ESR Researcher Project: Non-technical Summary

"Detecting pharmacodynamic drug-drug interactions"

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The statistical techniques developed during the PhD project are motivated by a case study which was part of the pre-clinical safety evaluation of a novel compound meant to be co-administered with a compound already available on the market.

For the marketed compound, a historical study was available to assess its safety. An extensive dose range, from 0.04 to 10 mg/kg, was investigated. For each animal, body temperature, the biomarker of interest, was assessed up to 24 hours after single oral administration. No plasma concentration-time profiles were measured in this study due to the possible impact of blood sampling on body temperature. With the intent to develop the novel compound for co-administration, 11 new studies were designed to evaluate whether a PD interaction between both compounds occurs (the absence of a PK interaction had already been confirmed). A total of 20 animals were used in each study, with 5 animals randomized to each of four treatment groups. Group 1 received a single dose of the vehicle, group 2 and group 3 received a single dose of the marketed and novel compound respectively. Finally, group 4 received a combination of both compounds. Body temperature was assessed every hour after administration for 4 hours. In each study, a different combination of dose levels was assessed, to understand this synergistic behavior.

The model proposed to analyze this type of data is an indirect response model which assumes that a virtual concentration of the marketed compound inhibits the production of body heat. In order to mimic the administration route, a one-compartment model with oral absorption is used. It is assumed that the co-administration of the novel compound increases the potency of the marketed compound for body temperature by expressing IC_{50} (the potency of the marketed compound) in function of both treatments' doses.

The model is developed in a Bayesian framework as it allows borrowing the information from the historical study on the marketed compound. In particular, two different Bayesian techniques are considered: on one side, the 11 synergy studies can be pooled together using the information of the historical data to choose the prior distributions for all parameters; on the other side, the synergy studies can be sequentially integrated so that the posteriors from a study are used to determine the hyperparameters of the priors of the following study.

The latter method is particularly appealing, as it allows to analyze each study immediately instead of waiting for the end of data collection. However, when non-linear hierarchical

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models are performed, the risk of parameter identifiability issues is pretty high, so several precautions should be taken. In this project particular attention is devoted to:

- prior specification;
- the choice of random effects;
- the type of sequential integration method.

The sequential integration using the proposed K-PD model for synergy produced satisfactory results only when informative priors were specified and when the random effect was allocated to a parameter that was not highly correlated with others. Moreover, each study should be carefully designed: if each synergy study evaluates one dose combination only, the identifiability issues encountered since the first integration steps cause the bias observed in the estimates. This result was confirmed by simulation studies, which clearly show that such issues only arise when non-linear models are performed, whereas no discrepancies are found between the two pooling techniques when linear models are performed.

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