Commentary

Commentary on Dartois *et al.* – model building in population PK–PD analyses.

A 2002–2004 literature survey

Goonaseelan (Colin) Pillai & Jean-Louis Steimer

Modelling and Simulation, Novartis Pharma AG, Basel, Switzerland

In this edition of the journal, a group of academic scientists [1] present a timely ‘audit’ of model-building strategies reported in population pharmacokinetic (PK) and PK–pharmacodynamic (PD) literature over the years 2002–2004. The authors first developed an objective measurement instrument which they call a data abstraction form (DAF) using Health Authority (HA) guidelines and expert modeller’s opinion and then proceeded to classify and analyse 324 manuscripts identified using specific keywords from a MEDLINE search. A companion paper by the authors using the same methodology and database has covered the important topic of model qualification and has been published in another journal [2]. These two papers offer interesting insights into the status of population PK and PK–PD analyses at a time when HAs have recently published their interest in model-based drug development (e.g. The Critical Path to New Medical Products; <http://www.fda.gov/oc/initiatives/criticalpath/2005>), and almost all research-based pharmaceutical companies have demonstrated human resource commitment towards modelling groups. The publication of the DAF as an addendum to the manuscript provides a good checklist that authors of population PK and PK–PD manuscripts might find useful. In this Commentary we draw attention to some interesting features of these two papers taken from an industry modelling and simulation (M&S) perspective.

Dartois *et al.* [1] note that reported modelling analyses were largely conducted for descriptive purposes (e.g. as opposed to predictive modelling), predominantly in the fields of oncology, antimicrobials and anaesthesiology and using rich rather than sparse data. NONMEM was the most frequently used software and the reported PK and PD models were rarely of a complex nature. The authors end their paper by making some fairly conser-

vative recommendations with respect to good scientific practices when reporting modelling analyses, i.e. subject characteristics (healthy/patient), dosage (single/multiple) and route of administration, total number of subjects and total number of observations or number of observations per patient, criteria used for model selection, nature of the submodels, estimation method and software. They present this against the backdrop of a finding that only 39% and 8.5% of the PK and PD analyses, respectively, provided sufficient detail in the description of the model-building steps to allow an independent modeller to repeat the analysis.

Population PK modelling for identification of covariates continues to fulfil one of the roles that it was originally developed for; however, Table 3 in [1] shows that covariates being identified are primarily demographic and ‘liver/kidney function’, suggesting that the analyses are currently being conducted as targeted analyses of the influence of those covariates where there is a high index of suspicion rather than ‘fishing expeditions’. In our opinion, this is a good trend.

The authors note that in the majority of cases, the PD models used were ‘simple’ $E_{\max}$ models and also appear to be disappointed that in only a few cases was the design optimized for a modelling analysis using optimal design methodologies as published by authors such as Retout, Mentre and Duffull [3, 4]. This is despite easy-to-use software that can help prospectively design population PK and PK–PD studies, which was already available during the period of this survey.

The paper by Brendel *et al.* [2] provides the results of the evaluation of model qualification and concludes that only 28% and 26% of PK and PD models, respectively, were adequately evaluated. The authors correctly distinguish between the level of rigor associated with model

qualification for a descriptive model vs. that required for a predictive model. The industry needs in this regard are clearly for predictive models that can influence decision making and ultimately support label claims. Partners on clinical teams require reassurance of the predictive performance of models prior to use in decision making – thus this is an important area for modellers to pay attention to in order to build credibility with drug development teams.

Important features that these reviews did not address are the questions . . . *Why was the modelling done?* or . . . *What value or impact did the analysis bring?* . . . These are crucial questions in the application of complex mathematical/statistical methodology, such as nonlinear mixed-effects modelling, to the development of novel therapeutic agents. Indeed, the reviews highlight that most of the work was done for ‘descriptive’ purposes. There also appears to be a ‘reporting gap’, since the reported analyses covered Phase I (PK) studies or drugs in the postmarketing authorization phase. Presumably, these two areas of drug development are generally non-controversial or help with marketing the compound. It was also interesting to note that the data used in the models were often homogeneous, e.g. comprising analysis of single clinical trials, single treatment arms, single compounds and rich data rather than sparse. Apparently, the important areas of opportunity for making an impact with M&S on drug development, i.e. Phase II and Phase III, might still represent areas that pharmaceutical companies like to keep confidential. Journal Editorial Boards should perhaps consider accepting manuscripts from pharmaceutical companies containing anonymized data where appropriate, especially when the purpose of the paper is to demonstrate the benefits of M&S in drug development. Nevertheless, we are optimistic that this may change in the future, as emphasized in 2000 by Sheiner and Steimer [5], towards cooperative model-building efforts in drug development. Recent efforts in 2007 (Drug Information Association meeting on *Sharing Data and Models to Improve Clinical Drug Development and Regulatory Decisions*, 24–25 January 2007, Washington, DC, USA) saw speakers from the Food and Drug Administration (FDA) encourage drug companies to share their models cooperatively in a ‘pre-competitive environment’. Although there are nontrivial logistical hurdles that still need to be surmounted, this effort is likely to be successful if HAs such as the FDA continue with their efforts at advocacy. This should be linked with incentives for companies (as well as aca-

demia and modelling contract organizations) to share their models for the ultimate benefit of bringing new therapies to patients in clinical areas such as human immunodeficiency virus, Alzheimer’s disease, Parkinson’s disease, osteoporosis and multiple sclerosis, where considerable knowledge continues to be generated in isolated silos within each pharmaceutical company. These efforts should highlight the value of M&S and bring forth tangible examples of the benefits when data are combined across studies, compounds and indications and then used in a predictive manner to optimize future studies or new scenarios within drug development. This should help change an academic discipline with a nice-to-have piece of methodology to one where M&S is an essential component of drug development.

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Correspondence

Jean-Louis Steimer, Modelling and Simulation, Novartis Pharma AG, Basel, Switzerland. Tel: +41 6 1324 4056 E-mail: jean-louis.steimer@novartis.com