Application of *in-silico* PBPK Absorption Modeling to Justify Drug Product Dissolution Specifications - Analysis of a Regulatory Submission Case Studies and its Impact on Concept of Virtual BE

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ABSTRACT

Recent advances in physiologically-based pharmacokinetic (PBPK) absorption modelling have enabled the translation of *in vitro* dissolution data to the predictions of the *in vivo* performance of drug product in a target population[1]. Such virtual trials thus can permit population variability to be taken into account and enable the setting/justifying wider dissolution specifications that may ensure greater likelihood of obtaining bioequivalence (BE). We present reported case studies used in regulatory interactions where verified PBPK models were used to justify drug product dissolution specifications thereby providing basis for biowaiver applications[2].

Population based PBPK modelling can be used to guide formulation design space specification and aid in identifying suitable enabling formulations in BA/BE studies, potentially reducing the cost/time of product development cycles. We demonstrate how verified PBPK models can be used to 1. justify set dissolution specifications 2. build a formulation safe space design and 3. provide basis for biowaiver arguments.

METHODS

The models were build to predict the '*in vivo*' performance of the dosage forms characterised by *in vitro* dissolution profiles using 'virtual trials' thereby potentially waiving clinical studies. Therefore, the sponsors needed to demonstrate the predictive performance of the developed PBPK model in *in vivo* (clinical) situation. Almost all of these successful studies used a systematic stepwise modelling approach, namely: PBPK Model Development < Model Verification < Model Application. The verification step is essential in building confidence in the model applications step.

A PBPK Model Development- Using Relevant Drug Physchem and Disposition Parameters

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Model Verification- Utilising Clinical Study Dataset of Different Doses, Dosage Regimen, Drug-Food & Drug-Drug Interaction Studies

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Virtual Population Prediction- Plasma Concentration time Profiles Predictions Using Relevant Parameters in Verified PBPK model

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Virtual Bioequivalence- Establishing Equivalence Between Target and Test Formulations

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Model Application- 1. Setting Dissolution Limit Specifications
2. Construction of Safe Space Design etc.

Case Study 1

Product- ORILISSA® Tablets[3]
Sponsor- Abbvie
API- Elagolix
Strengths- 150 and 200 mg Tablets
Application: Dissolution data for release of two commercial batches and additional long-term stability batches failed to meet the originally proposed dissolution acceptance criterion

A PBPK Model Initially Developed for Assessing DDI

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Developed Model was Updated to Incorporate *in vitro* dissolution data to Predict Dosage Form PK

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Modified PBPK Model Was Extensively Verified against the commercial batches and also against Food Effects Studies

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Using Verified Modelling Approach the Sponsor could demonstrate that the slower dissolution would not significantly affect the *in vivo* exposure of Elagolix

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FDA Accepted Widening of Dissolution Specifications of the Drug Product.

Case Study 2

Product- ZURAMPIC® Tablets[4]
Sponsor- Astra Zeneca
API- Lesinurad
Strengths- 200 mg and 400 mg Tablets
Application: PBPK modelling approach was submitted in support of the proposed specifications for dissolution and particle size that would ensure suitable clinical performance of batches.

A PBPK Model Was Developed Sequentially to Fit IV and Oral PK Studies

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The selected *in vitro D*issolution Input Model was Validated using Clinical Formulation Batches and tested for its ability to replicate observed Bioinequivalence Study

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Virtual BE Simulations Were then Performed Testing the Limits of Dissolution and Particle Size Distribution Providing Rational for Proposed Specifications

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A Verified PBPK modeling Approach was accepted by US FDA in support of the proposed control strategy

RESULTS AND DISCUSSION

Understanding the impact of scale-up and/or long term stability induced formulation changes on overall drug bioavailability is essential in order to ensure that the drugs' safety as well as efficacy is not compromised due to stability/manufacturing processes. As described in Case Study 1 such changes are in fact of more concern in post approval stages and often require clinical BE studies to ensure the formulation change/s are still within regulatory requirements when compared to that of the clinical bio batch. The scale-up and post-approval changes (SUPAC) guidance by the FDA explains the regulatory perspective to deal with the level of formulation changes[5].

Similarly, as described in Case 2, providing rational behind the set dissolution and particle size distribution specifications to ensure the product batches would be bioequivalent to the pivotal clinical batches is always critical.

Verified PBPK models, as described in these case studies, thus can be used to run virtual BE trials with potential application in formulation safe space design, setting of clinically relevant dissolution specifications, aiding justification of biowaivers to support SUPAC level changes, informing QbD and beyond.

CONCLUSION

Improved predictability of the PBPK modelling tools may further help to reduce, refine and partially replace number of (pilot) clinical studies for the drug companies. This in turn would have significant impact on regulatory decision making process, bring additional insight in the performance of drug products in subjects, help to reduce cost and speed up of drug development for both novel and generic drugs.

Further verification of the proposed virtual BE approach with more drugs and formulations of varying nature is needed to increase confidence in and spread awareness of this novel tool.

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