ESR Researcher Project: Non-technical Summary

"Bayesian knowledge integration for an in vitro–in vivo correlation model"

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Optimising the exposure of a compound becomes a key step during the drug development process. Formulation modification can occur throughout the lifetime of a compound, ranging from changes instituted during early pre-approval stages to supplementary formulation development after the initial marketing of the compound. Controlled release (CR) formulations, as opposed to traditional immediate release (IR) formulations, are a tool for such a release optimisation of the compound over time. The determination of the in vivo impact of a modification of the route of administration or the drug formulation is typically addressed in a clinical trial using bioequivalence testing. But studying the compound release and distribution in vivo through clinical trials is both time consuming and costly.

When a set of CR formulations is under development, establishing an 'in vitro–in vivo correlation' (IVIVC) model has become an integral part of the drug development process; it links changes in the in vitro dissolution or release to modifications of the compound exposure and, if required, can predict key PK parameters, e.g., area under the curve (AUC) or the peak serum concentration (Cmax). If the release remains within pre-existing specifications, the exposure is assumed to remain as anticipated. For these reasons, in vitro drug dissolution or release can often be used as surrogate for the in vivo drug absorption once a, possibly nonlinear, relationship exists between the two. Under appropriate circumstances, in vivo bioequivalence trials may not be needed.

To this end, many methods of developing IVIVC models have been proposed over the past 50 years. Their most important pitfalls are: usage of unstable deconvolution methods, lack of propagating the estimation uncertainty between the different submodels, loss of information through averaged data and slow convergence (or even non-convergence) of the model due to the simultaneous estimation of a vast number of unknown variables.

In this project, a new convolution-based approach to IVIVC modelling was developed that extends the current methodology. The Bayesian statistical method was chosen since it allows for the natural integration of knowledge from one source of information into the other by combining data from several submodels in the IVIVC model. The approach is illustrated on a case study, the controlled release (i.e., permeation) of a compound by a transdermal patch (TD), but can easily be applied to other CR routes as well. The IVIVC model was established by combining the in vitro release of the patch and the in vivo intravenous infusion blood serum concentration-time profiles of the IR formulation to predict the in vivo TD blood serum concentration-time profiles.

By following this approach, preclinical in vitro and in vivo IR data is used not only to extract the parameter estimates, but also to understand the CR model structure. Once the CR

model is built in this way the before acquired knowledge about the parameters of two separate sources (in vitro and IR data) enters the model together as prior information to predict the exposure of the new formulation in human blood serum. This step-by-step procedure is a general approach that can come flexibly into operation for many different kinds of dissolution or release, IR and CR studies. The method is also feasible in a very imbalanced data situation (i.e. high difference in sample size of in vitro and in vivo data), since it uses the first stage data to gather knowledge but stays flexible in the second stage (rather than fixing the parameters to their estimation in the first stage). Consequently, convergence is assured and uncertainty is accounted for in a more intuitive manner, i.e., both in the in vitro and the in vivo part of the IVIVC model.

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