing and some products which are also BE after a single dose. Figure adapted from (Gajjar, et al. 2022).*

This provides an alternative method of testing BE. Figure 3 shows the fits for two individuals when given a random product. The fitted parameters can be compared against the test product, and plotted on the parameter space in Fig 2B to see whether it is BE or not. The advantage of this method is that it allows BE assessment without the need to dose both the test and reference products, and it also takes inter-individual variability into account.

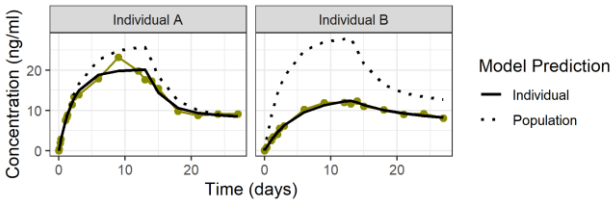

Fig. 3. *Individual PK profiles for two virtual individuals, overlaid with population PK model fits. Figure adapted from (Gajjar, et al. 2022).*

CONCLUSIONS

Population PK modelling provides a powerful tool for exploring the variation of PK profiles across a population, and thus, can be successfully utilised to examine the variation between different formulations across a given population. This can be used for predicting a range of BE products after both multiple and single dosing, and this parameter space of BE products can also be used in direct BE assessment through population PK fitting. The ideas here are meant as an illustration to stimulate further thinking in this area.

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