Sensitivity Analysis and Calibration for a Computationally Expensive PBPK Model: A Case Study for the PERSERIS™ In-Situ Forming PLGA-Based Implant

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A Meta-Modelling Approach Makes Global Sensitivity Analysis Feasible for Computationally Expensive PBPK Models!

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Background and Objectives

Sensitivity Analysis (SA) describes a class of methods for studying the relationships between the inputs and outputs of a model [1]. It is generally expected that SA forms part of PBPK-based regulatory submission to address data gaps, uncertainty, and variability in key model parameters [2]. Quantitative global SA (GSA) using a variance-based analysis requires thousands of model evaluations under study which is impractical for computationally expensive PBPK models. The objective of this work was to demonstrate application of a computationally efficient meta-modelling-based GSA using a PBPK model developed for the PERSERIS™ risperidone formulation, which is a Poly lactic-co-glycolic acid (PLGA) based in-situ forming implant. Due to the complexity of the underlying equations a single evaluation of the model requires several minutes resulting a GSA analysis taking several thousand hours!

PBPK model development

A published model for risperidone and its active metabolite paliperidone [3] was implemented in Simcyp V25 and verified using data from IV infusion and oral dosing studies [4,5]. This validated disposition model was used in conjunction with the Simcyp PLGA injectables absorption model to study plasma concentrations of the active moiety following a subcutaneous injection of 120mg of the PERSERIS™ formulation.

Information on the PERSERIS™ formulation was obtained from the literature. A recent reverse engineering study [6] provided key information on the PLGA. The implant was modelled as a cylinder with a radius assumed to correspond to the gauge of the needle, and a length inferred from the formulation mass, and assumed density and radius.

Several parameters relating to the burst release, internal pore structure of the implant, and the degradation of the PLGA were uncertain and ascribed probability distributions.

Table 1: Key parameters of the PLGA and implant

Parameter	Units	Value	Reference
PLGA			
Lactide to glycolide ratio	-	0.8	[6]
Polymer mean molecular weight	g/mol	22000	[6]
Polymer molecular weight CV	%	15	[6]
End group	-	Acid	[6]
Implant			
Mass of the implant	mg	800	[7]
Dose	mg	120	[7]
Length of the implant	cm	6.41	Assumed
Radius of the implant	cm	0.12	Assumed
Ionization proportionality constant	-	Unif(10,60)	Unknown
De-ionization rate constant	1/M/h	Unif(0.25, 2)	Unknown
Fractional volumetric porosity	-	Unif(0.01, 0.15)	Unknown
Average pore radius at start	µm	Unif(4, 40)	Unknown
Initial releasable fraction	-	Unif(0.01, 0.20)	Unknown

GSA workflow

The GSA workflow used several R packages (spacefillr, BACCO, sensitivity) for analysis and the Simcyp-R package to interface between R and Simcyp. Five parameters were studied in GSA, with uniform distributions ascribed to each parameter (Table 1). A space-filling design (128 points) of parameter combinations was generated. The PBPK model was run at each parameter combination, and plasma concentrations of risperidone and paliperidone were considered. A comparison of the total active moiety from these simulations against clinical data is shown in Figure 1.

Gaussian Process (GP) regression models were built to approximate the peak active moiety concentrations within and following the first 24 hours, $C_{max,\ burst}$ and $C_{max,\ main}$ respectively. After thorough validation checks to ensure adequate predictive performance, the GPs were used as a fast surrogate in GSA. A variance-based GSA was conducted on $C_{max,\ burst}$ and $C_{max,\ main}$. Results are shown in Figure 2.

Results and Discussion

Simulations showed a large range of PK profiles could be achieved through varying uncertain implant related parameters, with a subset of simulations capturing the broad trend of the clinical data. The burst release was primarily driven by the initial releasable fraction and volumetric porosity, with a significant interaction. The later peak was driven by two parameters which govern degradation of the PLGA. The GSA was achieved with just 128 runs of the PBPK model and several hours of CPU time. The 24,000 simulations required for conventional GSA would have taken over two weeks of computation.

References

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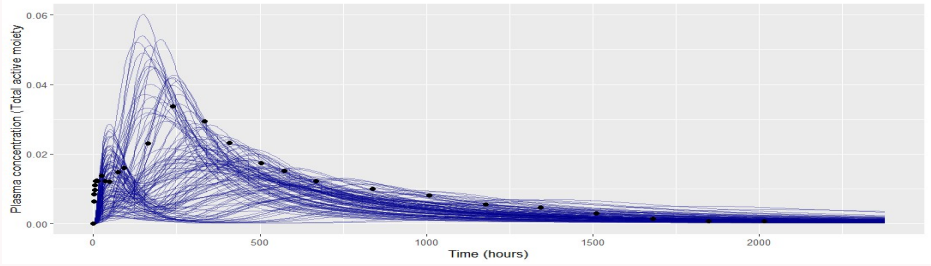

Figure 1: Comparison of simulations and clinical data

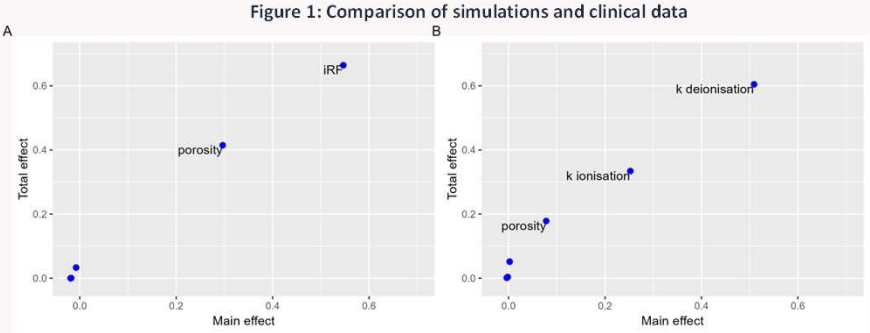

Figure 2: GSA results $C_{max,\ burst}$ (A) and $C_{max,\ main}$ (B)

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