PHYSIOLOGICALLY BASED BIOPHARMACEUTICS MODELING FOR VIRTUAL BIOEQUIVALENCE ASSESSMENT OF METFORMIN IMMEDIATE AND EXTENDED-RELEASE FORMULATIONS

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INTRODUCTION

Metformin (MTF) is a medication used to treat type 2 diabetes. It works by decreasing glucose production in the liver and improving insulin sensitivity in the body's tissues. [1] MTF is marketed as immediate release (IR) and extended release (XR) tablets; the XR tablet shows a longer time to reach maximum plasma concentration (Cmax) than the IR one. [1-2] The goal of this work was to develop a workflow for virtual bioequivalence (VBE) assessments using Physiologically Based Biopharmaceutics Modeling (PBBM). We conducted VBE on two IR and two XR MTF formulations as model products for the future development of the VBE workflow.

METHODS

A MTF PBBM model was developed using GastroPlus® version 10.1 (Simulations Plus, Inc., Research Triangle Park, NC, USA), including all critical mechanisms impacting MTF absorption and systemic disposition such as contributions of intestinal transporters and paracellular permeability to absorption, transporter-mediated uptake into kidney and liver, and transporter-mediated renal secretion. Intra-subject variability (ISV) was considered in gut physiology parameters targeting an ISV of 10% to AUC and 12% to Cmax. The model input parameters were a combination of literature sourced values, in silico predicted values (ADMET Predictor®), and values fitted against observed clinical data. The systemic disposition model for MTF was developed using intravenous data. In vitro dissolution data and the in vivo BE study data on two IR MTF and two XR MTF formulations (Study 1 and Study 2, respectively) were provided by Galenicum Health SLU. Reference (R) and Test (T) products were assigned in accordance with Studies 1 and 2. The *in vivo* dissolution for each of the IR and XR tablets was parametrized as single Weibull function fitted to corresponding in vitro dissolution data measured in USP II apparatus in media with pH 6.8 (Figure 1). The model was developed and validated using 20 pharmacokinetic (PK) datasets from the literature and refined against *in vivo* PK data from Studies 1 and 2. The VBE evaluations were performed using the validated model and involved 20 trials for each for the IR and XR tablets. The VBE study design mirrored single dose Studies 1 and 2: Study 1 enrolled 20 subjects in a 2x2 crossover design under fed conditions; Study 2 enrolled 58 subjects in a 2x2 crossover design under fasted conditions. The intra-subject variability (12–15% for Cmax and AUC) was applied to both formulations and addressed by adjusting virtual physiological parameters (e.g., stomach emptying time, clearance and Peff). Inter-subject variability was also incorporated (23–34% for Cmax and AUC) by tuning physiological parameters to reflect the variability observed in the in vivo studies.

RESULTS

Model performance for IR and XR tablets was satisfactory when simulated vs observed plasma MTF PK profiles were compared (Figure 2). The predicted-to-observed fold error for Cmax and AUC0-t ranged between 0.5-1.25 across all studies. Additionally, Tmax and the impact of inter- and intra-subject variability on Cmax and AUC across independent studies were considered in the model performance assessment. The VBE assessment results were consistent with Studies 1 and 2. Across all VBE studies, the 90% confidence intervals for the T/R geometric mean ratio ranged from 0.88–1.17 (point estimate range: 0.94–1.07) for AUC0–t and AUCinf, and 0.89–1.15 (point estimate range: 0.98–1.09) for Cmax, meeting the BE acceptance criteria(Figure 3).[3]

Figure 1: In vitro dissolution data measured in USP II apparatus in media with pH 6.8

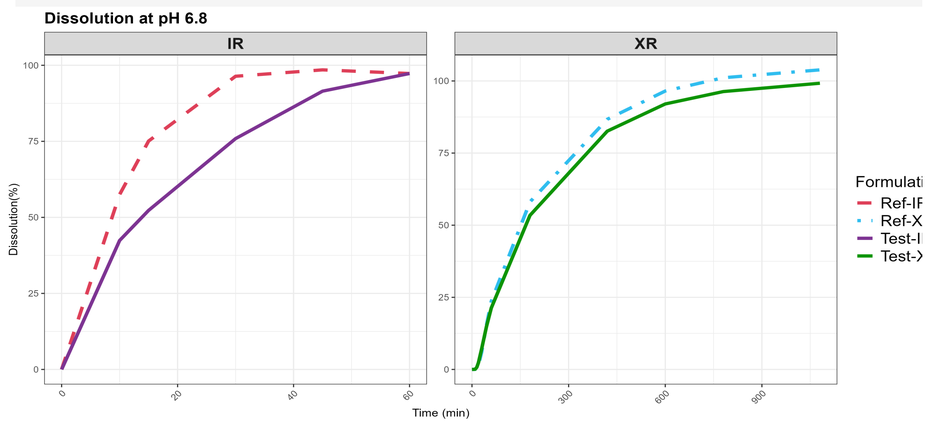


Figure 2: Prediction of IR and XR formulation

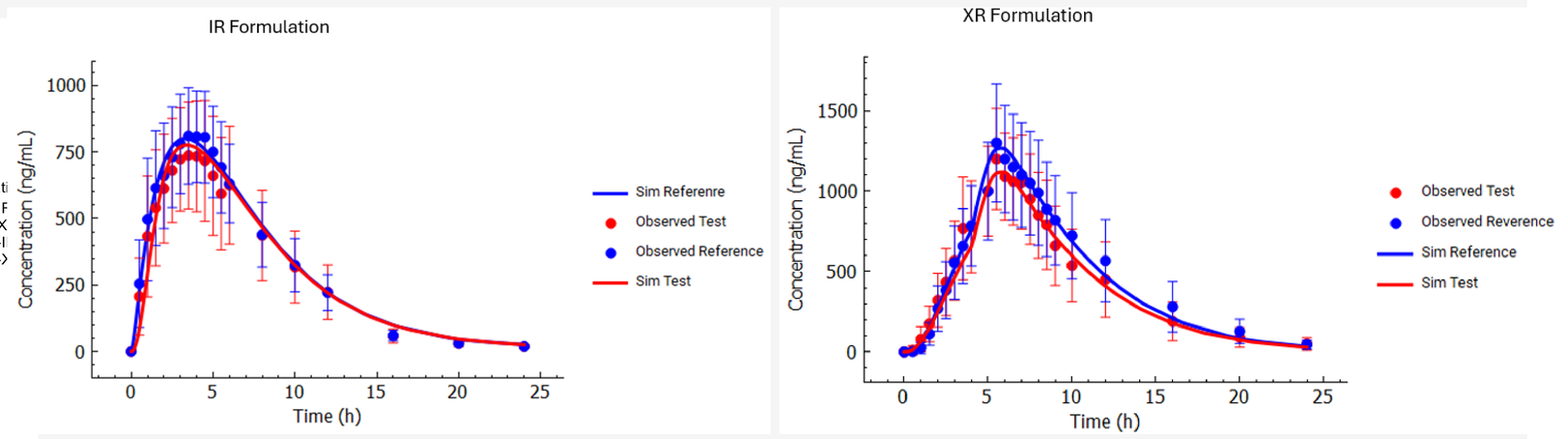
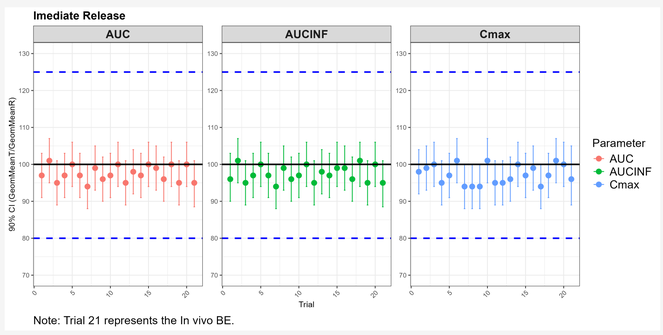
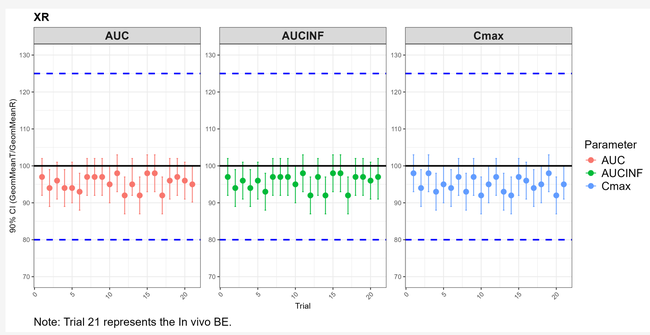


Figure 3: Virtual bioequivalence results



Note: Trial 21 represents the In vivo BE.



Note: Trial 21 represents the In vivo BE.

CONCLUSION. The developed PBBM approach effectively predicts the absorption and MTF PKs; predicted and observed data align well across multiple studies. The VBE assessments confirmed that both the IR R vs T and XR R vs T formulations were found bioequivalent, consistent with the Study 1 and 2 bioequivalence outcomes. These results suggest that PBBM, when appropriately validated, has the potential to support VBE evaluations. This work summarizes the initial efforts of the best practices for the performance of VBE assessments with considerations on model development and validation as well as VBE study design.

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To enhance research collaborations with the generic industry, and maximize the predictive capabilities of these VBE models, the Center for Research on Complex Generics (CRCG) announced open invitations for generic industry stakeholders (non-federal entities) to provide in vitro and/or in vivo preclinical and/or clinical study data for specific drug products within the scope of this Grant (refer to CRCG Announcement for Data Contribution to Grant U01FD007906 awarded to Simulations Plus (Center for Research on Complex Generics (CRCG). Call for Data Contribution #2. Available at https://complexgenerics.org/research-capabilities/funding-opportunities/call-for-data-contribution-2/. Last accessed Dec. 23rd, 2024). The goal was to afford the Grant awardee access to relevant experimental data that could be leveraged when developing and validating their models. Multiple generic industry stakeholders responded to the announcement and were willing to contribute experimental data to the awardees of these research Grants. Specifically, Adium, Galenicum Health S.L.U, Libbs Farmacêutica, and Sandoz agreed to contribute to the research under Grant U01FD007906. Note that the terms of the contribution were negotiated directly between the Grant awardee and each external contributor. Each awardee and contributor understood that the contributions would not result in undue influence on FDA regulatory decisions, not result in an endorsement of the identified contributors or any of their products or activities by FDA and not provide access to non-public product specific information from FDA. It was also agreed that the contributions may be publicly acknowledged by the identified contributors, but the contributors may not promote themselves as having a relationship with FDA.

References

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