Poster Abstracts PAGE 2010

Bambang Adiwijaya Applications of Discrete-Event Dynamic Simulation in HCV Treatment Dynamics

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Backgrounds: The treatment objective in patients chronically infected with Hepatitis C Virus (HCV) is viral eradication, which allows patients to achieve a sustained viral response (SVR). Mathematical models of HCV dynamics in interferon and ribavirin treatment have been useful in predicting the percentage of patients achieving SVR [1]. In treatment combinations with direct-acting antiviral(s) such as telaprevir, the HCV must be considered as a mixed population, consisting predominantly of wild-type (WT) and a small population of variants with varying levels of susceptibility to telaprevir [2,3]. The HCV population response to telaprevir treatment in monotherapy has been quantified previously with a multi-variant viral dynamic model [4].

Objectives: To develop a HCV RNA dynamic model that predicts viral eradication in HCV treatment with combination regimens utilizing specifically-targeted antiviral therapies for hepatitis C (STAT-C).

Methods: HCV RNA and drug exposure vs. time data from a total of 1162 patients, participated in clinical trials evaluating regimens including Peg-IFN-alfa-2a, ribavirin and telaprevir, were used to improve a model previously published [4]. Eradication of each viral variant was modeled as discrete events occurring at variable times during treatment, and solved using Jacobian® software (RES group, Inc.).

Results: The improved model was qualified by comparing the *a priori* predictions and the observed data from two subsequent studies. The model-predicted SVR rates were compared to observed SVR rates across different patient populations with various durations of treatment and two dose-schedule regimens. The discrete-event simulations yielded reduced rates of integration failures commonly observed in other dynamic simulation software not specifically tailored to solve discrete-event system such as NONMEM® or Matlab®.

Conclusions: A model of viral eradication that requires an algorithm to accommodate discrete-events accurately predicts treatment-driven viral eradications in clinical study setting. The modeling and simulation approach was useful to support decisions in clinical trials.

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Jurgen Bulitta Mechanism-based Modelling of the Synergy of Colistin Combinations against Multidrug-Resistant Gram Negative Bacteria

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Objectives: Design of rational antibiotic combination regimens is critical to treat infections by multidrug-resistant (MDR) *A. baumannii* (Ab), *K. pneumoniae* (Kp) and *P. aeruginosa* (Pa). As synergy of antibiotic combinations has been modelled empirically, we developed new mechanism-based models that specifically account for potential causes of synergy and that describe the rate of bacterial killing and regrowth for colistin alone or in combination with other antibiotics.

Methods: Checkerboard synergy panel studies were used to identify potent synergistic combinations of antibiotics that were then evaluated in time-kill studies. Combinations were: Colistin (C) & rifampicin (R) against Ab and Pa; C & meropenem (M) against Kp. Time-kill studies at an initial inoculum of 10^6 CFU/mL (8 samples up to 48 h per profile) included 8 concentrations each of C, R or M alone and 9 concentrations for combinations of C&R and C&M. Mechanism-based models with up to 4 populations with different susceptibility were fit to the time-kill data in NONMEM VI. An additive error model was used for viable counts on log-scale and a Poisson error was included to fit low viable counts (incl. observations with zero colonies on the agar plate).

Results: The combinations displayed more rapid killing and less regrowth at 24 and 48 h compared to each antibiotic alone. The curve fits for all three pathogens were unbiased and reasonably precise ($r>0.93$). The mechanisms of synergy were modelled as: R was estimated to substantially enhance (Emax = 244; EC50 < 0.1 mg/L for R) the rate of killing by C against Ab. C (EC50 1.1 mg/L for C) enhanced killing by M towards the meropenem-resistant population against Kp. R & C mutually enhanced the extent of killing of the other antibiotic against Pa.

Conclusions: The proposed mechanism-based models described the observed viable counts well and accounted for the presence of multiple bacterial populations. Such mechanism-based models that can propose and evaluate various mechanisms of synergy hold promise for rationally optimizing combination regimens in humans.

Emmanuel Chigutsa Parallel first order and mixed order elimination of pyrazinamide in South African patients with tuberculosis

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Background: An earlier zero-order input model with first order elimination of pyrazinamide[1] poorly described absorption in a new cohort of South African patients with tuberculosis (TB).

Objectives: To improve the model to describe the population pharmacokinetics of pyrazinamide in a new TB treated cohort.

Methods: Seventy-nine patients were sampled 4-8 times during 2 steady state dosing intervals one month apart. All patients were receiving treatment with rifampicin, isoniazid, ethambutol and pyrazinamide with directly observed administration. LC-MS was used for plasma concentration determination. Pharmacokinetic analysis was performed using NONMEM VI. Visual predictive checks were used for model evaluation. The model was validated using an external dataset.

Results: A combination of first order and Michaelis-Menten elimination best described the clearance of pyrazinamide. A sequential, dual, first order process was used to describe drug absorption. A Ka of 0.02/h changing to 1.0/h at 0.71h post-dose was estimated. A time dependent residual error model was used to account for changes in the residual error with respect to time. Vmax for elimination was estimated to be 14.3mg/h/70kg, whilst the Km was 0.52mg/L. First order clearance was 2.64L/h/70kg and volume was 42L/70kg after using allometric functions of weight. Relative bioavailability was 26% higher in females compared to males. Between subject variability (BSV) for the combined elimination was 17% whilst within subject variability (WSV) was 16%. BSV for the change point in Ka was 45% whilst the WSV was 48%. WSV was 82% for Ka. BSV for bioavailability was 16%. As part of model validation, an estimation was performed using this model on another dataset. Similar parameter estimates were obtained, except for higher absorption rate constants, and females having just 3% higher bioavailability than males.

Conclusions: The population pharmacokinetics of pyrazinamide in this population were described by parallel first and mixed order elimination, and a dual absorption rate constant model. This is the first time that mixed order elimination has been noted for pyrazinamide which may become important in small patients given standard doses.

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Isabelle Delattre Population pharmacokinetic modeling and optimal sampling strategy for Bayesian estimation of amikacin in critically ill septic patients

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Objectives: In severe sepsis and septic shock, appropriate antibiotic therapy plays a key role in the patient management. Since the sepsis-induced pharmacokinetic (PK) modifications need to be considered in the drug dosages [1], the present study aimed to develop a population PK model for amikacin (AMK) in critically ill septic patients, and to subsequently propose an optimal sampling strategy suitable for Bayesian estimation of the drug, taking into account clinical constraints.

Methods: Serum concentration-time profiles were obtained from 88 critically ill septic patients, during the first 24 hours of antibiotic treatment (AMK combined with a broad-spectrum β-lactam). The population PK model for AMK was developed using NONMEM (FOCEI method). Fourteen potential covariates, including demographic data, pathophysiological characteristics and co-medication, were evaluated for influence on PK parameters. Using population estimates as prior information, optimal sampling times were selected based on ED-optimality. Optimization was performed in PopED v.2.10. [2,3] on the individual level, as previously reported [4]. Taking into account clinical constraints, a two-point sampling strategy was investigated. Predictive performance of Bayesian estimates obtained with the optimal sampling strategy was assessed.

Results: A two-compartment model with first-order elimination best fitted the AMK concentrations. Population PK estimates were 19.2 and 9.34 L for the central and peripheral volume of distribution, 4.31 and 2.21 L/h for the inter-compartmental and total body clearance. Creatinine clearance (CrCL), calculated using the Cockcroft-Gault equation, was retained in the final model. Optimal sampling times were 2 replicated sampling times at 6 hours when optimizing samples between 1-6 hours. Predictive performance of Bayesian estimates obtained with this sampling strategy was satisfactory (MPE < 6%, RMSE < 30%).

Conclusions: The present study has highlighted the significant influence of the CrCL on the PK disposition of AMK, during the first hours of treatment in critically ill septic patients. Based on developed population estimates of the drug, an optimal sampling strategy has been proposed for this patient population. As it was found suitable for the Bayesian estimation, its prospective use could be considered as successful.

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Oleg Demin Application of systems pharmacology modeling approach to optimize Interferon therapy of hepatitis C

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Motivation: The interferon-based therapy is a common method of hepatitis C treatment. However, interferon-based therapy is lengthy (48 weeks), expensive and results in significant toxic side effects. Moreover, interferon-based therapy results in a positive outcome only in about 50% of patients. In accordance with individual susceptibility to interferon-based therapy, all patients can be subdivided into two main groups: (i) responders and (ii) non-responders. If 48 week course of interferon therapy results in complete recovery of a patient from hepatitis C this patient can be referred as responder. On the contrary, patients who failed to be cure of the disease during the 48 week course can be considered as non-responders. The main challenge of interferon therapy of hepatitis C is to predict before, or at the beginning of the interferon course, whether the patient is responder or non-responder.
One of the possible tools which can allow us to address the challenge is a systems pharmacology model of HCV dynamics and interferon-based therapy. This model could give an opportunity (i) to predict final therapy outcome for individual patients on the basis of his/her individual data profile, obtained at the initial stage of treatment; (ii) to design individual therapy regimen for each patient (or group of patients) in compliance with individual data of the patient such as interferon PK/PD characteristics. The monitoring of the main features (such as virus load, serum IFN concentration, biomarkers production etc.) during first weeks of therapy can provide us with individual sets of kinetic parameters for each patient. These sets of parameters could be used for prediction of therapy outcome for each patient and/or for development of individual therapy protocol (dosage and regimen), that is more suitable for each patient.

Objectives:

- to reconstruct molecular mechanisms of IFN action and HCV reproduction
- to develop system pharmacology model of hepatitis C dynamics for simulation of long-term interferon-based therapy
- to identify the set of kinetic parameters, that necessary for personalized prediction of therapy outcome (responder *vs* non-responder) with above mentioned system pharmacology model.
- to optimize dosing regime of classical and modified INFs for different groups of patients (e.g. responders/non-responders)

Methods: To address the problem a systems pharmacology modeling approach has been applied. This approach enables us to collect and integrate all known *in vitro*, *in vivo* and clinical data, to analyze possible regulatory mechanism involved in the response to the drug administration at intracellular, cellular and organism levels and to test various hypotheses to explain the phenomena observed.

Results: A mathematical model, combining (i) virus dynamics (Neumann model), (ii) interferon PK taking into account various dosage regimes, (iii) response to long-term therapy, has been developed. Parameters of the model have been identified on the basis of the published clinical data on dynamics of IFN and HCV RNA in serum during the first week of treatment measured for each patient individually. The outcome of full-scale (48 weeks) therapy for the individual patient has been predicted. It has been shown, that the model predicts outcome of full-scale (48 weeks) interferon-based therapy for 88% of the patients involved in the clinical trials. Thus, the model can be used as a tool for choice of personalized interferon therapy of hepatitis C patients.
The model enables us to predict following ways to increase efficacy of interferon therapy for potential non-responders: (i) to modify preparation of peg-interferon in such a way to reduce absorption from subcutaneous site of injection; (ii) to identify optimal (personalized) interferon administration regimen (reducing of single dose with corresponding increasing of injection frequency)

Thomas Dorlo Optimal Dosing of Miltefosine in Children and Adults with Leishmaniasis

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Introduction & Objectives: Pharmacokinetics and –dynamics (PK/PD) of miltefosine in children suffering from visceral leishmaniasis (VL), a fatal neglected parasitic disease, remain ill-characterized. In a large phase 4 trial in India, the number of treatment failures was significantly higher in the pediatric population than in adults (≥12 years) while given a similar dosage of 2.5 mg/kg [1]. Based on this and the previous finding that the mean steady-state concentration in children in the last week of treatment was 24 μg/mL, while in adults 70 μg/mL has been reached [2], our hypothesis was that the current linear mg/kg dosage is too low for children and that a dose based on allometric scaling might result in a similar exposure to miltefosine between children and adults.

Methods: A population PK analysis was performed, based on pooled PK data from three separate studies, including Indian children (n=39), Indian adults (n=40) and European adults (n=31) with median body weights of 15, 35.5 and 85 kg, respectively. Linear and allometric scaling of CL and V by either total body weight (BW) or fat-free mass (FFM) were evaluated as body size models and compared.
Based on the developed PK model, a dosing-formula for miltefosine in children was proposed. Exposure to miltefosine (time and AUC above various thresholds) and the probability of target attainment (targets were set at exposure values that were achieved by 90% of the adults) after the currently used 2.5 mg/kg dose and the proposed new dosing algorithm were compared between Indian adults and children by Monte Carlo-simulations (n = 1000). All calculations and simulations were performed with software packages NONMEM, R and Pirana.

Results: The population PK model with allometric power scaling fitted best to the pooled miltefosine data. Moreover, allometric scaling by FFM reduced unexplained between-subject variability (BSV): linear scaling by WT or FFM, and allometric scaling by WT or FFM resulted, respectively, in a BSV of 50%, 43%, 35% and 32% for CL, and 43%, 37%, 38% and 34% for V. Based on this allometric model, we proposed a miltefosine dose, scaled with a power 0.75 from a standard adult (60 kg) receiving 150 mg (Dose = 150*(Weight/60)**0.75). Simulated exposure to miltefosine was similar between adults receiving 2.5 mg/kg and children receiving the new allometric dose (e.g. median Time>10 μg/mL was 34.4 and 34.7 days, respectively). More importantly, only 74-78% of the children receiving the currently used linear dose of 2.5 mg/kg achieved a similar minimal systemic exposure as 90% of adults receiving 2.5 mg/kg or children receiving the allometric dose.

Conclusion: The currently applied dose of 2.5 mg/kg results in a significantly lower exposure to miltefosine in children than in adults. We recommend the use of an allometric dose formula for

miltefosine in children with leishmaniasis, which results in a similar exposure to miltefosine between adults and children and probably improves clinical outcome in children. An easy-to-use table will be presented for implementation of this dose in the clinic. More data are urgently needed on both PK and PD of miltefosine in VL, certainly in children, to further improve the treatment of this fatal neglected disease.

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Monika Frank Population Pharmacokinetic Model Building for Mothers and Newborns using Additional Information from a Different Nevirapine Dataset

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Objectives: Risk of HIV transmission from mother to newborn could be reduced by prophylaxis of nevirapine (PMTCT). 62 HIV-1 mothers and newborns received nevirapine-based (NVP) PMTCT. Due to sparse data population pharmacokinetic (PK) analysis was performed to describe NVP PK in mothers and newborns. Data of NVP in healthy men from a clinical study were used to supplement the sparse data.

Methods: Medication was a single oral dose of 200 mg NVP tablet for pregnant women and healthy males and 2 mg/kg NVP syrup for newborns. For PK analysis 113 mother and newborn plasma and 95 breast milk samples were available. Investigation of PK in 26 men resulted in 15 plasma samples per subject. Firstly a combined population PK model for mothers/newborns was developed using NLME approach implemented in NONMEM^{TM} VI (ADVAN6, TOL5, FOCE INTERACTION). Appropriateness of model fit and performance was guided by various diagnostic tools.

Results: First results demonstrated appropriateness of 1-compartment (CMT) models for separate analysis of maternal and newborn data, respectively [1]. These experiences were used to build a combined model for both groups. Due to sparse data in a first step, absorption rate constant (KA) was fixed to prior reported value[2]. NVP input through plasma/placental transfer before delivery was modelled with a rate constant to link mother and newborn data. For the change of situation before/after delivery time-dependency was introduced. First results assume sufficient model performance. A transit absorption model adequately described the highly variable absorption in healthy males. For disposition PK a 1-CMT model was adequate and provided PK parameters in the same range as for the adult female population (clearance 1.5 L/h (IIV: 21% CV), KA 3.3 h^{-1} (IIV: 155% CV) and V 99 L (IIV: 16% CV), MTT 1 h). In a subsequent step, knowledge from population PK analysis of healthy men will be implemented in the combined PK model especially for the absorption process.

Conclusions: A first combined PK model for maternal and newborn data was developed. Due to sparse data situation additional rich data of healthy men will be used to describe the complex absorption process of NVP more adequately. Final PK model could guide dosing regime for newborns to assist prevention strategies for HIV transmission from mother-to-child.

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Jeremie Guedj Design Evaluation and Optimization for models of Hepatitis C viral dynamics

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Objectives: The Neumann's model of viral dynamics is the standard explanation for the biphasic decline of Hepatitis C virus (HCV) during frequent administration of Interferon (IFN) and has brought important insights for understanding HCV pathogenesis [1]. This model can be extended to account for pharmacokinetics variation, when drug is administered on a weekly basis [2]. Since this model is based on a complex system of non-linear Ordinary Differential Equations (ODE), the parameter estimation is challenging and requires a rich data set if individual estimation is performed. By borrowing strength from the between-patients variability, nonlinear mixed effect models (NLMEM) allow sparser design within each patient to analyze the observations of the whole sample. Yet, the accuracy of the viral parameters that can be expected using NLMEM has not been investigated so far.

Methods: : In the context of non-linear dynamics without a closed-form solution, the computation of the exact FIM in NLMEM involves heavy computation [3]. Here we use an approximation of the FIM based on the first-order linearization around the mode of the random effects that allows to avoid most of the computation burden [4,5].
We show that this approximation, implemented in the software PFIM, provides a good estimation of the FIM. We compare the ability of different popular designs in HCV clinical trials to estimate the parameters of viral dynamics. Furthermore, we propose different optimal designs according to the maximal number of sampling measurements that is allowed for each patient. We show how an appropriate choice for the sampling measurements can dramatically improve the identifiability of the most critical viral parameters for the prediction of the treatment outcome.

Conclusions: The results can be used for both clinical and methodological purposes.

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Seong Bok Jang Population Pharmacokinetics of Amikacin in Korean Clinical Population

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Objectives: This study aimed to develop a pharmacokinetic model of amikacin and to assess the influence of demographic and clinical covariates in Korean patients.

Methods: Amikacin pharmacokinetics was studied in 308 Korean adult patients who received 125-1000mg once- or twice-daily dosing of amikacin. Peak and trough plasma samples at steady state were drawn in every patient, with the peak sample drawn 30-60 minutes after the completion of 30 minute infusion of amikacin and the trough sample drawn within 60 minutes before the next infusion. The 308 patients were randomly allocated into an index dataset (n=200) and a validation dataset (n=108).Covariate selection was made using a step-wise approach within NONMEM 7, using forward addition and backward deletion followed by model refinement [1]. The predictive performance of the developed model was evaluated by the percent prediction error defined as the typical predicted concentration minus the measured concentration divided by the typical predicted concentration [2].

Results: Amikacin population pharmacokinetics was best described by a one-compartment model with a proportional inter-individual error model and a combined intra-individual error model, and the FOCE interaction method was used. For covariate selection, the effects of creatine clearance and ward (intensive care unit versus general ward) were found significant for clearance, and the effects of body weight and cholecystitis were found significant for volume of distribution, with creatine clearance most significant ($p<<0.0001$), and body weight next ($p<0.0001$) although somewhat different from the finding in the literature[3]. The estimates of pharmacokinetic parameters for a typical individual were 2.5 L/hr for clearance, and 15.4 L for volume of distribution. Interindividual variabilities (CV%) were 32% and 9% for clearance and volume of distribution, respectively. The mean (sd) of percent prediction errors was 0.56(26.9)% at peak concentrations and -108(473)% at trough concentrations, which were not significantly different from zero ($p=0.527$ and 0.095, respectively).

Conclusions: Our results show that the developed population pharmacokinetic model may be used as a basis to find an optimal amikacin dose in Korean patient population without a significant bias. Further studies will be needed to validate the proposed results.

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Siv Jonsson Population Pharmacokinetics of Ethambutol in South African Tuberculosis Patients

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Objectives: Ethambutol (EMB) is one of four drugs in the first-line antitubercular regimen and is used to protect against rifampicin resistance in the event of a pre-existing resistance to isoniazid [1]. The aim was to describe the population pharmacokinetics (PK) of EMB in South African tuberculosis patients.

Methods: Data were obtained from patients with pulmonary tuberculosis treated with EMB (oral doses 800-1500 mg qd) combined with standard anti-tubercular medication from 2 centres employing different dosing and sampling schedules. Blood samples were collected following multiple dosing and plasma concentrations of EMB were determined using a validated HPLC-tandem MS method. A population PK model was developed in NONMEM VI (FOCE INTER) [2] with a covariate model established using the *scm* procedure in PsN 3.0.0 [3, 4]. The model was qualified using visual predictive checks and non-parametric bootstrapping.

Results: PK observations were obtained from 189 patients (54% male, 46% female) weighing 47 kg on average (range 29-86) and with a mean age of 36 years (range 16-72). Twelve percent were HIV positive. The estimated creatinine clearance (CLCR) was 79 mL/min (range 23-150). A two-compartment model with two transit compartments prior to first-order absorption and elimination described the data. Allometric body weight scaling was introduced on all clearance and volume terms and oral clearance (CL/F), central and peripheral volume of distribution in a patient weighing 50 kg were 40.9 L/h, 139 L and 1110 L, respectively. Presence of HIV decreased bioavailability by 16%. Inter-occasion variability exceeded inter-individual variability for oral clearance (45 *vs* 20 %CV).

Conclusions: The estimated typical CL/F concur with Lee [5], but is roughly half of CL/F reported by Peloquin [6] and Zhu [7]. The latter can partially be due to differences in body weight between studies. The decrease in bioavailability is consistent with earlier findings [7, 8]. CLCR and body weight were positively correlated and most patients (86%) had CLCR ³ 60 mL/min, possibly explaining why renal function was not identified as a covariate although EMB is mainly excreted unchanged in urine.

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Dalia Khachman Population pharmacokinetic analysis of ciprofloxacin in intensive care unit adult patients

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Objectives: To propose optimal dosage regimens for Intensive Care Unit (ICU) patients in order to achieve relevant PK/PD targets. It is the largest ciprofloxacin population PK analysis performed to date in this population of patients.

Methods: Serum ciprofloxacin concentrations of 119 ICU patients were determined at various times after i.v. infusion at standard doses and on several occasions using a validated HPLC method. Two-thirds of the patients were used for model building (N=79, 453 concentrations) and one-third for model evaluation (N=40, 242 concentrations). Population PK analysis was carried out with NONMEM 6 (FOCE-I). In contrast to previous studies [1,2], interoccasion variability was assessed. Evaluation of the model was performed using visual predictive checks and normalised prediction distribution errors [3]. AUC_{24h}/MIC and C_{max}/MIC ratios were calculated for each patient to assess whether the respective targets of 100 h and 8 were reached for the dosage regimens given in the study (mainly 400 mg b.i.d.). PK/PD simulations were further carried out to assess other dosage regimens of ciprofloxacin with respect to the AUC_{24h}/MIC target.

Results: A 2-compartment model was found to best fit concentration data. Creatinine clearance using Cockcroft and Gault formula and total protein concentration in blood were identified as relevant covariates on ciprofloxacin clearance and explained a large part of interindividual variability. Only moderate interoccasion variability on clearance could be estimated (26%). Finally, PK/PD assessment showed that the dosage regimen of 400 mg b.i.d. used in 83% of patients did not allow to reach the PK/PD target for *P. aeruginosa* nor *Enterobacteriaceae*. The percentage of patients reaching the target was much higher with other tested dosage regimens (400 mg t.i.d., 600 mg b.i.d or 1200 mg o.d.) with small differences between them.

Conclusions: The present analysis confirms previous findings i.e. a large interindividual variability on ciprofloxacin clearance which is partly explained by creatinine clearance [1,2]. More importantly, PK/PD assessment support the use of ciprofloxacin dosages higher than the one currently used in the majority of our ICU patients. More complex PK/PD simulations are on the way to account for the whole distribution of MIC and other PK/PD targets.

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Holly Kimko Modeling & Simulation Exercise to Recommend Dosage Regimens for Patients with End-Stage Renal Disease Receiving Hemodialysis

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Objectives: End-stage-renal-disease (ESRD) is a condition when kidney does not adequately excrete wastes via urine to regulate hormones and chemicals in the body, which requires hemodialysis. Due to kidney failure, drug exposure in the body is higher than that of subjects with normal renal function; hence dose adjustment is necessary in ESRD patients. Ceftobiprole [1] is a first broad-spectrum cephalosporin to treat bacterial infections including those caused by methicillin-resistant *Staphylococcus aureus.* This modeling and simulation exercise was performed in order to recommend ceftobiprole dosage regimens for ESRD patients who require hemodialysis thrice a week.

Methods: A final population PK model [2], developed from Phase 1/2/3 subjects, was used to evaluate the PK profiles of a separate ESRD subject study. After model qualification, PK profiles (median and 90 % interval) of various dosage regimens were simulated by superpositioning to account for drug extraction (60% extraction ratio) by hemodialysis. Corresponding % Time-above-MIC as a PK/PD target were calculated. A logistic regression of nausea events with respect to Cmax was conducted.

Results: The PK model predicted the observed ESRD study PK results well. Three dosage regimens were identified as viable options, considering %T>MIC, probability of causing nausea and patient-convenience. To be conservative, the lower band of 90% prediction interval of PK profiles should yield higher than 50 %T>MIC. The incidences of observed and model-predicted nausea events increased around ceftobiprole concentration of 40 ug/ml. None of the simulated dosage regimen yielded a highest median concentration above 40 ug/ml.

Conclusions: Based on modeling and simulation three dosage regimens may be suitable for patients with ESRD: (1) 250 mg, 1-hr infusion, Q24h, (2) 500mg, 1-hr infusion, Q48h with an additional 250 mg 1-hr infusion on the 7^{th} day, and (3) 500mg, 1-hr infusion, Q48h, twice, followed by 750 mg, 1-hr infusion on the 5^{th} day. Each regimen will achieve > 50% T>MIC over the dosing intervals. Maximum predicted ceftobiprole concentrations do not exceed those that have been observed previously.

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Maria Kjellsson Penetration of Isoniazid, Rifampicin, Pyrazinamide and Moxifloxacin into Pulmonary TB Lesions in Rabbits

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Background: About one third of the world's population has latent tuberculosis (TB), whereof about nine million cases of active tuberculosis emerge annually and a majority of the cases being pulmonary TB (PTB) [1]. An essential factor in halting the global increase in tuberculosis is effective treatment, with a combination of antimicrobial drugs against *Mycobacterium Tuberculosis*. Factors influencin response to treatment include the degree of drug penetration into the target tissue. Bacterial resistance development has been hypothesized to be dependent on drug penetration into TB lesions. With so many aspects of the TB treatment success being dependent on drug penetration into the site of action, it is surprising how little is known of the pharmacokinetics (PK) of anti-TB drugs inside PTB lesions. Patients with TB are known to have lung lesions that display diversity in size, location, structure and cellular/acellular content and physiochemical environment, with an associated difference in drug penetration.

Objective: In this study the PK and penetration of four anti-TB drugs into PTB lesions in rabbits was investigated. Covariates like lesion type and size was also explored.

Methods and data: Rabbits infected with TB were given isoniazid (INH), moxifloxacin (MXF), pyrazinamide (PZA) and rifampicin (RIF). Drugs were given in different regiments (multiple and single dosing) and at different time points, (from 0.5 h to 16 h) before sacrifice. Measurement were made of drug concentrations in healthy lung and PTB lesion tissue and also serial sampling of plasma was performed before time of sacrifice. PK into lesions and healthy lung was described using effect compartment models where the drug was assumed to partition to lesions and lung tissue from the central plasma compartment with an estimated delay. For the parameters related to penetration into the PTB lesions the impact of lesion size and type was investigated.

Results and conclusions: INH's and PZA's plasma PK in rabbits were best described using a 2-compartment model while MXF's and RIF's plasma PK were best described using a 1-compartment model. MXF showed the highest penetration into lesions of the four drugs.

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Jebabli Nadia Population Pharmacokinetics Of Vancomycin In Tunisian Patients

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Objectives: Vancomycin (VCM) is a glycopeptide antibiotic generally used for the treatment of gram-positive infections. For individualized optimal VCM dosage we develop a pharmacokinetic model for VCM in a population of Tunisian patients.

Methods: The population pharmacokinetics of VCM was investigated in 202 patients aged eight month to 64 years (40±20 years), following sepsis. Dose of VCM was varied between 0.04 to 6 g per day with median equal to 1.5 g and was administered by intravenous infusion. Patients benefited from two plasma samples: T0 immediately before VCM infusion and Tmax: 60 minute following completion of VCM infusion. The serum concentrations of VCM were measured by a fluorescence polarization (Axym® *Abbott*). The population data set comprised 473 concentration measurements and was analysed using NONMEM®. A one-compartment PK model with zero order input was used. The following clinical factors were tested for their influence on clearance (CL) and volume of distribution (V): sex; age, weight and creatinine clearance. Model comparisons were based on the change in objective function value (OFV).

Results: The values of PK parameters (inter-individual variability %) obtained from the base model are: CL=4.09 (59.3%) L/hr and V=55.10 (320%) L. Covariate selection revealed that total body weight (TBW) affected V, and creatinine clearance influenced VCM clearance. A good correlation was obtained between Bayesian estimated and experimental concentrations (r^2=0.84).

Conclusions: The models could be used to estimate appropriate VCM dosage guidelines, which are not clearly defined for this high-risk population. Their simple structure should allow easy implementation in clinical software and application to dosage individualizes using Bayesian approach.

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Michael Neely High-dose amoxicillin pharmacokinetics (PK) and pharmacodynamics (PD) in children

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Objectives: We are unaware of any published PK data addressing oral amoxicillin (amox) dosages >25 mg/kg in children. Since amox absorption is saturable, we wished to estimate the percentages of the dosing interval that the plasma amox concentration would exceed newly updated pneumococcal breakpoint MICs (T>MIC), and the percent of children with the target T>MIC of ≥50%, after the commonly used dose of 45 mg/kg.

Methods: We used a published adult four-compartment model with delayed, saturable, time-limited amox absorption into a central compartment with linear elimination and transfer to/from a peripheral compartment.[1,2] Parameters were log-transformed and allometrically scaled. Individual time-concentration data from the original study (6 adults, each given 500 and 3000 mg separated by ≥1 week) were used to fit the model using non-parametric methods implemented in MM-USCPACK, with standard visual/numerical checks. Upon comparison of simulated profiles with published Cmax and AUC ranges for doses ≤25 mg/kg in children,[3] age multipliers were added to the allometric volume and elimination terms until the pediatric profiles could be accurately simulated. Single-dose T>MIC were simulated in 1000 representative 15 month, 12 kg children.

Results: For 500 mg in an adult, the Cmax mean (SD) of 1000 simulations was 8.4 (2.6) mg/L vs. 8.8 (1.8) in the study (P=0.71). Simulated AUC0-12 was 24.4 (6.1) mg*h/L vs. 25.0 (3.0) observed (P=0.24). For 3000 mg, Cmax was 29.5 (11.0) vs. 26.8 (3.9) (P=0.55) and AUC was 96.2 (28.8) vs. 91 (17) (P=0.44). For a child given 15 mg/kg, simulated Cmax was 6.6 (1.8) vs. observed 6.9 (3) (P=0.40) and AUC was 25.7 (6.5) vs. 24.9 (9.6) (P=0.53). For 25 mg/kg, Cmax was 10.7 (3.0) vs. 10.6 (5.1) (P=0.87). AUC was 42.6 (10.8) vs. 44.1 (24.6) (P=0.50). The geometric mean (interquartile range) amox dose at which absorption was 50% of maximum was 785 (337 - 2304) mg. Two further simulations are shown below.

	45 mg/kg t=12 h		30 mg/kg t=8h	
Cmax	18.7 (5.1)		12.8 (3.5)	
AUC0-t	75.7 (18.9)		51.0 (12.8)	
MIC	T>MIC	T>MIC ≥50%	T>MIC	T>MIC ≥50%
2 (Susceptible)	63 (12) %	91%	79 (14) %	99%
4 (Intermediate)	48 (11) %	41%	58 (15) %	75%
8 (Resistant)	32 (10) %	3%	33 (15) %	10%

Conclusion: This simulation suggests that amox plasma exposure after doses of 45 mg/kg (up to 540 mg) is proportional to lower doses, but requires confirmation. Even with the higher concentrations, treatment of intermediately susceptible pneumococcus should be with 90 mg/kg divided into 3, not 2, daily doses.

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Thu Thuy Nguyen Population pharmacokinetic of linezolid in inpatients

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Objectives: Linezolid is the first antibiotic of a new class of antimicrobial agents, the oxazolidinones, to be approved for clinical use in United States in 2000 and in Europe in 2002. It is active against gram-positive bacteria. We performed a prospective trial to study the impact of linezolid on human commensal flora in inpatients. A pharmacokinetic (PK) substudy was performed. The objective of the present work is to characterize linezolid PK in inpatients using a population approach.

Methods: 28 inpatients treated by linezolid for the first time were enrolled in the trial. Linezolid was administrated orally (17 patients) or intravenously (8 patients) with an identical dose of 600 mg twice a day. Two patients were switched from intravenous (IV) to oral administration before day 7 (D7) and 1 patients after D7. At D7, blood samples were collected before dosing, 1.5, 4 and 8 hr after dosing. Linezolid concentrations were assayed by high performance liquid chromatographic method. The relay IV/oral before D7 was taken into account in the PK modelling. We described the population PK of linezolid by a model combining the two administration modes, using MLXTRAN in MONOLIX 3.1 [1]. We first performed an analysis without covariate. We fixed the absorption rate constant (ka) to 2.7 [2] and tested if the biodisponibility (F) is equal to 1 using likelihood ratio test. The SAEM algorithm [3] in MONOLIX was used to estimate population parameters. We then also performed an analysis with covariates (height, weight, age and sex) using forward selection.

Results: A one compartment model with first order linear elimination and with first order absorption for oral administration adequately described concentrations for all patients. F was not significantly different from 1 [4], and was consequently fixed to 1 in the chosen model. We found significant effects of weight ($p=0.0013$) and age ($p=0.0026$) on clearance (CL). When weight increased of 10kg from the mean weight, CL increased of 18.6%. When age increased of 10 years from the mean age, CL decreased of 11.1%. With inclusion of these covariate effects, the inter subject variability in CL decreased from 61.1% to 44.5%.

Conclusions: We described the population PK of linezolid by a model combining oral and IV administrations using MLXTRAN in MONOLIX 3.1. The 100% bioavailability of linezolid was confirmed in this study. We also pointed out the effect of inpatient weight and age on linezolid clearance.

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Elisabet Nielsen Pharmacokinetic-Pharmacodynamic Modelling for Antibiotics: Static and Dynamic In Vitro Time-Kill Curve Experiments

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Objectives: In vitro time-kill studies are commonly conducted with the aim to assess efficacy of antimicrobial agents. Previously a general semi-mechanistic PK-PD model describing the time course of antimicrobial effects has been developed based on data from in vitro time-kill curve experiments with static antibiotic concentrations (1). The aim of the present study was to investigate the ability of the developed PK-PD model to describe and predict data from time-kill curve experiments with dynamic concentrations.

Methods: In vitro time-kill curves were performed in which cultures of *Streptococcus Pyogenes* were exposed to five different antibiotics; benzylpenicillin, cefuroxime, erythromycin, moxifloxacin, and vancomycin. In the experiments with dynamic concentrations an in vitro kinetic model (2) was used to simulate a half-life of the drug. In total 187 experiments with a range of concentrations for each drug were included in the analysis (static n=135, dynamic n=52). The previously developed PK-PD model based on static time-kill curve experiments was applied to the dynamic experiments. Observations from the dynamic time-kill experiments were compared to model predictions based on parameter estimation using a) only static data, b) only dynamic data and c) combined static and dynamic data.

Results: Differences in experimental settings between static and dynamic time-kill curve experiments did not have a significant effect on the growth kinetics of the bacteria. The dynamic experiments were well predicted using the earlier developed structural model with parameter re-estimation. For the majority of the antibiotics, the dynamic experiments were also adequately predicted using parameter estimates based on only the static experiments. However, adding data from dynamic experiments in the estimation, did improve the model fit for cefuroxime and vancomycin, indicating some differences in sensitivity to experimental design for these antibiotics.

Conclusions: The previously developed PK-PD model could well characterize the data from dynamic time-kill curve experiments. Further, for most antibiotics, the parameter estimates based on data from static time-kill curve experiments provided a good prediction of data from dynamic experiments implying a limited need to perform labour intensive dynamic experiments.

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Rada Savic Ciprofloxacin Integrated Plasma, Saliva and Sweat Population Pharmacokinetics and Emergence of Resistance in Human Commensal Bacteria

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Objectives: Emergence of resistance to fluoroquinolones is an increasing therapeutic problem (1). One of the routes for resistance development is from selection in commensal bacteria. The ciprofloxacin pharmacodynamic AUC/MIC ratio linked to efficacious outcome in bacterial infection is well established; however its impact on the emergence of resistance in commensal bacteria is unknown. Our aim is to determine the PKPD link associated with the emergence of resistance in healthy volunteers receiving different dosages of ciprofloxacin for 14 days.

Methods: A prospective study was conducted in 48 subjects randomly assigned to six different therapeutic dosages of oral ciprofloxacin . Blood, sweat and saliva samples were collected at days 1, 7 and 14. Population PK analysis was performed using non-linear mixed effects. Drug exposure ratios in saliva:plasma and sweat:plasma samples were estimated. Model-based individual drug exposures in saliva/plasma in combination with ciprofloxacin MIC and/or mutant prevention concentration against viridians group streptococci in the pharyngeal flora and Escherichia coli in the fecal flora were used to assess potential relationship with emergence of resistance patterns using logistic regression analysis.

Results: Ciprofloxacin PK was best described by a two compartment model linked to the transit compartment absorption model. Data from all fluids were fitted simultaneously. Apparent clearance (CL) and volume of distribution (Vd) were 38.5 L/hr and 165 L (2). The saliva:plasma concentration ratio was determined to vary over time with a baseline of 0.33 exponentially decreasing to an asymptote of 0.07. The sweat:plasma concentration ratio was stable over time, indicating no accumulation of drug in sweat. Resistance emerged in the fecal (25%) and pharyngeal flora (33%) and it largely coincided with local concentrations less than the MIC. However, no variable that integrated PK data and PD parameters was found to differ significantly between the subjects in whom resistance emerged and those in whom it did not. Furthermore, probabilities of the emergence of resistance were not significantly different across the different antibiotic dosages (3).

Conclusions: Ciprofloxacin population PK in plasma, saliva and sweat was simultaneously described for the first time. Selection of resistant commensal bacteria during ciprofloxacin therapy is a frequent ecological side-effect that is not preventable simply by dosage optimization.

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Wynand Smythe A Semi-Mechanistic pharmacokinetic enzyme model for the characterisation of rifampicin pharmacokinetics in South African pulmonary tuberculosis infected adults

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Objectives: Rifampicin, together with other first line regimen drugs, is used to treat drug sensitive Mycobacterium Tuberculosis. Rifampicin is known to have highly variable absorption (1, 2) and to induce its own metabolism (3). These characteristics result in low rifampicin concentrations in many patients, and may increase the likelihood of treatment failure and emergent drug resistance. The primary objective of this pharmacokinetic analysis was to determine the population pharmacokinetics of rifampicin at pre-induced and fully auto-induced states amongst African patients with pulmonary tuberculosis using mixed-effects modelling.

Methods: Adults (n=173) with pulmonary tuberculosis received once daily doses of either 450 mg (below 50 kg) or 600 mg (above 50 kg) of rifampicin together with isoniazid, pyrazinamide and ethambutol for 6 days of the week. Three blood samples per patient were taken after the first dose (pre-induction) and repeated after approximately 28 days (steady state) yielding a total of 998 samples for analysis of rifampicin concentrations in plasma. A semi-mechanistic pharmacokinetic model incorporating an enzyme turn over model to address rifampicin's auto-inductive properties, together with a multiple dosing transit absorption compartment model to describe the drug's highly variable absorption was developed using the first order conditional method in NONMEM.

Results: Rifampicin displayed potent auto-induction with an estimated EC50 of 0.133 mg/L which is less than most plasma concentrations following a standard rifampicin dose. The model estimated un-induced oral clearance at 5.97 L.h-1. The enzyme turn-over half-life was fixed to approximately 24 hours (kENZ fixed to 0.029 h-1) reaching steady state in approximately 1 week (5) since samples were collected only at pre- and post-induced occasions. Based on the VPC stratified by occasion, the model adequately predicted rifampicin pharmacokinetics both at the pre-induced and induced state.

Conclusions: The semi-mechanistic model describing the pharmacokinetics of rifampicin at pre-induced and induced states will be extended to investigate potential drug-drug interactions seen between RIF and the other drug components of the anti-tuberculosis regimens.

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Ami Fazlin Syed Mohamed Predictions of Dosing Schedules of Gentamicin in Neonates Based on a Pharmacokinetic/Pharmacodynamic Model Considering Adaptive Resistance

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Objectives: Adaptive resistance, a pharmacodynamic process of aminoglycosides, is a reversible refractoriness to the bactericidal action. It is developing during the first dosing interval, is enhanced by higher doses, and augmented by consecutive doses if administered before the bacteria return to their susceptibility stage [1, 2]. A previous PKPD model of bacteria kill of gentamicin in vitro [3] consisted of a compartment of resistant bacteria added to a semi-mechanistic model developed for other antibiotics [4] but there was a lack of fit to some of the experimental dosing schedules. The aim of this work was to explore a different PKPD model and to conduct predictions that can be used to suggest optimized dosing schedules in neonates based on the time-course of bacteria kill and adaptive resistance, as well as previous information on risk for toxicity.

Methods: In vitro time kill curve experiments were conducted for 24-48 hours on a strain of *Escherichia coli*. Gentamicin exposure was either at constant concentration ranging between 0.125-16 times the MIC or in a dynamic kinetic system with different dosing regimens; 1-8 times the MIC every 12 or 24 hours with simulated two-compartment kinetics. Bacterial counts were monitored with frequent sampling throughout the experiments. All data were fit simultaneously in NONMEM. The adaptive resistance was modeled as a binding function where the degree of binding resulted in a reduction of Emax of the bacteria kill. Predictions were conducted for neonates of different weights and ages by allowing the concentrations predicted by a previously developed 3-compartment PK model to drive the bacteria kill [5].

Results: The model could describe the data that showed that gentamicin has a fast bactericidal effect with clear indication of adaptive resistance. Full development of adaptive resistance was predicted to occur after approximately 2 days of exposure and therefore 24 hour dosing intervals was predicted to be more efficacious in bacterial killing than those with a 36 or 48 hour time interval. The predictions also suggested that because the concentrations were around the estimated Ec50 of 10 mg/L, the benefit to increase the dose from the standard 4 mg/kg to 5 mg/kg was limited.

Conclusion: The semi-mechanistic model with the binding process was superior to the previously described model with a compartment of resistant bacteria. For the sizes and ages of neonates investigated, the PKPD model predicted a 4mg/kg dose of gentamicin witha 24-hour dose interval to be more efficacious compared to a higher dose with a 36 or 48 hour dosing interval.

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Joel Tarning Population pharmacokinetics of antimalarial drugs in the treatment of pregnant women with uncomplicated malaria

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Objectives: Pregnancy has considerable effects on the pharmacokinetic properties of many of the drugs used to treat uncomplicated falciparum malaria. Several studies have shown reduced antimalarial drug concentrations in later pregnancy. Unfortunately, pregnant women are especially vulnerable to malaria and the fetus is adversely affected. No reports have described the pharmacokinetic properties of piperaquine, amodiaquine or desethylamodiaquine in pregnant women with uncomplicated malaria.

Methods: A pharmacokinetic study were conducted in Thailand (24 pregnant and 24 non-pregnant women) and in Sudan (12 pregnant and 14 non-pregnant women). These studies investigated the pharmacokinetic properties of piperaquine after a standard oral three-day fixed dose regimen of dihydroartemisinin-piperaquine in patients with uncomplicated falciparum malaria. Pharmacokinetics of amodiaquine and its principal biologically active metabolite desethylamodiaquine was investigated in the treatment of vivax infections in 28 pregnant women during pregnancy and again after delivery. Dense venous plasma samples were collected and drug measurements conducted according to published methods. Concentration-time profiles were characterized using NONMEM. Different structural models and the impact of different covariates on pharmacokinetic parameters were investigated in full for all three antimalarials.

Results & Conclusions: Population pharmacokinetics of piperaquine, amodiaquine and desethylamodiaquine was accurately described using a population pharmacokinetic modeling approach and results were compared with available literature for a full understanding of potential pregnancy related changes on pharmacokinetics and the impact of these on the pharmacodynamics.

Toshihiro Wajima Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling for Integrase Inhibitors with a Simple Viral Dynamic Model

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Objectives: S/GSK1349572, S/GSK1265744 and S/GSK364735 are potent, low nanomolar inhibitors of both recombinant HIV integrase and HIV replication in cell culture assays. Currently in clinical development, S/GSK1349572 and S/GSK1265744 are unboosted, once daily integrase inhibitors with different resistance profiles than raltegravir or elvitegravir. A mathematical representation of viral dynamics for integrase inhibitors combined with a pharmacokinetic model are useful to assess dose-effect and concentration-effect relationships and thus aid in dose selection for clinical studies. The objective was to develop a simple and practical PK/PD model for describing plasma concentration profiles and viral dynamics of integrase inhibitors.

Methods: A simple viral dynamic model was developed. The PK part of the model is a conventional 1 compartment model with first-order absorption, and the PD part consists of 1 compartment for describing viral dynamics with first-order viral depletion and viral count-related viral replication, which is inhibited by integrase inhibitors with a Emax model. The model was applied to the profiles of plasma concentrations and HIV-1 RNA counts from 3-Phase IIa 10-day monotherapy studies. The model was fitted to 3 integrase inhibitors with adjustment by *in vitro* protein-adjusted IC50 (PA-IC50). Model evaluation was performed using classical diagnostic plots and the visual predictive check.

Results: The simple viral dynamic model described well the profiles of plasma concentrations and HIV-1 RNA counts in short-term monotherapy studies for these integrase inhibitors. The PD profiles for these 3 integrase inhibitors were described with a common virus-related PD parameter (first-order viral depletion constant) using *in vitro* PA-IC50 for each compound with adjustment by *in vitro-in vivo* scaling parameter. The first-order viral depletion constant was estimated to be 0.00305 hr^{-1}. The *in vivo-in vitro* scaling factor was estimated to be 2.26, suggesting *in vivo* IC50 was higher than in vitro PA-IC50. Simulations suggest that S/GSK1349572 and S/GSK1265744 will have robust efficacy with once daily dosing.

Conclusions: A simple PK/PD model was developed for describing the relationships between PK and PD for integrase inhibitors. This model can be used to predict future clinical trial results for the drugs of interest but can also be used for predicting the PK/PD relationships for other drugs in the same class.

Simbarashe Peter Zvada Effect of Four Different Meals Types on the Population Pharmacokinetics of single Dose Rifapentine in Healthy Male Volunteers

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Objectives: Rifapentine and its primary metabolite, 25-desacetyl rifapentine, are active against mycobacterium tuberculosis. The objectives of this study were to describe the population pharmacokinetics of rifapentine and 25-desacetyl rifapentine in fasting and fed states.

Methods: Thirty-five male healthy volunteers were enrolled in an open-label, randomized, sequential, five-way crossover study. Participants received a single 900 mg dose of rifapentine after meals with high fat (meal A), bulk and low fat (meal B), bulk and high fat (meal C), high fluid and low fat (meal D) content, or with 200 mLs of water (meal E). Venous blood samples were collected over 72 h after each RFP dose. Plasma concentrations of rifapentine and 25- desacetyl rifapentine were determined using a validated high-performance liquid chromatography (HPLC) method. Pharmacokinetic data for rifapentine and 25-desacetyl rifapentine were analysed in an integrated model using nonlinear mixed-effect modeling in NONMEM IV version 2 (FOCE INTER). First the rifapentine model was developed. The fixed and random effects estimates of oral clearance (CL/F), volume of distribution (V/F), first-order absorption rate constant (k_a), mean transit time (MTT), oral bioavailability (F) and number of hypothetical transit compartments (NN) were fixed and the 25-desacetyl rifapentine model was developed using all data assuming rifapentine was completely metabolized to 25-desacetyl rifapentine. Meal effects were investigated as categorical covariates and were found to be significant on the oral bioavailability.

Results: The pharmacokinetics of RFP were best described by a one-compartment model with first order absorption rate constant and time-varying clearance. 25-DRFP data were described by two-compartment model with time-varying clearance. Compared with the fasting state, meal A had the greatest effect on rifapentine oral bioavailability, increasing it by 86%. Meals B, C and D resulted in 33%, 46%, and 49% increases in rifapentine oral bioavailability, respectively. Similar trends were observed for 25-desacetyl rifapentine.

Conclusions: As RFP has exposure-related activity, concomitant food should be considered when evaluating optimal RFP doses in RFP-based regimens, under the meal conditions that can feasibly be provided by tuberculosis control programs in high-burden countries.

Marion Dehez Bayesian framework applied to dose escalation studies for biologics

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Introduction: In phase I dose escalating studies aiming at investigating pharmacokinetics and safety of novel drugs, a range of doses has to be explored and has to be relatively high in order to define the maximum tolerated dose. As the study progresses through the cohorts, a decision has to be made concerning the escalation at the next dose level which is constrained by the tox cover from the toxicological data (NOAEL). Limited PK data are usually available to derive the $AUC_{(0-\infty)}$ at a given dose level before selecting the next dose level, especially for long half life compounds such as biologics. This results in a difficulty to predict the rest of the concentration time profile and therefore to derive an accurate value for $AUC_{(0-\infty)}$.

Objective: The primary objective was to define a strategy to compute the predictive probability of the $AUC_{(0-\infty)}$ to exceed the NOAEL limit at the next dose level using prior information and limited PK data available at the time of dose escalation.

Methods and Results: FIH study type of data for biologics were used to implement this approach. A two compartment PK model was used to analyse the data expected to be available before each dose escalation step. Since using a PK model based approach, for initial doses levels, it may not be possible to estimate accurately $AUC_{(0-\infty)}$, a linear model was also used to fit the $AUC_{(0-\infty)}$ versus dose in which $AUC_{(0-t)}$ was empirically extrapolated to obtain the $AUC_{(0-\infty)}$. The corresponding predictive probability to exceed the tox cover at the next dose level was computed for each approach. Three sets of criteria (relative bias, coefficient of variation and predictive probability) were used to assess the quality of the estimations and to decide at which cohort it would be possible to switch from the linear model to the PK model approach. A range of residual errors and IIV values were tested. Two sets of priors were used: informative priors (in-house or literature from similar compounds) and non-informative priors. The analysis was performed in WinBUGS version 1.4.3. Simulations were performed in R2.9.
When using WinBUGS, for both models, a good prediction of the probability of the $AUC_{(0-\infty)}$ to exceed the NOAEL level was obtained. The PK model approach can be already used after collection of the very first timepoints of the first cohort. In the case of informative prior, this prediction is more accurate compared to non informative priors. For this biologic, with only 7 days PK time points and relevant priors the full PK profile can be predicted accurately.

Conclusions: A framework has been defined to combine prior information on biologics and PK data collected during dose escalation studies to allow accurate prediction of the exposure at the next dose levels and therefore helping in the dose selection to avoid exceeding the toxicological cover.

Amit Garg A Mechanism Based Population Pharmacokinetic-Pharmacodynamic Model for Epoetin Alfa and Darbepoetin Alfa in Chronic Kidney Disease Patients

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Objectives: The purpose of this study was to develop a mechanistic longitudinal pharmacokinetic / pharmacodynamic (PK/PD) model for the characterization of the erythropoietic effects of epoetin alfa, darbepoetin alfa and switching of one agent to another, in chronic kidney disease patients on hemodialysis.

Methods: Long term dialysis data for darbepoetin and epoetin was obtained from dialysis center. About eleven hundred male and female subjects (52% males and 48% females) were included in the analysis. The dataset contained laboratory values (hemoglobin, reticulocytes), records of dose adjustments, patient demographics (body weight, age, sex, BMI etc.) and other factors such as creatinine clearance, concomitant medications, etiology of CKD etc. for a treatment duration of 3-12 months for each patient, during the period of 2002 and 2008. The time course of red blood cell production (reported as hemoglobin concentration) on epoetin and/or darbepoetin was described based on the hematopoiesis processes. Darbepoetin and epoetin PK parameters were obtained from published literature [1, 3]. The population analysis was performed using the non-linear mixed effects modeling approach implemented in NONMEM V. The predictive performance of the final model was assessed by conducting a posterior predictive check (PPC) and by external predictive check.

Results: A catenary cell production and life-span based indirect response model was developed to describe the pharmacodynamics of epoetin and darbepoetin alfa. This mechanistic model modified from published work [2, 3] consisted of cell life span of normoblasts, reticulocytes, and red blood cells. A linear concentration-response model was selected to describe the effects of epoetin and darbepoetin on erythropoiesis, as data didn't support nonlinear relationships such as Emax and Power models. The mean hemoglobin values from the observed data were in good agreement with the distribution of hemoglobin values obtained from the simulated data (internal PPC). In addition, the simulated hemoglobin data from PK/PD model were in good agreement with the observed external data, confirming the predictability of the model. At 0.45 μg/kg/week dose (darbepoetin phase 2 dose-finding and dose-scheduling study protocol 960245), the observed change in hemoglobin from baseline at 4 weeks was 1.27 (0.55, 2.00) g/dL - mean (95% CI) while the model predicted change from baseline was 1.06 g/dL (0.3, 1.9), whereas, the observed change from baseline for the darbepoetin protocol 980211 was 1.1 g/dL (0.82, 1.37) while the model predicted change from baseline was 1.05 g/dL (0.77, 1.32) (top 10% of the non-responders were excluded from simulated data to represent clinical study population and exclusion/inclusion criteria).

Conclusion: The PK/PD model adequately described the longitudinal hemoglobin-time data in chronic kidney disease patients. The PK/PD model has the potential to inform future trial design including switching from one agent to the other and to evaluate dose titration strategies.

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Kenneth Luu A Mechanistic Approach to Predicting Human Pharmacokinetics of Monoclonal Antibodies from Preclinical Data: A Case Example

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Objectives: The objective of this study was to develop a mechanistic approach to predicting human pharmacokinetics (PK) from in-vitro mechanistic data and in-vivo nonhuman primate PK data based on the construct of a target-mediated drug disposition (TMDD) model (1).

Methods: A fully human IgG2 monoclonal antibody (mAbX), currently under development in the oncology therapeutic area, directed against a membrane-bound target was evaluated in this case study. A two-compartment, full TMDD model (in contrast with quasi-steady state TMDD models) was implemented to describe the nonlinear PK profiles observed in monkeys. Mechanistic parameters were obtained from in-vitro experiments (kon and koff binding kinetics and the mAbX-target complex internalization rate) and from the literature (degradation rate of the free target). Unique in this approach is the estimation of the in-vivo receptor abundance as a parameter which was intended to be scalable to human. Human PK was predicted using a hybrid approach: allometric scaling of physiological parameters such as kel, and k12 and k21, but mechanistic parameters specific for human targets were used. The mean predicted human PK profiles were compared against the currently available clinical PK data of patients receiving mAbX from 0.5 up to 6.75 mg/kg.

Results:. The two-compartment TMDD model described the nonlinear single-dose and multiple-dose PK profiles of mAbX in monkeys and estimated all parameters with reasonable precisions. The model predicted the human PK to follow TMDD which was confirmed by the clinical data. By visual inspection, the mean predicted PK profiles reasonably overlapped with the spread of the observed individual patient PK profiles. Furthermore, noncompartmental analysis of the mean prediction and the observed data indicated that predicted and observed CLs, and AUCs, were within 1.5 fold of each other.

Conclusion: The PK of monoclonal antibodies, especially those directed against membrane-bound targets that are of significant abundance, is often greatly affected by the binding and target kinetics. Thus, incorporating target kinetics into a mechanistic PK model to be used for interspecies scaling is a sensible approach for human PK prediction. Based on the mAbX case example, such an approach successfully predicted the human PK based on the preclinical data including in-vitro target kinetic data and in-vivo non-human primate PK data.

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Peiming Ma Predicting Free Sclerostin from Free AMG 785 and Total Sclerostin

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Objectives: Therapeutic mAbs often exhibit complex nonlinear pharmacokinetics as a result of the targets' facilitating their elimination or inactivation. Our objective is to characterize the disposition of AMG 785, an anti-sclerostin IgG2 compound, using a mechanistic model, the target mediated drug disposition (TMDD) model.

Methods: Nonlinear mixed-effects modeling with FOCE-interaction estimation in NONMEM was used to fit various TMDD models to log-transformed unbound AMG 785 and total sclerostin concentrations from two Phase 1 studies in healthy men and PMO women. Single doses studied were 1 and 5 mg/kg IV; 0.1, 0.3, 1, 3, 5, and 10 mg/kg SC; multiple ascending SC doses studied were 1 and 2 mg/kg Q2W; 2 and 3 mg/kg Q4W. The analysis data set included 1521 AMG 785 and 962 sclerostin concentrations from 118 subjects, which was simultaneously modeled with between-subject and within-subject variability estimated.

Results: The final PK model is a quasi-steady state TMDD that assumes a balance between synthesis and elimination of sclerostin. Age and sex did not affect PK. Absorption is best described by two parallel first-order processes in which approximately 44% of available dose absorbed at a faster rate.

Conclusions: Quasi-steady state TMDD described the mechanism of nonlinear clearance and PK in AMG 785 over a wide dose range studied. Patient factors did not affect the disposition of AMG 785 in the current population. The model is useful in predicting the time course of unbound and complex sclerostin concentration that could be related to AMG 785 efficacy on bone mineral density.

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David Ternant Methotrexate influences neither pharmacokinetics nor concentration-effect relationship of infliximab in axial ankylosing spondylitis

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Objectives: The pharmacokinetics of infliximab (IFX), an anti-TNF-α monoclonal antibody, is modified during methotrexate (MTX) coadministration in rheumatoid arthritis[1]. The objective of this study was to assess the influence of MTX on IFX pharmacokinetics and PK-PD in axial ankylosing spondylitis (AAS) patients.

Methods: In this prospective study, 26 AAS patients were randomly assigned to IFX alone (MTX– arm) or to MTX-IFX combination (MTX+ arm) and were treated by 5 mg/kg IFX infusions at weeks 0, 2, 6, 12 and 18. Infliximab concentrations were measured weekly, before and 2 and 4 hours after each infusion. The recommanded clinical endpoint in AAS, BASDAI score, was measured weekly. IFX pharmacokinetics were described using a 2-compartment model with first order transfer constants. The relationship between IFX and BASDAI score was described using an indirect response model. The BASDAI 'input' was described by kdis which was inhibited by IFX, and ksub which described nocebo effect; Em was the part of kdis not inhibated by IFX, C50 was IFX concentration leading to 50% of maximum kdis inhibition, and kheal was BASDAI 'output'. A population approach was used (MONOLIX 3.1 software). The influence of MTX was tested as a covariate on each pharmacokinetic and PK-PD parameter.

Results: Estimated pharmacokinetic parameters (interindividual CV) were: volumes of distribution for central (Vc) = 2.4 L, (10%), and peripheral (Vp) compartment = 1.8 L, (20%), systemic (CL) = 0.21 L/day, (22%), and intercompartment (Q) clearance = 2.3 L/day. Body surface area influenced both Vc and Vp, and antibodies toward IFX increased CL thrice. Estimated pharmacodynamic parameters were: kdis = 0.22 day-1 (85%), ksub = 0.018 day-1 (59%), kheal = 0.034 day-1 (95%) Em = 46%, (59%) and C50 = 6.3 mg/L. Methotrexate influenced neither pharmacokinetic nor PK-PD parameters. The strong negative correlation (–0.97) between ksub and Em interindividual distributions suggests that nocebo effect was higher when IFX efficacy was low. A C50 value lower than most measured IFX concentrations and a value for Em close to 100% in non-responders suggest that the absence of response was not due to under-exposure to IFX, but to IFX inefficacy.

Conclusions: Methotrexate influenced neither pharmacokinetics nor PK-PD of IFX. Therefore its combination with IFX cannot be recommanded to treat AAS. The absence of response to IFX in some patients may be due to a minor role of TNF-α in their disease.

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Paweł Wiczling Pharmacokinetics and Pharmacodynamics of Anti-CD3 Monoclonal Antibody, Otelixizumab, in Subjects with Diabetes and Psoriasis

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Objectives: Otelixizumab, a targeted T cell immunomodulator, is a monoclonal antibody directed against the CD3e part of the T-cell receptor complex (CD3/TCR). Otelixizumab administration causes rapid transient redistribution of lymphocytes from blood and down-modulation of CD3/TCR from the T cell surface. Additionally, if the T cell modulation is of sufficient duration these signals induce the up-regulation of T regulatory cells which may lead to long-term immunologic remission. These observed effects of otelixizumab are promising for treatment of various disorders, such as type 1 diabetes, psoriasis, or other T cell mediated autoimmune diseases. This study describes a population pharmacokinetic (PK) model to account for serum otelixizumab concentrations following intravenous administration. It also characterizes the pharmacodynamics (PD) of otelixizumab effects on the absolute counts of CD4+ and CD8+ T cells and on the modulation and saturation of CD3/TCR receptors. The last were determined based on quantitative flow cytometry assays.

Methods: Population nonlinear mixed-effect modeling was done using NONMEM. Data was obtained from three clinical trials involving subjects with diabetes and psoriasis. Total otelixizumab doses ranged from 0.3 mg to 64 mg. The diabetes subjects in Study I received a first dose of 24 or 8 mg, followed by 8 mg doses per day for 5 consecutive days. The psoriasis subjects in Study II received a single dose of 1, 2 or 4 mg. The diabetes subjects in Study III received doses ranging from 0.1 to 0.75 mg per day for 3 to 8 consecutive days.

Results: The one-compartment model with Michaelis-Menten elimination characterized otelixizumab PK. Nonlinearity was manifested at high concentrations (Km = 1.06 μg/ml). For low doses, such as for Study III, the PK was linear with a t1/2 of 0.52 day. The Vd of otelixizumab was 12.8 L suggesting distribution outside the plasma. Lymphocyte dynamics were captured by an indirect response model simplified to the direct inhibitory effect. The initial lymphocyte count was in the normal range of and decreased after otelixizumab administration. In diabetes a 50% decrease in pretreatment CD4+ and CD8+ counts was achieved at otelixizumab concentrations $IC_{50,CD4,D}$ = 0.0220 μg/ml and $IC_{50,CD8,D}$ = 0.0133 μg/ml. The corresponding values for psoriasis were lower: $IC_{50,CD4,P}$ = 0.000670 μg/ml and $IC_{50,CD8,P}$ = 0.000306 μg/ml. In both cases the values of IC_{50} indicate that low otelixizumab concentrations are effective at redistributing lymphocytes to the peripheral tissues. The equality between the total (sum of unbound and otelixizumab bound) CD3/TCR and unbound CD3/TCR was observed indicating a small number of otelixizumab-(CD3/TCR) complexes at the T cell surface. The down-modulation of CD3/TCR was described by a direct inhibitory effect. The 50% change in unbound CD3/TCR was not dependent on the disease and was achieved for CD4+ and CD8+ cells at otelixizumab concentrations: $IC_{50,FR,CD4}$ = 0.0164 μg/ml and $IC_{50,FR,CD8}$ = 0.0191 μg/ml.

Conclusions: The integrated PK/PD model was proposed and successfully applied to understand otelixizumab pharmacokinetics and the array of PD responses in subjects with psoriasis and diabetes.

Ronald Niebecker Impact of Different Body Size Descriptors on the Population Pharmacokinetics of a Monoclonal Antibody

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Objectives: Pharmacokinetics (PK) of monoclonal antibodies and in particular their clearances have been reported to be related to body size [1]. Covariate relations in population PK models utilised different body size descriptors (BSD), including body weight (BW), body surface area (BSA) or ideal body weight (IBW) [2]. The objective of this analysis was to compare the suitability of different BSDs in a sibrotuzumab population PK model, to suggest the optimal BSD and to investigate the impact of extremes in body size on drug exposure.

Methods: Sibrotuzumab PK has best been described with a two-compartment model with both linear and nonlinear elimination (parameterised with Vmax and Km) from the central disposition compartment, interindividual (IIV) and interoccasion variability (IOV). BW was included as a covariate on 4 structural model parameters, in a linear covariate relation [3]. Nonlinear mixed-effect modelling with NONMEMTM was applied to estimate model parameters for the baseline model excluding covariates and for the models including the following BSDs: BW, patient height, body mass index (BMI), BSA, fat-free mass, IBW, lean-body mass.

Results: (i) Compared to the baseline model, incorporation of body size significantly improved model performance: the objective function value decreased, unexplained variability was reduced, particularly IIV on the volumes of distribution and Vmax. Despite the highest relative covariate effect, IIV of linear clearance (CLL) was only marginally reduced. IOV remained virtually unaffected. (ii) The different BSDs performed similar, with the exception of BMI, being inferior. (iii) Covariate relations in patients with median and “extreme“ (0.05 and 0.95 percentile) BSD values indicated considerable influence of body size on CLL and the central volume of distribution. (iv) These influences were confirmed by deterministic simulations of the concentration-time profiles for a 12 week treatment period with weekly dosing of 100 mg sibrotuzumab. Minimum Css in patients with “extremely low” body size even exceeded maximum Css of patients with “extremely high” body size.

Conclusions: The analysis confirmed that body size does have an impact on sibrotuzumab PK. No single BSD appears to be superior. In order to further evaluate this hypothesis, different covariate models including the allometric power model will be investigated, and stochastic simulation will be implemented.

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Neil Attkins Model based analysis of antagonist binding kinetics at CRF-1 receptors in vitro and in vivo

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Objectives: Both in-house and literature[1]data show that CRF-1 antagonists display differing degrees of insurmountable antagonism in standard competition binding assays. We have optimised the use and analysis of data from a non-equilibrium binding assay to measure the kinetics of these compounds[2]. The kinetically derived association and dissociation rates were used in conjunction with the compounds pharmacokinetic parameters in the rat to simulate the receptor occupancy vs. time profiles. Our aim was to use these simulations as a replacement for *in vivo* receptor occupancy studies to enable faster triage of compounds with slow offset at an early stage of discovery, to enable quicker progression to compound selection and first time in man. Compounds with slower off-set from the receptor have the potential to sustain the duration of efficacy due to an increased residence time at the receptor.

Methods: Data from the non-equilibrium binding assays was fitted in NONMEM v6.2 to obtain estimates of the compounds association and dissociation rates[3]. The receptor occupancy versus time simulations were performed in Berkley Madonna.

Results: The kinetic parameters derived from the non-equilibrium binding assay made it possible to classify compounds as slow, moderate or fast dissociating compounds. With the exception of DMP-904, all of the *in vitro* association rates were slower than *in vivo* and the simulations tended to either under-estimate the degree of occupancy or take longer to reach the maximum occupancy level. In contrast to this, the dissociation rates were better estimated and the rank order of the compounds dissociation half-life was translatable *in vitro* to *in vivo*.

Conclusions: Whilst there appeared to be a consistent discrepancy between *in vitro* and *in vivo* receptor association rates, the rank order of the compounds in terms of their rate of dissociation from the CRF-1 receptor translated well. Therefore, this PKPD model based approach proved to be useful to triage between compounds at an early stage of the project where it is not feasible to perform *in vivo* receptor occupancy studies on a large number of compounds.

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Marcus Björnsson Modeling of Pain Intensity Measured on a Visual Analogue Scale and Informative Dropout in a Dental Pain Model after Naproxcinod and Naproxen Administration

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Objectives: The objective of this model was to describe the pain intensity (PI) and dropout due to request of rescue medication after administration of naproxcinod, naproxen or placebo after wisdom tooth removal.

Methods: In a double-blind dose-finding study 242 patients that requested pain relief after removal of mandibular wisdom teeth were randomised to naproxcinod 375, 750, 1500 or 2250 mg, naproxen 500 mg, or placebo [1]. Plasma was collected for analysis of total and unbound naproxen plasma concentrations, and PI were measured on a 100 mm visual analogue scale (VAS) for up to 8 hours post-dose. Patients needing additional pain relief could request rescue medication, and the time of requesting rescue medication was recorded. The pharmacokinetic/pharmacodynamic (PK/PD) analysis was performed using NONMEM VI. Goodness of fit was assessed using objective function values, standard errors, graphics and visual predictive checks (VPC).

Results: A one-compartment model with transit compartment absorption and saturable protein binding described the concentrations of naproxen. An exponential model described the placebo response on the PI, and the drug effect was described using a sigmoid E_{max} model. Typical maximal placebo effect was a decrease in PI by 20.2 %, and EC_{50} was 0.135 μmol/L. The dropout was modelled using a Weibull time-to-event model, where the hazard was dependent on the model predicted PI as well as baseline PI. Since the dropout was not at random, it was necessary to include the simulated dropout in the VPCs of PI.

Conclusions: This model provides a pharmacometric platform that describes the placebo effects and relationship between PI measured on a VAS and dropout after dental extraction. The effects of naproxcinod and naproxen on PI and dropout were well described. VPCs created by simultaneous simulations of a continuous variable and time to event provide a good way of assessing the goodness of fit when there is informative dropout.

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Jacob Brogren Transit Compartment Model Useful for Describing Absorption of Quetiapine XR and IR

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Objectives: Quetiapine fumarate is an atypical antipsychotic that has demonstrated efficacy in patients with schizophrenia, bipolar mania, bipolar depression, major depressive disorder, and generalized anxiety disorder. Quetiapine is available in two different formulations: XR (extended release) and IR (immediate release). Quetiapine XR exhibits a slower absorption compared with quetiapine IR, with generally lower Cmax and longer tmax. The objective of this work was to develop a population PK model for both these quetiapine formulations in order to facilitate simulations of quetiapine PK across formulations, regimens, and the clinical dose range.

Methods: The population PK model was developed based on data from a randomized, double-blind, crossover study in healthy volunteers (n=58, ClinicalTrials.gov Identifier NCT00702676) with the aim to study the sedation profile following administration of quetiapine XR and IR. The details of the study have been reported elsewhere [1]. In order to simultaneously describe the quetiapine PK profiles obtained with both formulations, a population PK model utilizing transit compartments [2] was applied to data using NONMEM VI.

Results: A two-compartment model with transit compartment absorption feeding directly into the central compartment was successfully fitted to data. Separate estimates of mean transit time (MTT) and number of transit compartments (NB) were obtained for the different formulations. MTT for XR and IR was estimated to be 4.65 h and 1.14 h, respectively. Other structural model population parameters were the same regardless of formulation. CL/F for quetiapine was estimated to be 96.8 L/h and Vss to be 515 L/h. Interindividual variability (IIV) in bioavailability was similar (40%-45%) for both formulations. The IIV in MTT was 45% for the IR formulation and 23% for the XR formulation. As opposed to the original noncompartmental analysis, it could be shown in this study that quetiapine XR gave similar exposure in terms of AUC as quetiapine IR. This was because a single value of CL/F was valid for both of the formulations.

Conclusions: The transit compartment model was able to describe absorption characteristics of both quetiapine XR and IR. The exposure in terms of AUC as well as the variability in bioavailability was similar following administration of either quetiapine XR or IR, thus providing further support for the bioequivalence of the two formulations.

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Yu-Yuan Chiu Population Pharmacokinetics of Lurasidone in Healthy Subjects and Subjects with Schizophrenia

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Objectives: Population pharmacokinetic (PK) analysis was performed to characterize lurasidone concentration-time profiles in healthy subjects and subjects with schizophrenia. Effects of covariates on lurasidone PK parameters were investigated to derive a final predictive PK model.

Methods: Nonlinear mixed effects modeling methodology was implemented in this analysis using NONMEM® (version 6). The first-order conditional estimation (FOCE) method with interaction was used to fit the lurasidone serum concentration data. A two stage, stepwise forward selection and backward elimination procedure was used to identify relationships between population PK parameters and selected covariates including baseline body weight, age, race, gender, and meal status. Standard goodness-of-fit diagnostics and posterior predictive checks were used to evaluate the adequacy of the PK model fit and predictions.

Results: A three compartment model with first-order absorption, absorption lag time, and first-order elimination characterized the lurasidone PK in 11735 lurasidone concentrations from 1353 healthy subjects and subjects with schizophrenia. Seven covariate effects out of 19 covariate effects investigated were included in the final parsimonious model following forward selection and backward elimination procedures. Parameter estimates were generally estimated with good precision (less than 30% SEM). Diagnostic plots and posterior predictive check results stratified by dose suggest that total lurasidone exposure increases in a linear fashion within the dose range tested (10 to 600 mg/day). Similarly, peak serum concentrations suggest a dose-proportional increase within the range of 10 to 160 mg/day. There was insufficient evidence of an age effect on the PK of lurasidone as assessed by the population PK analysis. Race, gender, and weight were individually associated with less than two-fold changes in typical predicted $AUC_{(0\text{-}24)}$ or C_{max} values. Food increased lurasidone exposure which is consistent with clinical findings.

Conclusions: The population PK model adequately characterized lurasidone PK in healthy subjects and subjects with schizophrenia. Changes in exposure from age, race, gender, and weight are not regarded as clinically relevant.

Vincenzo Luca Di Iorio Impact of Seizures and Efflux Mechanisms on the Biophase Kinetics and CNS Effects of Anticonvulsant Drugs

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Background: Several classes of efflux transporters are present at the blood-brain barrier (BBB). They are considered to act in tandem in hindering efficient drug delivery to the brain. Over-expression of active efflux mechanisms has been described in epileptic brain areas and is suggested to play a substantial role in pharmacoresistance to antiepileptic drugs. In addition, during seizures the integrity and selective permeability of the BBB is compromised causing regional drug concentration differences within the brain.

Objectives: The aim of this work was to develop a PKPD model to describe the impact of seizures and active efflux mechanism on the biophase kinetics and CNS effects of antiepileptic drugs.

Methods: Recently, an integrated pharmacokinetic (PK) model has been developed, which simultaneously describes the pharmacokinetics of 10-hydroxycarbazepine (MHD), the active metabolite of oxcarbazepine, in plasma and brain during seizures and p-glycoprotein inhibition[2]. Like many other antiepileptic drugs, MHD was shown to stimulate hippocampal dopaminergic and serotoninergic neurotransmission and these neurotransmitter modulations were demonstrated to be partly responsible for the anticonvulsant effects[1]. In the current investigation, we have used these monoamine transmitters as pharmacodynamic (PD) markers for the efficacy of MHD. An integrated PKPD model was built to characterise the effects of MHD on extracellular hippocampal dopamine and serotonin levels using nonlinear mixed effects modelling. Concomitantly, the impact of acute seizures and efflux transport mechanisms on the PD of MHD was quantified. Data analysis was performed in NONMEM v6.2. R was used for data manipulation, statistical and graphical summaries. Model validation procedures consisted of mirror plots, visual predictive check (VPC) and bootstrap.

Results: A sigmoid Emax model could best describe the increase in hippocampal dopamine and serotonin. Furthermore, our findings show that biophase disposition of antiepileptic drugs can differ significantly from plasma pharmacokinetics and that seizure-induced regional changes in drug disposition are often not correlated to alterations in plasma kinetics.

Conclusions: These experiments demonstrate that the PD effects of MHD are highly affected by seizures and active efflux transport blockade. These results also highlight that knowledge of the biophase kinetics is imperative to accurately describe drug effects under disease conditions.

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Eunice Yuen A population pharmacokinetic/pharmacodynamic model for duloxetine in diabetic peripheral neuropathy, plus methods for handling missing data.

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Objectives: Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of diabetic peripheral neuropathic pain (DPNP). The population pharmacokinetics of duloxetine have been previously described [1]. In three phase 3 double-blind placebo-controlled trials, the efficacy of duloxetine was evaluated over a 12 week acute therapy phase. Patients receiving 60mg QD and 60mg BID duloxetine showed significant improvement in pain scores, starting from week one [2,3,4]. The aim of the current analyses was to develop a population PK/PD model in DPNP patients and to compare the different methods of imputing missing data for dropouts.

Methods: A total of 1106 patients (12549 PD observations) were randomised into placebo (N=327), 20mg QD (N=110), 60mg QD (N=335) and 60mg BID (N=334) groups. PK parameters from [1] were used to simulate duloxetine concentrations at steady state, and weekly average painscores (Likert scale, 0 to 10) calculated from 24-hour average scores were used as PD measures. Population Pk/PD analysis was carried out in NONMEM, describing the pain scores as well as a proportional odds model describing the probability of achieving clinically meaningful pain relief. Missing data for dropouts were imputed using last observation carried forward (LOCF), multiple imputation, and pattern mixture model methods. The PK/PD model was applied to these various enriched datasets and parameters obtained compared to those from non-missing data.

Results: The placebo response was described by an exponential decline model for each pain severity group, whilst drug effect was additive and described by a single Emax model. Across the 3 trials, completion rate was approximately 72%. More patients in the 60mg treatment groups discontinued due to adverse events, whilst more patients in the placebo group discontinued due to lack of efficacy. For the comparison of imputation methods, EC50 was the most sensitive estimate to the different methods. LOCF produced the smallest parameter estimates describing placebo slope. Both the multiple imputation and pattern mixture methods produced parameter estimates similar to the model with non-missing data.

Conclusions: The Likert scale pain scores were well described by the population PK/PD model. Overall, the different methods of handling dropouts produced comparable PD parameters to the model with non-missing data, mostly within 20% of the estimates using non-missing data.

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Martin Gnanamuthu Johnson Evaluation of a Mechanism-Based Pharmacokinetic-Pharmacodynamic Model for D2 Receptor Occupancy of Olanzapine in Rats

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Objective: Two structurally different mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) models were developed to predict the time course of dopamine receptor occupancy (D_2RO) in rat striatum following the administration of olanzapine, an atypical antipsychotic drug. These models included the characterization of association and dissociation rate constants (Kon and Koff) as the determinant of time delay between the brain concentration and D_2 receptor occupancy. Model A was developed with an assumption that receptor binding affects the free concentration of olanzapine in the striatum. Model B was developed with an alternative assumption where receptor binding does not affect the free drug concentration in the striatum. The objective of this study is to evaluate these assumptions in a systematic way by testing both models and assessing parameter(s) sensitivity using a simulation based approach.

Methods: A population approach was utilized to quantify both the pharmacokinetics and pharmacodynamics of olanzapine using the drug exposure (plasma and brain concentration) and D_2 RO profile obtained at various doses (0.1-30 mg/kg) administered by different routes. A two-compartment pharmacokinetic model was used to explain the plasma pharmacokinetic (PK) profile. Two structurally different binding models were developed to characterize the D_2 receptor binding at striatum and were fitted sequentially to the PK data. The effect of binding was evaluated using a dataset simulated from Model A including low dose levels (0.01-0.03 mg/kg). PK-PD parameters were estimated for this simulated dataset using Model A and Model B. The parameters were estimated using NONMEM VI, level 2.0. The binding parameters (Kon, Koff) and Bmax were subjected to a parameter sensitivity analysis, where these parameters were perturbated with different range of values and doses. The effect of these perturbations on the D_2RO profile was examined.

Results: The PK-PD time profiles were well described by both models. PK-PD parameter estimates obtained from models A and B did not differ significantly for both the real dataset and simulated dataset including low doses. Bmax did not influence D_2RO when perturbated to different values, whereas Kon, Koff did influence to some extent.

Conclusion: The relatively simple model (Model B) recapitulated the essential features of the Model A to predict D_2RO and reduced the need for Bmax which is difficult to identify from the available data/information.

Gordon Graham Continuous time Markov modelling of relapse sojourns for relapse-remitting multiple sclerosis patients

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Objectives: To develop an exposure-response model for the sojourns in either a relapse or remitting disease state in relapse-remitting multiple sclerosis (RRMS) patients using data from two phase III longitudinal studies. Secondly, to explore the effect of demographic and disease status covariates to describe the transition rates from a relapse state to a remitting state and vice versa.

Methods: A total of 2552 MS patients were included in the analysis from two phase III studies: study A was of one year duration (1272 patients) and study B was of two years duration (1280 patients). Data were available from two dose levels of FTY720 in both studies. Study A had an active comparator arm and study B was placebo controlled. A population pharmacokinetic model was developed to describe the steady state concentrations of FTY720 phosphate (FTY720-P), investigating the effect of demographic variables on the estimated steady state concentrations. A continuous-time two-state Markov model was developed to describe the times at which relapses began and ended since the start of FTY720 treatment (Jones et al, 2006). Proc NLMIXED in SAS v9.1 was used to perform the analysis. The mean sojourn in a state was calculated as 1/lambda_lm, where lambda_lm is the model estimated transition rate from state l to state m. The aggregate relapse rate (ARR) was estimated by 1/(lambda_12+lambda_21).

Results: The transition rate from a relapse state to a remitting state was found to be independent of FTY720-P concentration and patient demographic and disease status covariates. The transition rate from a remitting state to a relapse state was modeled as an inhibitory Emax model of FTY720-P concentration. The baseline was found to be a function of the number of gadolinium enhanced lesions (T1B), the disability score (EDSS) and the number of relapses in the two years prior to the study start, such that patients with the most active or severe disease had a higher ARR. The Emax parameter (maximum reduction in transition rate) was dependent on T1B and EDSS. The sojourn in a remitting state was estimated to be at least twice as long for the FTY720 treated patients than for the active control or placebo assigned patients.

Conclusions: The exposure-response model demonstrated the efficacy of FTY720 to increase the sojourn in a remitting state compared to the active control or placebo, and that the transition rate was dependent on the disease activity and severity. A natural modelling extension would be to develop a model linking the number of lesions, the relapse rate and the disability score to further improve the understanding of the disease progression and the beneficial effect of FTY720.

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Andrew Hooker Title: Modeling exposure-response relationships in the rat self-administration model

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Background: There is a growing emphasis on the development of methodologies to derisk the abuse potential of drug candidates [1]. Numerous pre-clinical animal models have been proposed for investigation of the likelihood that a drug will sustain patterns of non-medical self-administration (abuse potential). One proposed model uses rats, with dual intravenous catheterization for infusion of drug and blood sampling, placed in a chamber with a lever that administers a possibly reinforcing test compound. Responding on the lever delivers a specific dose of the compound. The rats can then continue to respond on the lever to administer more of the compound; a specific time out between infusions limits the dosing. By varying dose per response the concentration at which reinforcing behavior occurs (if it occurs) can be determined. A limitation of the current paradigm is that it provides minimal insight into the exposure-response relationship and therefore can only be used to help define abuse potential in a qualitative manner.

Objective: To model the reinforcing behavior vs. concentration relationship and give a prediction of the dose regimen/exposure where no reinforcing behavior would be induced (with reasonable certainty) for an abused reference compound (cocaine).

Methods: Multiple study sessions with a total of 38 animals were performed. The studies included a single dose PK study (no lever presses) and numerous PKPD studies where dose per response was adjusted (including placebo) as well as the number of responses needed for each cocaine infusion. Studies were performed with animals at different stages of cocaine self-administration i.e.: those that have undergone repeated cocaine self-administration sessions (trained) and those in which the response has subsequently been extinguished (extinguished). A population PKPD model was then developed sequentially for this data using NONMEM.

Results: A two-compartment model described the PK data well. The PD variable time-to-infusion was modeled with a repeated time-to-event model. The rats exhibited different baseline characteristics if they were trained or extinguished (exhibit fewer level presses). Thus the placebo model included terms for both states. When cocaine was available, time-to-infusion decreased at very low concentrations, increased at mid-concentrations and at very high concentrations tended to decrease; a bell shaped hazard vs. concentration profile was used to describe this process.

Conclusions: A model that adequately describes the cocaine concentration-reinforcing behavior relationship for this animal model has been developed. With this model as a reference, new studies with

other test compounds will be analyzed with the goal of creating a platform model to describe and predict patterns of non-medical self-administration for new compounds.

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Matts Kågedal Estimation of occupancy and radioligand kinetics in the CNS from PET-data in the absence of a reference region.

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Objectives: With traditional methods calculation of occupancy is based on the specific uptake (binding potential) estimated individually from each PET-measurement. Estimation of occupancy is not possible with this approach when a reference region void of receptors is lacking. In order to estimate the *in vivo* affinity, a population model was developed for receptor binding kinetics by use of measured concentrations of ^{11}C AZDX in plasma and CNS as well as concentrations of unlabelled AZDX in plasma.

Methods: The analysis was based on data from a PET study in six healthy volunteers. On four occasions each subject was examined by a 60-90 minute PET measurement after injection of tracer amount of the radioligand. The radioligand (^{11}C-AZDX was given alone on one occasion and at 3 hours after oral administration of different doses of unlabelled AZDX on the other occasions. The time course of radioligand concentration in regions of interest in the CNS was derived from the PET-measurements and the time course of unchanged drug in plasma was derived from measurements in arterial blood and plasma.

In order to improve the ability to separate between receptor bound and non-specific uptake in the CNS, the two regions with the highest (ventral striatum) and lowest (cerebellum) uptake were included in the analysis. Differential equations were used to estimate the transfer between plasma and CNS and the binding to the receptor. It was assumed that the extent of non-specific uptake as well as the receptor binding kinetics were the same in both regions while the rate of CNS uptake and the receptor density could differ. The model accounted for the difference in residual error in the regions as well as the correlation between them. The relationship between free receptor concentration and drug concentration in the brain was included as a saturation model.

Results: The results show that AZDX binding at the receptor is saturable with an estimated Kd_{plasma} of approximately 200nmol/L and that the density of the receptor binding sites are approximately 800nM and 200nM in VST and CER respectively.

Conclusions: By simultaneously analysing data from several PET-measurements in a non-linear mixed effects framework it is possible to estimate parameters of interest that would otherwise be difficult to assess. It is also possible to include a changing cold drug concentration during the PET-assessment rather than having to approximate the concentration with a mean value.

Kristin Karlsson Clinical trial simulations using a stroke disease progression model

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Background: Combined categorical-continuous models such as the stroke disease progression models [1-3] are of particular use where data are relatively sparse, which is a typical scenario when analysing stroke scale data. Maximal use is made of the available information, and even missing observations can be informative. These models may provide significant advantages over current analytical methodology used in the interpretation of the score data routinely collected during stroke trials.

Objectives: To perform clinical trial simulations to calculate the power to detect a drug effect different from zero, using a disease progression model for NIH stroke scale (NIHSS) [2], and to assess the bias and precision of the drug parameter, under various conditions.

Methods: To be able to perform clinical trial simulations a drug effect parameter had to be introduced in the NIHSS disease progression model. Due to the complexity of the model, several options on where to introduce a drug parameter were available but initially the drug effect was added linearly on the magnitude of improvement. The dose-effect relation was calibrated such that a low, medium and high dose level would result in 25%, 33% and 50% fully recovered patients at end of study (the definition of a fully recovered patient was NIHSS

Results: Initial results, with 100 patients per dose arm, indicate a sufficient power to detect a drug effect parameter different from zero and that the bias and precision of the drug parameter are low. A rough assessment of the type-I error indicated that the nominal p-value for a 5% error rate was close to 0.05.

Conclusions: These initial results show the possibility to use a model based analysis within the stroke therapeutic area. This area has previously suffered from the requirement of very large trial sizes and a model based approach could enhance the feasibility of performing stroke trials.

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Magdalena Kozielska Predictive performance of two PK-PD models of D2 receptor occupancy of the antipsychotics risperidone and paliperidone in rats

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Objectives: The level of dopamine D2 receptor occupancy is predictive of efficacy and safety in schizophrenia. Population PK-PD modelling has been used to link observed plasma and brain concentrations to receptor occupancy. The objective of this study was to compare the predictive performance of two structurally different PK-PD models for rats. In one model receptor binding was assumed to influence brain distribution of the drug and in the second model receptor occupancy was derived from brain concentration, but did not affect it.

Methods: Based on the plasma, brain and D2 receptor occupancy data for risperidone in rats, mechanism-based PK-PD models were developed previously. The model in which binding to D2 and 5-HT2A receptors was taken into account and this binding influenced brain kinetics of the drug resulted in the best fit to the data. However, if only data for higher doses were used, also the model where receptor binding did not affect brain kinetics fitted well to the data. Here, we used simulations to compare how well the two models, can predict brain concentration and receptor occupancy for different doses of risperidone.

Results: Predicted brain concentration differed between the two models, especially for lower doses. Only the model in which receptor binding influenced brain kinetics correctly predicted the brain to plasma ratio observed in the data, which was higher at lower concentrations and decreased to a relatively constant level for higher plasma concentration (when receptor binding is maximal). However, both models predicted receptor occupancy similarly well for all the doses.

Conclusions: A mechanistic model in which brain kinetics of the drug are affected by its binding to receptors is necessary to accurately predict brain to plasma ratios. However, simpler models might be sufficient to accurately predict receptor occupancy. Inclusion of binding to receptors in the drug brain kinetics may be especially important for drugs with active efflux where concentrations in brain are lower and therefore drug bound to receptors may constitute relatively large fraction of total drug in the brain.

SeungHwan Lee A population analysis of Intravenous Dexmedetomidine in Korean

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Objectives: Dexmedetomidine is a selective alpha2-adrenoreceptor agonist used for sedation in critically ill patients. The aim of this study was develop a population pharmacokinetic model of intravenous dexmedetomidine in Korean and compare previously reported pharmacokinetic data.

Methods: Dexmedetomidine concentration-time data were obtained from a randomized, double-blind, placebo-controlled, phase 1 study in three parallel dosage groups. Three intravenous dexmedetomidine dosing regimen was used; 3 μg/kg/h for 10 minutes followed by 0.17 μg/kg/h for 50 minutes, 6 μg/kg/h for 10 minutes followed by 0.34 μg/kg/h for 50 minutes and 3.7 μg/kg/h for 35 minutes followed by 0.7 μg/kg/h for 25 minutes. Plasma samples for pharmacokinetic analysis were taken at pre-dose and 0.17 h, 0.58 h, 0.75 h, 1 h, 1.17 h, 1.33 h, 1.5 h, 2 h, 3 h, 4 h, 7 h, 10 h, 12 h postdose. Population pharmacokinetic model was developed using NONMEM®, version VI) and PsN.

Results: : A total of 208 concentrations form 16 subjects were included in population analysis. Mean (±SD) age was 26.4 ± 2.7 years and weight was 71.2 ± 8.0 kg. Pharmacokinetic of dexmedetomidine was best described using a two-compartment model with first-order kinetics. Population mean estimate (SE) of clearance (CL) was 33.0 (0.756) L/h, central volume of distribution (V1) was 19.7 (0.565) L, inter-compartment clearance (Q) was 65.8 (3.41) L/h and peripheral volume of distribution (V2) was 61.4 (2.47) L. Most of the data were within 5th and 95th percentile in visual predictive check, which indicated that the model describes the pharmacokinetics of dexmedetomidine adequately.

Conclusions: A two-compartment model with first-order elimination adequately characterized the pharmacokinetics of dexmedetomidine. Application of population pharmacokinetic model will be helpful for dose selection in clinical use.

Gailing Li Towards Quantitative Prediction Of In Vivo Brain Penetration Using A Physiology Based CNS Disposition Model

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Background: Drug discovery for CNS disorders has been challenged with markedly high attrition rate. This has driven extensive preclinical and clinical CNS pharmacokinetic (PK) and pharmacodynamic evaluation recently. In clinical programs, human cerebrospinal fluid (CSF) sampling and positron emission tomography (PET) studies have become "routine" but at high cost. In contrast to the data collection efforts, predicting brain penetration *in vivo* in animals and humans has remained a largely untouched area.

The aim of this report is to share our recent efforts in developing a mathematical model for predicting CNS disposition *in vivo* and to demonstrate the integral role of multiple drug and system parameters on brain penetration through simulations.

Methods: A physiology based CNS disposition model in rats (only passive mechanisms) was developed. Simulations were performed using Berkeley Madonna Version 8.0.1 to explore (1) the interrelationships between drug concentrations in brain parenchyma, CSF, and plasma; and to (2) identify critical influencing factors for CNS penetration. In addition, evaluations of the model prediction versus experimental observation *in vivo* were conducted.

Results: Drug concentration in brain is determined by the plasma PK, permeability cross BBB and non-specific binding, but not quantitatively affected by the distribution between brain interstitial fluid (ISF) and CSF. Plasma kinetics can predict brain kinetics reasonably well only if there is a large proportion of free drug with a rapid transport cross BBB. CSF kinetics does not always follow the time course of unbound brain concentration. The level of resemblance of CSF kinetics to unbound brain kinetics is largely dependant upon the distribution rate between ISF and CSF domain, and CSF turnover rate.

Conclusion: The physiology based CNS disposition model has provided a valuable framework for quantitative understanding of time course of CNS disposition.

Venkatesh Pilla Reddy Modeling and Simulation of Placebo Response and Dropout Patterns in Treatment of Schizophrenia

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Objectives: Unpredictable variation in placebo response within and among clinical trials can substantially affect conclusions about the efficacy of new antipsychotic medications. Developing a robust placebo model accounting for factors like dropouts, disease progression and trial design is crucial in order to facilitate better quantification of drug effect. The objectives of this study were i) to develop a model for placebo response in schizophrenia as measured with the Positive and Negative Syndrome Scale (PANSS) under varying clinical trial conditions, accounting for dropout and other relevant predictors of the placebo response, ii) to compare different Time to Event (TTE) modeling approaches used to describe the dropout patterns following placebo treatment in schizophrenia.

Methods: Pooled PANSS data from 15 clinical trials (n=1338), which included both acute and chronic schizophrenic patients with different study periods (6, 8, 12 and 54 weeks), were used to describe the time course of PANSS using NONMEM VI. Several placebo models with determinants of placebo response were tested [1]. Influence of dropouts was investigated by exploring three TTE hazard models in conjunction with the best performing placebo models. Different patterns of dropping out were examined by exploring Missing Completely At Random (MCAR), where dropout does not depend on PANSS; Missing At Random (MAR), where dropout depends on last observed PANSS; Missing Not At Random (MNAR), where dropout depends on predicted PANSS [2].

Results: The Weibull model and an indirect response model (IRM) with exponential infusion type of kinetic-PD function described the PANSS data well compared to other placebo models. Proportional, Weibull and Gompertz hazard models (GHM) performed equally well for short-term trials, while for long-term trials and for the entire pooled dataset, GHM was shown to be superior. Preliminary covariate analysis indicated that females, subjects in long-term studies and chronic patients had lower probability of dropping out from trials compared to males, subjects of short-term studies and acute schizophrenic patients.

Conclusions: Placebo-associated change in PANSS was well described by Weibull and the IRM model. Results of simultaneous modeling of dropout model with placebo model indicated that the probability of patients dropping out from a clinical trial is associated with both the last observed PANSS measurement and unobserved PANSS score as predicted by the placebo model.

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Mahesh Samtani Switching to Paliperidone Palmitate[1,2] from Other Depot Antipsychotics: Guidance Based on Pharmacokinetic Simulations

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Objective: Population PK models have been developed for paliperidone palmitate (PP) and risperidone long-acting injection (RLAI) based on data from schizophrenia subjects. The final models, including significant subject covariates, were used as simulation tools to investigate dosing strategies for patients switching from other depot antipsychotics to PP.

Methods: A 1-compartment model with parallel zero/1st order absorption described the PK of PP. A 1-compartment model with 3 parallel absorption pathways described the PK of RLAI. Covariates of interest were obtained by resampling subject covariates available in the PK database for PP. To evaluate outcomes of simulation scenarios, the population median and 90% prediction interval of the simulated concentration vs. time profiles were plotted together. In addition, a literature search was also performed to understand the PK characteristics of other depot injectable antipsychotics.

Results: The literature search results showed that, for other depot antipsychotics, the administration interval is in the range of 1-2 half-lives for each product. This indicates that at the time of switching to PP (instead of the scheduled injection of the previous depot antipsychotic) there will be sustained therapeutic levels of the prior drug in the systemic circulation. Given that significant levels of the previous antipsychotic would be present in the systematic circulation, there would be no need to administer the second initiation dose of PP on Day 8, which is otherwise needed to quickly elevate concentrations to therapeutic levels. This concept of not needing a Day 8 loading dose when switching to PP from other depot antipsychotics was illustrated through simulations using RLAI, which contains the active moiety of PP. Plasma concentrations were simulated with PP injection, 2 weeks after the last RLAI injection followed by monthly injections of PP. The results indicate that drug levels are maintained close to steady-state right after the switch. During the switch, neither the Day 8 injection nor oral supplementation is necessary. Thus this simple strategy of (a) Initiating PP instead of the regularly scheduled injection of the previous depot antipsychotic; and (b) Following up with monthly injections of PP, is considered to be both convenient and practical.

Conclusions: These PK simulation scenarios provide important guidance on PP dosing in patients previously treated with depot antipsychotics.

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Monica Simeoni Clinical and Genetic factors affecting Alzheimer's disease progression in subjects on stable acetylcholinesterase inhibitor therapy: a comparison between mechanistic and empirical disease progression modelling approaches

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Objectives: The objectives of the analysis were to compare empirical and mechanistic AD progression models based on subjects on stable Acetylcholinesterase inhibitors (AChEIs) therapy using an individual patient meta-analysis approach and to quantify the impact of MMSE, age, gender, and APOE ε4 status as covariates.

Methods: Longitudinal ADAS-Cog scores collected from 926 subjects with mild to moderate AD from the placebo arms of two 54-week clinical trials were included in the analysis. These studies investigate the effects on cognition and overall clinical response of rosiglitazone as adjunctive therapy to donepezil (REFLECT-2), or to galantamine, rivastigmine and donepezil (REFLECT-3) [1]

***Empirical Model*:** Two empirical modeling approaches were explored:

$$ADAS_{ij}=ADAS0_j+K_j\cdot t_{ij}-A_j\cdot(e^{-kelj\cdot tij}-e^{-Keqj\cdot tij})+e_{ij} \quad (1)$$

$$ADAS_{ij}=ADAS0_j+K_j\cdot t_{ij}-A_j\cdot(e^{-kelj\cdot tij}-1)+e_{ij} \quad (2)$$

$$ADAS_{ij}=ADAS0_j+K_j\cdot t_{ij}+e_{ij} \quad (3)$$

$$ADAS_{ij}=ADAS0_j\cdot e^{-\frac{tij}{lhj}}+K_j\cdot t_{ij}+e_{ij} \quad (4)$$

where: ADAS0 is ADAS-Cog at baseline, K_{el} and K_{eq} are the rate constant for the offset and onset rate of the placebo effect, A is the magnitude of the placebo effect, h is the time to response of placebo, ε is the residual error, i and j are the time and subject suffixes. One (Models 1, 2 and 3) characterized the ADAS-Cog longitudinal change from baseline with an additive placebo transient effect [2,3], while the other (Model 4) with a multiplicative placebo effect [4].

Mechanistic Model: Using a novel Disease System Analysis approach [5], the loss of cognitive functions (ADAS) can be described by:

$$dADAS/dt=kin-kout\cdot ADAS \quad (5)$$

$$kin=f(p_i,t,cov_j)$$

where: k_{in} is a time-dependent deterioration of ADAS-cog, p_i are parameters characterising the degenerative process, cov_j is a set of covariates and K_{out} is the first order constant characterizing the compensatory regulatory response by the homeostatic control systems.

Results: Model-fitting was performed using a population-analysis approach (NONMEM Version VI). Only Models (3), (4) and (5) always successfully converged. Model (5) with a linear time-varying disease progression rate (k_{in}) adequately fitted the data. The inclusion of covariates for K and k_{in} provided a statistically significant improvement in the data fitting.

Conclusions: Among the empirical models, model (4) better described AD progression in placebo-treated patients on stable AChEI therapy. A mechanistic model for AD fits the observed data as precisely as model (4). Baseline MMSE severity, Age, and APOE ε4 genotype were relevant predictors of AD progression. These findings support the mechanistic-modelling approach for AD as the reference for developing and implementing a disease-drug-trial model strategy.

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Monica Simeoni Disease System Analysis: Evaluate the structural properties and the physiological implications of an indirect physiologic response model describing the degenerative progression of Alzheimer's disease using a closed-form solution

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Objectives: In a previous communication [1] a novel Disease System Analysis approach has been proposed to describe the degenerative process in Alzheimer's disease (AD) and to account for drug action using indirect physiologic response models [2]. The objectives of the present effort were to derive a closed-form solution of this indirect-response model with a time-varying impairment of the cognitive function, and to evaluate the physiological implication of this mechanistic model.

Methods: ***Disease System Analysis***: The best performing mechanistic model was:

$$dADAS(t)/dt=kin(t)-kout(t)\cdot ADAS(t) \quad (1)$$

$$kin(t)=k0+k1\cdot t;\ kout(t)=kout;\ ADAS(0)=ADAS0$$

where: ADAS(t) is the time-varying level of cognitive function expressed by the cognitive portion of the AD Assessment Scale (ADAS-cog), ranging from 0 to 70, with higher scores indicating greater cognitive impairment, $k_{in}(t)$ is the time-varying impairment rate of ADAS(t), k0 is the deterioration rate of cognitive function at baseline, k1 is a constant characterising the time-varying rate describing the loss of cognition in patients with AD and kout is the first order constant controlling the compensatory regulatory response performed by homeostatic control systems.

Results: The closed-form solution of the equation (1) was derived using the Laplace transform method:

$$ADAS(t)=(k0/kout-k1/(kout^2))+(k1/kout)\cdot t+(ADAS0-k0/kout+ k1/(kout^2))\cdot exp(-kout\cdot t) \quad (2)$$

The analysis of the first derivative of equation (2) indicates that ADAS(t) will be monotonically increasing (impairment in cognitive functions) when:

$$ADAS0<k0/kout$$

This relationship discriminates subjects with a transient improvement on cognitive degenerative process (for which this relation does not hold) from subjects where the process is purely degenerative. The degenerative process occurs when the ratio between the loss of cognition (k_{in}) and the homeostatic

controlling process (k_{out}) becomes greater than the current disease status (ADAS0) and the system is no longer able to compensate for the natural fluctuations in cognitive functioning.

When k0=k1/kout, the model takes the reduced form:

$$ADAS(t)=k1/kout\cdot t+ADAS0\cdot\exp(-kout\cdot t) \quad (4)$$

a simplified empirical model to describe AD progression [3].

Conclusions: An explicit solution of the indirect-response model with a time-varying impairment of cognitive function was derived. This equation was used to evaluate the physiological meaning of the model parameters and for discriminating subjects with a transient improvement on cognitive degenerative process from subjects where the process is purely degenerative.

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Armel Stockis Exposure-response modeling of daily seizure counts in focal epilepsy trials

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Objectives: To describe the change from baseline in individual seizure occurrences after treatment with brivaracetam or placebo in adjunctive treatment of focal epilepsy, and to establish an exposure-response relationship.

Methods: Individual daily seizure records were obtained from 1580 patients having participated in 5 brivaracetam double-blind, placebo-controlled trials: Four studies had a fixed dose parallel-group design and one had a flexible dose (optional titration) design. Individual plasma exposures were derived from a population PK model. Seizure probability was modeled on the log scale with NONMEM VI using statistical distributions appropriate for count data (Poisson, inverse binomial, with or without zero inflation, with or without Markovian feature) and was expressed as a function of baseline, placebo, dose or exposure, and subject-specific random effects.

Results: Inter-individual variability was implemented for baseline, placebo and Emax but not for ED50. Emax was allowed to take negative (improving patients) or positive values (deteriorating patients). The final model described the probability of seizure as a zero-inflated negative binomial distribution with between-patient variability on the zero inflation fraction and with Markovian feature. The latter allowed for a different seizure probability depending on whether the preceding day had seizures or not. Compared to the basic Poisson model, this model resulted in a drop of ~29,000 units in the Objective Function Value. Replacing the doses by individual exposures (AUCt or trough concentration) did not improve the goodness of fit.

The model was initially developed using the four fixed dose studies while the flexible dose study was used as external validation data set. Simulations showed that data of this type could be described well, even though the actual dose titration strategy based on clinical judgment could only be approximated. Analysis of the full data set including the flexible dose study resulted in model estimates that were clearly capable of describing the observed clinical endpoints, as demonstrated using visual predictive checks.

Conclusions: An exposure-response relationship was demonstrated with brivaracetam in patients with uncontrolled focal seizures. The daily count model provided superior goodness of fit due to its more detailed statistical structure and provided enhanced flexibility due to its ability to incorporate day-to-day changes in dose and covariates even in flexible dose designs.

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Mita Thapar Population Pharmacokinetics of Safinamide and its Effect on Disease Progression in Parkinson's Disease

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Background: Safinamide (SAF), a first-in-class agent in Parkinson's disease (PD), is an α-aminoamide derivative with dopaminergic and non-dopaminergic mechanisms of action in development as an add-on therapy to a dopamine agonist or l-dopa.

Objectives: To describe the population pharmacokinetics (PPK) of SAF and its effect on clinical endpoint (ON-time including minor dyskinesia) to develop a disease progression (DP) model.

Methods: The PPK model was developed using concentration-time data from two Phase 3 studies:

1. 177 PD patients on a single dopamine agonist and 50-200mg/day of SAF (1099 SAF concentrations)
2. 446 PD patients with motor fluctuations on stable l-dopa dose and 50 or 100mg/day of SAF (1620 SAF concentrations).

The DP model was based on ON-time values from 668 patients in Study 2 (SAF or placebo arms; 3603 ON-time scores). ON-time was modelled as a linear function of time with baseline ON-time, intercept (INT; effect with onset before the 1st post-dose visit at 4 weeks) and slope (SLOP) parameters, modelling the effect of steady-state SAF exposure/dose as covariate. The tested covariates were weight, age, gender, creatinine clearance, (change in) l-dopa dose and SAF exposure. Nonlinear mixed-effects modelling with NONMEM 6.2 (FOCEI method) was used. Final models were evaluated using predictive check simulations (VPC and PC-VPC) and bootstrap analysis.

Results: PPK: A linear 1 compartment model with 1st order absorption described the data well. CL/F, Vd/F and KA (95% CI) were 4.96 (4.73-5.21) L/h, 166 (158-174) L and 0.582 (0.335-0.829) h^{-1}, respectively, all estimated with good precision (RSE <22%). CL/F and Vd/F were allometrically related to weight (power 0.75 and 1, respectively). The inter-individual variability (IIV) was low (<30%).

DP: INT was 0.73 (0.51-0.94) h for SAF, 0 for placebo; SLOP was 0.117 (0.078-0.156) h/month, non differentiable between SAF and placebo. RSE was low (<17%). IIV was 304% for SLOP and 249% for INT. Refined modelling using SAF exposure as covariate on INT and SLOP was unsuccessful.

Conclusions: The models adequately describe the PPK of SAF and its effect on ON-time. SAF resulted in a typical ON-time increase of 0.73 h. High IIV in the model parameters and the limited duration of the study (in relation to persistence of placebo effect) prevented differentiation of the various SAF doses with respect to ON-time. Age, gender, renal function and l-dopa dose did not influence the PK and pharmacodynamics of SAF, suggesting dose adjustments are not required in a broad population.

Pyry Välitalo Plasma and Cerebrospinal Fluid Pharmacokinetics of Naproxen in Children

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Objectives: There has recently been interest in the mechanism of action of NSAIDs in CNS. We evaluated the cerebrospinal fluid (CSF) penetration of naproxen in children undergoing lower body surgery in spinal anaesthesia. Also, while there have been studies of naproxen pharmacokinetics in children, none of the studies have investigated the pharmacokinetics of naproxen in children younger than 5 years [1]. We estimated the pharmacokinetics of naproxen in 51 children aged 3 months to 13 years.

Methods: 53 children were enrolled in the study. The children received 10 mg/kg dose of oral naproxen suspension. 270 total plasma concentrations, 52 unbound plasma concentrations and 52 CSF concentrations were analyzed and included in the data. Modeling was performed with NONMEM VI 2.0 and PsN 2.3.2 [2]. To describe the distribution and accumulation of naproxen into CSF, an intercompartmental clearance QCSF and an uptake factor UPTK were estimated. The case-deletion diagnostics feature of PsN was used to detect potential outliers in the dataset.

Results: The plasma data were best described with a 2-compartmental model with first-order absorption. Some individuals had remarkably low concentrations of naproxen. Case-deletion diagnostics identified two individuals with Cook score >1 and covariance ratio
Bodyweight predicted plasma clearance of naproxen linearly (with an exponent of 1), and age did not seem to affect the clearance after weight had been included as a covariate. When scaled to 70kg, the apparent clearance of naproxen was 0.59 l/h and the apparent volumes of distribution were 7.4 l and 4.4 l for central and peripheral volumes, respectively.
The CSF uptake factor UPTK was 7.8 (20 % RSE). The fraction of unbound naproxen in plasma was 0.14% (7.9 % RSE).

Conclusions: The concentrations of naproxen in CSF are markedly greater than the concentrations of unbound naproxen in plasma. This is probably a result of protein binding in CSF, and is typical for lipophilic drugs with high protein binding [3].

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Marcel van den Broek Optimal dosing of lidocaine for seizure control in preterm and term neonates using population pharmacokinetic modelling and simulation

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Objectives: Lidocaine is widely used around the world for different indications. It has anaesthetic, sedative, antiarrhythmic and anticonvulsive properties. The exact mechanism of its anticonvulsive effect is unknown. It is administered to neonates that are not responding to first-line anticonvulsant therapy, such as phenobarbitone. Since lidocaine also has antiarrhythmic properties, therapeutic drug monitoring (TDM) is considered useful to prevent the occurrence of cardiac arrhythmias, mainly in the form of bradycardia, although a therapeutic window for its anticonvulsant action has never been fully established. For term neonates a dosing regimen has been developed. However, this regimen was not evaluated for preterm neonates [1]. Lidocaine pharmacokinetics (PK) may be different in preterm neonates because of differences in maturation of metabolic enzymes and body size [2]. The objective of this study was to develop an optimal dosing strategy for lidocaine in preterm and term neonates using population PK modelling and simulation.

Methods: Pharmacokinetic data were available of term and preterm neonates admitted to the neonatal intensive care unit (NICU) that were treated with lidocaine intravenously. After completion of the loading dose and during the maintenance dose, blood samples were collected using an arterial line to determine efficacy and/or toxicity. Lidocaine plasma concentrations were measured in plasma using a fluorescence polarization immunoassay (FPIA). The PK-analysis was performed using NONMEM 6.2 using FOCE-I. The log-likelihood ratio test was used to discriminate between hierarchical models, based on the objective function value (OFV). Goodness-of-fit plots were used for diagnostic purposes. The influence of body size (body weight, WT) and maturation (gestational age, GA, and postnatal age, PNA) was assessed. The bootstrap re-sampling method (n=1000) was used for model evaluation. Distribution of the bootstrap parameter estimates were compared to parameter estimates of the original data set. Simulations were used to establish optimal lidocaine dosing strategies for preterm and term neonates. Several requirements for this dosing strategy were defined:

1. The dosing strategy should be easy to implement on a NICU and insensitive to calculation errors, therefore, dosing per kg WT was preferred; 2. Seizures require rapid intervention, therefore an initial bolus dose should be administered followed by an infusion during 4 hours; 3. Seizure control requires only a short duration of dosing, however, doses should be reduced slowly to decrease the occurrence of neurological withdrawal symptoms; 4. Although a therapeutic window for lidocaine for neonatal seizure control has not been established, neonatologists regularly use a target plasma concentration (at the end of the 4-hour infusion) of 6 to 7 mg/L. Lidocaine plasma concentration of >9 mg/L have been

associated with increased risk for cardiac arrhythmias and should therefore be avoided. However, these findings are based on studies in a cardiological setting [3].

Results:

Model development

A total of 163 plasma concentrations from 48 neonates (WT 0.84-4.46 kg, GA 25.0-42.7 weeks) that received lidocaine were obtained. All neonates received lidocaine within 10 days after birth (PNA 0-10 days). 38% had a GA of less than 34 weeks (i.e. premature). A one-compartmental PK model was selected. As expected, body size (WT) and age (GA and PNA) were closely related. The effects of body size (allometry) and GA/PNA (maturation) on PK could therefore not be described independently. Both effects were captured by the significant relationship between WT and clearance (CL) and distribution volume (V) using: $CL = \theta_1 * (WT/3)^{**}alpha$ and $V = \theta_2 * (WT/3)^{**}beta$. Parameter estimates were $\theta_1 = 1.41$ L/h (RSE 7.87%) and $\theta_2 = 8.95$ L (RSE 4.13%). The allometric power coefficients (alpha and beta) were estimated at 1.32 (RSE 13.5%) and 1.13 (RSE 5.50%), respectively. Interindividual variability (IIV) on CL and V was 49.4% (CV14.2%) and 19.4% (CV 23.1%), respectively. Values obtained by bootstrapping were very close to the typical values and parameter precision was adequate for all PK-parameters.

Simulations

We developed a new infusion strategy based on simulations. Our strategy consisted of an initial bolus of 2 mg/kg (for all weight categories, to allow rapid administration within the NICU) in 10 minutes, followed by a body weight (WT) based infusion during 4 hours, with different doses for the different weight categories. After the 4-hour infusion, a first dose reduction is applied which is half of the loading infusion rate for 6 hours. Then a second dose reduction is applied. Again, this is half of the previous infusion rate, but now for 12 hours. The selected optimal dosing regimen is displayed in Table 1.

Table 1. Optimal dosing regimen based on simulations

Body weight (kg)	Initial bolus	Infusion (during 4h)	First dose reduction (during 6h)	Second dose reduction (during 12h)
0.8 - 1.5	2 mg/kg in 10 minutes	5 mg/kg/h	2.5 mg/kg/h	1.25 mg/kg/h
1.6 - 2.5		6 mg/kg/h	3 mg/kg/h	1.5 mg/kg/h
2.6 - 3.5		6.5 mg/kg/h	3.25 mg/kg/h	1.625 mg/kg/h
3.6 - 4.5		7 mg/kg/h	3.5 mg/kg/h	1.75 mg/kg/h

With this dosing regimen, the median concentration achieved at the end of the 4-hour infusion was 6.4 mg/L (IQR 5.5 - 7.3). At this moment only 3.8% of the simulated individuals had a concentration above 9.0 mg/L (median 9.5 mg/L, IQR 9.2-9.9). One hour later only 2.5% still had a concentration above 9.0 mg/L (median 9.4 mg/L). The initial bolus resulted in a median concentration of 0.68 mg/L (IQR 0.59 - 0.78). Results were comparable for the different body weight categories.

Conclusions: The effects of body size and maturation on the pharmacokinetics of lidocaine in this population could not be estimated separately. Therefore, bodysize (body weight) was the only significant covariate remaining in the PK model. Estimates of the allometric power coefficient were higher than 1, strongly suggesting an effect of both maturation and body size. Therefore, extrapolation with the current model beyond conditions on which the model was developed will need further validation. Based on the PK model, a dosing strategy for lidocaine for neonatal seizure control within the first 10 days after birth has been developed, which allows rapid and safe administration of lidocaine in this population. With this strategy routinely TDM would not be necessary anymore and would only be advised in case of (suspected) toxicity. This dosing strategy will be implemented on the NICU, which will allow prospective validation of this study

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Anders Viberg Using an Innovative Design in Behavioural Pharmacology Studies Saves Money and Animal Lives

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Objectives: Results from pre-clinical efficacy studies are of importance for many decisions in drug development. Being used to estimate active concentrations in the biophase in man, these results have a direct impact on the evaluation of toxicology and Phase I results and they are also an aid in dose setting in Phase II studies. Typically, pre-clinical studies in analgesia consist of at least three different studies; dose-finding, effect-duration and tolerance development studies. In typical behavioural models, the exposure is measured in a parallel group of animals, which may compromise the precision in describing PKPD relationships. The objective of this study was to investigate if pre-clinical analgesic studies in rats could be more effectively performed using sparse PK sampling in the PD tested animals and thereafter evaluate the results using a population approach.

Methods: A refined dosing strategy was developed and applied for drug X in the rat Chung heat hyperalgesia model. PD measurements were done on day 1, 3 and 5. Two PK samples per day were taken in day 2 and 4. In a separate group PD measurements were done on rats without PK samples taken. Data was analyzed using a population approach in NONMEM.

Results: The animals with PK sampling had the same therapeutic response as the animals without PK sampling. A direct concentration-effect relationship with good precision could be established and no tolerance development was observed. When comparing the new design with to the old design, substantial savings was done. The number of animals was reduced with 44% and the number of working hours in the lab was reduced with 63%.

Conclusions: The new suggested design makes substantial savings in both animal lives and money. Moreover, the exposure response relationship was described with higher statistical precision compared to using the old design.

Stefano Zamuner The assessment of convulsion risk: a translational PK/PD modelling approach

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Objectives: Among the different central effects monitored during preclinical safety studies, convulsions are the one of the most concerning. After the preclinical characterization, the therapeutic window to be used for convulsions in the subsequent clinical development is typically obtained applying a multiplicative factor (e.g., 10 or 100-fold) to the no adverse event level [1]. This introduces a substantial level of subjectivity in the definition of the convulsion risk. A more thorough interpretation of the convulsion findings in preclinical experiments is recommended to define the safety margin to be applied in humans. In particular, the risk assessment should be more appropriately based on the level of systemic exposure, rather than dose, after having identified the most relevant pharmacokinetic parameters and metrics (e.g., Cmax, AUC) [1].

The objective of this communication is to propose a logistic model to assess the relationship between plasma concentrations and the probability of convulsions observed in preclinical studies and predict the risk for humans.

Methods: The non-clinical convulsion data obtained in different animal species for a compound under development were evaluated using nonlinear mixed effect models with the aid of NONMEM. A logistic model was developed, exploring the potential role of compound plasma concentrations, free fraction in plasma, species (mouse, rat and dog) and gender as independent variables. Model selection was based on statistical tests (Wald Test and Likelihood Ratio Test) and diagnostic plots such as Visual Predictive checks (VPCs) for categorical data [2].

Results: A statistically significant log-linear relationship was observed between total plasma concentrations and the probability of convulsion. Species was identified as statistically significant predictor. According to the model, it was estimated that the risk of human convulsion at the plasma concentrations anticipated to be associated to therapeutic benefit was less than 0.01%.

Conclusions: For the characterization of the convulsion findings, relevant metrics/parameters of exposure should be selected based on a thorough evaluation of the toxicokinetic data. Based on this and on the proposed PK-PD approach, an objective assessment of the hazard can be made, leading to a more robust definition of the safety margin to be applied in the subsequent clinical development.

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Hesham Al-Sallami A rationale for the routine monitoring of anti-activated factor X (anti-Xa) during enoxaparin treatment

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Objectives: Enoxaparin is a low molecular weight heparin (LMWH) used in the treatment of thrombosis. Unlike unfractionated heparin (UFH), no routine monitoring of plasma activity is recommended for enoxaparin treatment. The activity of enoxaparin in plasma is determined by assaying anti-activated factor X (anti-Xa). The aim of this study is (1) To identify an anti-Xa treatment target for enoxaparin. (2) To determine whether routine monitoring of anti-Xa concentrations in patients receiving enoxaparin treatment is warranted.

Methods: From a cohort study (Motalescot, 2004) and through a meta-analysis of a randomised controlled trial (Barras, 2008), a target peak and trough anti-Xa concentration was obtained. Based on this target, and using a two-compartment PK model for enoxaparin, 10000 virtual patients were simulated with a dosing regimen of 1 mg/kg total body weight twice daily. Patients with creatinine clearance < 30 mL/min were excluded. Activated partial thromboplastin times (aPTTs) were also simulated for UFH when it was given as a constant infusion at 1500 units/hour assuming a Michaelis-Menton PK model with an empirical PD model linking concentration to aPTT.

Results: The target anti-Xa concentration of enoxaparin for effectiveness and safety was 5 mg/L. Twice daily dosing regimens that achieve this target have peak concentrations that exceed 5 mg/L and trough concentrations that fall below 5 mg/L. Based on this target, 46% of patients had peak or trough concentrations outside the proposed target. This figure was comparable to the UFH heparin model where 52% of patients had an aPTT outside the target range (1.5-2.5 x initial aPTT).

Conclusions: Based on the current dosing practice for enoxaparin only 54% of patients are dosed optimally. This success rate is as poor as with UFH. Given that monitoring PD endpoints is strongly recommended with UFH, it follows that the same approach should also apply for enoxaparin and probably should be generalised to all LMWHs.

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Anna-Karin Hamberg Internal and external evaluation of a K-PD model for warfarin using prediction corrected visual predictive check (PC-VPC)

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Objectives: To evaluate the performance of a warfarin K-PD model using PC-VPCs in both an internal [1] and [2] external dataset.

Background: Warfarin therapy is challenging due to its narrow therapeutic range and pronounced variability in individual dose requirements. Variability in both PD and PK contribute to the more than 20-fold difference in maintenance dose. We have developed a population model for the relationship between warfarin dose and anticoagulant response (INR) using data from a Swedish study with patients starting on warfarin (n=1426) [1]. The model includes age and genetic variations in CYP2C9 and VKORC1 as covariates, and together these factors explain more than a 10-fold difference in dose. Visual predictive checks (VPCs) are rapidly becoming an important diagnostic tool for model evaluation [3]. A prediction corrected VPC (PC-VPC) is an adaptation of the standard VPC, which is more suited for data collected in studies with adaptive design [4], as for warfarin where the dose is individually adjusted based on anticoagulant response.

Methods: The final model and parameter estimates obtained from the analyses of the Swedish study [1] were used in the internal and external model evaluation. PC-VPCs were constructed with median, 5th and 95th percentiles for the observed data. Model predictions were based on 100 simulated datasets and presented as non-parametric 95% confidence intervals for the median, 5th and 95th percentiles. The procedure was repeated on an external dataset derived from a British study of patients starting warfarin therapy.

Results: The PC-VPCs based on internal data did not indicate any major differences between observations and model predictions. Preliminary results suggest that the model was not able to describe the external dataset appropriately.

Conclusions: Preliminary results suggest a difference in the dose-response relationship for warfarin between Swedish and British patients. Reasons for this may for example be differences in INR methods, demographics, compliance patterns, and/or vitamin K intake between the two countries.

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Anne Chain Not-in trial simulation : Prospective use of Not-In-Trial Simulation

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Objectives: Previously, the concept of Not-In-Trial Simulation model was introduced to describe QTc in a real life cohort using a model-based approach [1]. The model consisted of QTc = age-dep. baseline value + drug effects + effects from comorbidities and co medications. In this model, however, variability descriptors were not included which are required to enable prospective use of such a tool in drug development. The aim of this study is to further evaluate the variability associated with age and to explore the interactions with other covariates.

Methods: The relationship between age and baseline QTc observations was modelled using NONMEM VI. The age-effect model was created with healthy subjects and patients without comorbidities and comedications. An interaction model was created by including patient data with comorbidities and comedications. Model comparisons were made using objective functions with the criteria of p=0.05 while model performance was tested using diagnostic plots, VPCs and NPDEs. After model completion, we used a QT-prolonging drug (d,l-sotalol) to mimic a drug development scenario, which was previously modelled according to a two- comp. model with weight on the clearance. Drug-induced QT-prolongation was added to the underlying effect of the covariates.

Results: The QTc vs. age relationship is described by a linear model. Gender, arrhythmia, myocardial infarction, diabetes and heart failure are found to be covariates to the intercept of the relationship. Diabetes and heart failure also are found to be covariates on the slope of the equation. Simulations from the improved Not-In-Trial tool confirm greater effects from comorbidities and comedications than the drug-induced QTc prolongation.

Conclusions: Age-effects play an important role in QTc observations in clinical trials and real life cohort irrespective of drug treatment. This study shows that baseline QTc values are also dependent on the various health conditions. In contrast to the current implementation of TQT trials, the assessment of the cardiovascular liability must take into account those factors to accurately describe individual patient risk under therapy in real life conditions.

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Carolyn Coulter Prediction of Torsades de Pointes from QT interval: analysis of a case series with amisulpride

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Background and objectives: Torsades de Pointes (TdP) is a potentially fatal ventricular arrhythmia that is associated with a drug-induced QT prolongation[1]. Despite numerous methods to assess the risk of TdP based on the presence of QT prolongation few studies have investigated the importance of the magnitude of QT prolongation and the risk of TdP. In addition, previous studies have generally provided data on a wide spectrum of drugs and therefore confound the causal relationship of the magnitude of QT interval prolongation with the inherent cardiotoxicity of the drug. The objective of this study was to assess whether the magnitude of QT prolongation is a better predictor of TdP than dose alone in a series of amisulpride poisonings[2].

Methods: The study included 457 ECGs from 86 patients with amisulpride overdoses who ingested a median dose of 6 g (range: 1.2 g to 120 g). The QT interval was manually measured on each ECG using a standardised method. The QT interval was measured in 3 chest and 3 limb leads and the median was calculated[3]. For cases of TdP the longest QT interval was chosen that occurred prior to the episode of TdP, and for controls the longest QT interval was selected over the entire admission period. For each ECG the following measurements of QT were used: the absolute QT, corrected QT values using Bazett's formula [QTcB][4] and Fredericia's formula [QTcF][5], and the orthogonal QT interval defined as the shortest distance of the QT-HR [HR = heart rate] pair from the "at risk" line on the QT-nomogram[6], termed orthogonal distance (OD). Logistic regression using NONMEM (version 6) was performed to investigate the association between dose, RR interval, and the various measurements of the QT interval, on the probability of TdP.

Results: TdP occured in 8 (9.3%) of the patients. The dose of amisulpride in these patients ranged from 4g to 80g. Both dose and RR interval improved the prediction of TdP over and above simply the presence of a prolonged QT interval. All four QT measures, the absolute QT, QTcB, QTcF, and OD, were superior to both dose and HR interval. No metric proved superior than any other. Conclusions: For all QT measures, QT, QTcB, QTcF, and OD, the extent of the prolongation was a useful predictor of TdP compared to dose. The different QT measures were indistinguishable from each other.

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Vincent Dubois Translation of drug-induced QTc prolongation in early drug development.

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Objectives: Assessment of the propensity of non-antiarrhythmic drugs in prolonging QT/QTc interval is critical for the progression of compounds into clinical development. Given the similarities in QTc response between dogs and humans, dogs are often used in pre-clinical CV safety studies [1]. However, it's unclear how the changes in QTc interval in dogs can be translated into risk of QTc prolongation in humans. We suggest the use of Bayesian hierarchical modelling taking into account the concentration-effect (PKPD) relationship to predict drug effects in terms of the probability associated with QTc prolongation. The objective of our investigation was to characterise the PKPD relationships and translational gaps across species following the administration of three compounds with known QT-prolonging effects.

Methods: Pharmacokinetic and pharmacodynamic data from experiments in conscious dogs and clinical trials following administration of moxifloxacin, d,l-sotalol and cisapride were used. First, pharmacokinetic models were developed in NONMEM VI v2.0 to derive drug concentrations at the time of each QT measurement. The PKPD model used to describe QT prolongation was based on a previous analysis of sotalol data by Krudys et al[2]. A threshold of >10msec was used to explore the probability of prolongation following drug administration. The relevance of a model-based approach is further illustrated by simulations using preclinical parameter estimates to predict drug effect in humans following administration of the three compounds. PKPD modelling was performed using WinBUGS v1.4.3.

Results: Preliminary results from experiments in a limited number of animals suggest that PKPD relationships in the dog are predictive of the risk for QTc prolongation in humans. Probability curves based on dog data showed that QTc prolongation >10 msec could be predicted for drug concentrations associated with therapeutic dose range in humans.

Conclusions:: The liability for QTc prolongation can be expressed in terms of the probability associated with an increase >10 msec. This allows direct comparison between pre-clinical and clinical data. These findings also indicate that PKPD parameter estimates in conscious dogs may be used as basis for the prediction of drug-induced QTc prolongation in humans. However, characterisation of pharmacokinetics and protein binding in both species is critical for the assessment and interpretation of the actual risk in humans.

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Anne-Kristina Frobel Physiologically-Based Pharmacokinetic (PBPK) Modelling of Bisoprolol in Adults and Children and External Model Validation in a Paediatric Clinical Trial

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Objectives: Although beta-adrenoceptor-blockers have been proven to reduce morbidity and mortality in adult congestive heart failure, there is not enough evidence to recommend or discourage their use in children; neither is sufficient pharmacokinetic data available (Frobel et al. 2008). The aim of our work was therefore to investigate the pharmacokinetics of the beta-1-selective beta-blocker bisoprolol creating both a PBPK model and clinical data in order to provide scientific grounds for dosing in future clinical trials..

Methods: A PBPK model for bisoprolol in adults was created using PK-Sim® software. Main elimination pathways were glomerular filtration and hepatic metabolism via CYP3A4. The model was fitted to adult pharmacokinetic profiles from literature and was then shown to represent healthy volunteer profiles created in our research group. The PK-Sim® clearance scaling module was then used to adapt bisoprolol clearance to age, and pharmacokinetics were predicted for virtual paediatric populations covering the age range from newborns to 18-year-olds. Pharmacokinetic parameters were analysed for different paediatric age groups. We then conducted a clinical trial at Duesseldorf and Hamburg university hospital investigating the pharmacokinetics of bisoprolol in children in order to create experimental data for model validation.

Results: The PBPK-model adaequately described the pharmacokinetics of bisoprolol in adults. Clearance scaling predicted dynamic changes of total bisoprolol clearance over age compared to adult values with a minimum body-weight normalised clearance in the newborns and a maximum in the one- to four-year-old. These predictions for virtual populations will now be compared to pharmakokinetic profiles in “real” paediatric patients (clinical trial ongoing at time of abstract submission).

Conclusions: We present a PBPK model for bisoprolol in adults representing literature as well as own experimental data. This model was adapted to age-dependent changes in physiology and was used to predict bisoprolol pharmacokinetics in paediatric populations. These predictions are currently evaluated in a clinical pharmacokinetic trial. The results of our work may contribute to establish rational dosing in future paediatric trials investigating bisoprolol in children.

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Florence Hourcade-Potelleret Preliminary Population PK-PD of Dalcetrapib: an Agent Targeting CETP to Raise HDL-C and Prevent Cardiovascular Morbidity and Mortality

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Background: In a meta-analysis, after 1 year of statin treatment, a 23% reduction in the incidence of 1st major coronary events was observed per mmol/L reduction in LDL-C.[1] However, despite standard of care, substantial residual cardiovascular (CV) risk remains. A strategy to further decrease CV risk is to increase HDL-C levels, by reducing activity of cholesteryl ester transfer protein (CETP). Dalcetrapib effectively decreased CETP activity, increased HDL-C, and was generally well tolerated in Phase II studies; the dal-OUTCOMES study to assess the effect of dalcetrapib on CV outcomes is ongoing.

Objectives: A PK-PD analysis to characterize the effect of exposure to dalcetrapib on levels of HDL-C as a function of CETP activity.

Methods: Data were obtained from a phase II randomized study in which patients received dalcetrapib 300, 600 or 900 mg/day or placebo, in combination with pravastatin 40 mg for 12 weeks (84 days). PK evaluations were performed on trough samples (before dosing) on days 14, 28, 56, 81 and between 1.5-5 hours post-dose on day 84. HDL-C levels and CETP activity were measured in trough samples during pre-randomization, on days 0 (baseline), 14, 28, 56 and 84, and at follow-up on day 112. A population PK-PD analysis was performed using NONMEM VI and a sequential PK-PD approach. First, a model describing the cascade of events i.e. dose-exposure-CETP activity-HDL-C was developed. Thereafter, a simplified model of dose-exposure-HDL-C was developed to investigate if change in HDL-C level could be predicted directly from drug exposure data.

Results: An effect compartment model was used to describe the drug exposure-CETP activity relationship. The relationship between CETP activity and HDL-C level was described using an indirect type II ‘turnover' model incorporating an inhibition Emax model with a baseline. The relationship between drug exposure and HDL-C (omitting CETP) was also described using an indirect type II ‘turnover' model incorporating an inhibition Emax model with a baseline. Full covariate analysis was not performed. The diagnostic plots and posterior predictive check showed that both models described the data adequately.

Conclusions: Using the empirical models described here, exposure data can be used to predict CETP activity decreases and HDL-C increases caused by dalcetrapib treatment. The model describing HDL-C as a function of exposure could be used to describe dalcetrapib-induced HDL-C changes where CETP activity is not measured.

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Sergej Ramusovic An integrated whole-body physiology based pharmacokinetic/pharmacodynamic model of enalapril and the RAA-system

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Objectives: Integrated physiology based (PB) modelling could provide comprehensive platforms to simulate the mechanistic interactions between the pharmakokinetic and pharmacodynamic behavior of a drug. Here, we built a physiology based model of intravenous enalaprilate (Enaat) and oral enalapril (Ena) application to study their effect the RAA-system.

Methods: First, a PBPK model of Ena and its conversion metabolite enalaprilate (Enaat) was developed in PK-SIM (v. 4.1, BTS) and the software MoBi (v. 2.2, BTS). Then, using MoBi, the pharmacodynamic RAA-system model (PD) was built. In both models literature data on biomarker concentrations, enzymatic and drug specific parameters were used. Missing parameters were obtained by fitting procedures using MATLAB (v. R2008b). Resulting PK and PD models were merged in MoBi. The final model then served as the basis for simulations and comparison to literature data.

Results: The final model encompasses hepatic/intrarenal conversion of Ena to Enaat, Enaat binding to ACE, urinary excretion of Ena and Enaat, generation and degradation of RAA components including angiotensin (Ang)1, Ang2, renin and the negative feedback of Ang2 on renin production. The simulations (Sim) provide a description of the literature data on plasma concentration time profiles of Ena and Enaat [1,2], their fractional urinary excretion after intravenous (Enaat: after 1440 min 86.65% Sim, 85.5 ±13.5% data [3]) and oral application (Ena: 24.29% after 4320 min Sim, 19.87% data; Enaat: 34.37% after 4320 min Sim, 30.41% data [4]) as well as Ang1 and Ang2 concentrations [5] after oral Ena application.

Conclusions: Coupling a PB model of Ena pharmacokinetics and a PB pharmacodynamic model of the RAA-system, we were able to develop an integrated whole body PBPKPD model of intravenous Ennat and oral Ena application that describes plasma concentrations of Ena, Enaat, Ang1 and Ang2 as well as urinary excretion data of Ena and Enaat. The modular nature of this model allows for expansion to other drugs and further investigation of PBPK and PBPD relationships.

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Anna Largajolli Assessment of the oral glucose minimal model by nonlinear mixed-effects approaches

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Objectives: The oral minimal model (OMM) coupled with a parametric model of Ra, the piecewise linear model (PLM) (1), has been proposed and validated to estimate, at individual level, the rate of appearance of glucose (Ra) and the insulin sensitivity (SI) from plasma glucose and insulin concentrations measured after an oral glucose perturbation. The current study aims at investigating the performance of the nonlinear mixed-effects modeling to the OMM.

Methods: Population modeling was performed using a dataset comprising 50 normal subject (20 males and 30 females, age 47.42±24.7, body weight 69.72±10.6 Kg) who received a triple tracer mixed meal (10 kcal/kg, 45% carbohydrate, 15% protein, and 40% fat) containing 1 ± 0.02 g/kg glucose. The plasma samples were collected at -120, -30, -20, -10, 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240, 260, 280, 300, 360, 420 minutes. The OMM coupled with the Ra PLM was used for identification of [SI, p2, α1, α2, α3, α4, α5, α6, α7] where α1,...,α7 are the PLM parameters, and p2 is the insulin action. First, individual parameters were estimated using SAAM II (2) and, from these values, population parameters were obtained with the Standard Two-Stage method (STS). This approach provided the individual results considered as reference (REF) for further comparisons. After, the model was implemented and identified in NONMEM by using the FO Conditional Estimation (FOCE) INTERACTION since it has been proved suitable for a similar model (3). The population parameter distribution was assumed lognormal, BSV was modeled with a diagonal covariance matrix, proportional error structure was assumed and the scale parameter for the residual unknown variability (RUV) was optimized along with the other fixed effects. was assumed to be normally distributed with mean 0.11 and variance 0.011. Parameter uncertainty was assessed with a non parametric bootstrap (200 repetitions).

Results: Population estimates of SI were very similar for FOCE and REF (8.45 10-4 vs 8.52 10-4 min-1 per μU/ml respectively), whereas the FOCE estimate of SI variability was smaller than REF (2.22 10-7 vs 2.35 10-7). However, overestimation of BSV has been previously reported for STS (4). At individual level, the FOCE individual estimates of SI are also well correlated with the REF values (r2=0.99). We also detected high correlations among the REF and FOCE individual estimates of the parameters of PLM (average r2 = 0.92). Similar agreement we also found with both population and individual estimates of p2. In addition, to investigate the discrepancy in the goodness of fit provided by the reference model and that obtained with population modeling, we compared the residual sum of squares of each subject via linear regression. The high correlation that we obtained (r2=0.93) indicates that the two approaches provide comparable goodness of fit at individual level. .

Conclusions: These results show that the population approach to the OMM parameter estimation is consistent with the already validated individual approach. This paves the way for further exploration of

the application of population analysis methods in the context of an information-rich protocol like the meal glucose tolerance test.

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Elba Romero Development of a mechanistic-based pharmacodynamic model to describe the effect of a prolonged administration of a GnRH agonist on testosterone levels

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Objectives: The implementation of PD models to characterize specific processes between drug administration and its effect, are now substantially explored in order to describe the behavior of receptor mediated drug effects. To analyze the performance on the pharmacodynamic (PD) of an agonist, we developed a receptor-mechanism-based PD model able to describe the changes in testosterone concentrations observed after prolonged exposure of a GnRH agonist.

Methods: Pharmacokinetic profiles in order to develop the PD model were simulated from Bayesian predictions parameters previously reported [1]. Structural design of model was developed using the Systems Dynamics framework that combines the power of differential equations with a graphical design and representation of the variables [2]. The model and initial parameters estimates were developed and simulated in the VENSIM (Ventana Systems, Inc., MA, United States.) computing environment.The effect-versus-time data were evaluated during the analysis by the program NONMEM v7. The designed model was compared against models previously described in literature [3]. Performance evaluation between models was done by the exploration of visual predictive check and other statistical evaluation tools [4].

Results: The presence of the agonist in the developed model is responsible of the fractional receptor occupancy increase (R*/RT), enhancing testosterone levels (up-regulation) at the beginning of the treatment. This increase provokes in return a decrease in the number of total receptors. Therefore the number of active receptors drastically diminishes and reduces the synthesis of testosterone (down-regulation). The model includes a positive feedback loop, which is responsible of the recovery of the total receptors once the concentrations of the agonist were cleared from plasma. Such receptor recovery allows testosterone levels to return to homeostasis (recovery). Comparison between models revealed differences at the times of suppression and duration of the testosterone concentration needed to achieve castrate levels, recovering time of testosterone to homeostasis and type of recovery (linear, exponential).

Conclusions: A mechanism-based PD model was successfully developed allowing us to explore the influence of receptors occupancy and the the effect of a prolonged administration of a GnRH agonist on testosterone levels.

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Nicolas Azzopardi Pharmacokinetics and concentration-effect relationship of cetuximab in metastatic colorectal cancer

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Objectives: Cetuximab is a chimeric monoclonal antibody targeted against epidermal growth factor receptor (EGFR). The aim of our study was to identify factors influencing cetuximab pharmacokinetics and progression-free survival (PFS) in metastatic colorectal cancer (mCRC) patients treated by cetuximab combined with irinotecan and 5-fluorouracil.

Methods: One hundred and two mCRC patients were included in a multi-centric, non-comparative, open-label, phase II study. Cetuximab was administered as an infusion loading dose of 400 mg/m² followed by weekly infusions of 250 mg/m². Irinotecan dose was adjusted according to UGT1A1 genotype. Cetuximab concentrations were described using a two-compartment model with both first-order and saturable (Michaelis-Menten) elimination. A population approach was applied using MONOLIX 3.1. PFS was analyzed using a Cox model.

Results: A total of 1320 blood samples were available for analysis. Population values for pharmacokinetic parameters (between-subject variability, percent coefficient of variation) were: central volume of distribution (V1) = 3.05 L (3.8%), elimination clearance (CL) = 0.47 L/day (24%), peripheral volume of distribution (V2) = 4.41 L (6.1%), intercompartimental clearance (Q) = 0.88 L/day (-), maximum rate (Vmax) = 11.4 mg/day (1.3%) and Michaelis constant (Km) = 0.04 mg/L (-). The parameters V1, V2 and Vmax were influenced by body surface area (BSA). PFS was influenced by total dose/AUC at progression time ($p < 10\text{-}4$), irinotecan dose ($p = 0.03$) and tumour KRAS status ($p = 0.01$).

Conclusions: The pharmacokinetics of cetuximab was satisfactorily described using a model combining linear and nonlinear elimination rates. Irinotecan dose, KRAS status and cetuximab pharmacokinetics all influence clinical response to cetuximab.

Anne Drescher Pharmacokinetic/Pharmacodynamic Modeling of Platinum-DNA-Adduct Formation in Leukocytes after Oxaliplatin Infusion

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Objectives: The cytotoxic efficacy of platinum (Pt) complexes relies on their ability to bind to DNA, what in turn leads up to apoptosis [1]. Furthermore the unbound fraction of the Pt complexes is understood to be the active species [2]. The primary aim of this study was to describe the possible relationships between Pt pharmacokinetics and Pt-DNA adduct formation in leucocytes (WBC) in patients with solid tumours after administration of oxaliplatin.

Methods: Oxaliplatin was administered as a two hour infusion with doses of 50 mg/m² and 130 mg/m². Blood samples were drawn within the first two cycles of treatment. A total of 982 concentrations of ultrafiltrable Pt from 59 patients were measured using a validated GF-AAS method. Furthermore, Pt-DNA adducts were measured in 245 leukocyte samples from 37 patients by absorptive voltammetry. A sequential population PK/PD analysis was performed using NONMEM 6.2. Possible differences in the area under the adduct curve (AUA) between responders and non-responders were investigated by using the Mann-Whitney U-test. To proof selectivity and sensitivity of the chosen test scenario, a receiver-operating-characteristic (ROC) was generated.

Results: The PK of Pt in ultrafiltrated plasma after i.v. administration of oxaliplatin could be adequately described with a two-compartment model and resulted in parameter estimates similar to published data [1,2]. The significant covariate relationship of creatinine clearance to total Pt clearance only explained 6.7 % of inter-subject variability The relationship between the unbound platinum to platinum-DNA-adduct formation could be best described by a receptor-binding model. A former platinum-containing chemotherapy was found to be a significant covariate on the baseline Pt-DNA adduct. Using the model-predicted AUA a significant difference ($p < 0.01$) between responders and non-responders was found. Responders showed approximately three fold higher AUA values than non-responder.

Conclusions: Time course of the DNA platination could be successfully described with the developed PK/PD model. Exposure to oxaliplatin is, through DNA-adduct formation, the major determinant of tumour response in this population. Hence these results may contribute to therapy individualization and optimization with the aim to improve tumour response and reduce toxicity.

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Jeroen Elassaiss-Schaap Allometric scaling in oncology disease progression from xenograft tumor growth to human non-small-cell lung cancer

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Objectives: Derive an allometric conversion between published models on tumor volume of human cell lines in xenografts and on clinically observed tumor size growth in non-small lung cancer.
Y. Wang and colleagues reported in 2009 a disease progression model of tumor size in non-small-cell lung cancer (NSCLC) [1]. Their model was developed on a clinically relevant parameter, tumor size as the sum of longest dimensions as determined by CT scans. In contrast, the majority of preclinical experiments are performed on mouse xenograft implants with tumor growth in volume. A tumor volume growth inhibition model developed by Simeoni and Rochetti [2] is commonly applied in PK-PD analysis of newly discovered compounds. These two widely recognized approaches are however challenging to integrate. And yet inter-conversion is essential if one sets out to translate preclinical data in order to predict human efficacy of new compounds.

Methods: In this presentation it is shown how geometrical algebra was applied to inter-convert between clinical 1-dimensional total tumor length and preclinical 3-dimensional tumor growth. Rate constants not affected by the dimensional differences were translated by uninformed allometric conversion. Simulations were performed using the xenograft parameters for doxacetel, present in both papers, and checked against Wang-based predictions.

Results: The Wang model predicts a disease progression that is independent of treatment effect, i.e. the model classified the treatment as symptomatic. The Simeoni model on the other hand allows full tumor regression. The outcomes therefore can only be compared up to the point where growth in the Wang model overtakes the treatment effect, about 6 months of treatment in the doxacetel case. The resulting inhibition relative to placebo at 25 weeks is 55.6 % as predicted by the Wang model and 55.0% as predicted by the scaled Rochetti model.

Conclusions: A new approach for interspecies scaling of efficacy in oncology is presented using general allometric and geometric conversions. The prediction resulting from this scaling in conjunction with clinical PK information was in excellent agreement for published data on one particular compound, doxacetal. While this is a first sign on the applicability of this approach, analysis on multiple other compounds is warranted before wider application.

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Iñaki F. Trocóniz Predictive ability of a semi-mechanistic model for neutropenia in the development of novel anti-cancer agents: two case studies using diflomotecan and indisulam

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Background: In cancer chemotherapy neutropenia is a common dose-limiting toxicity. The ability to predict the neutropenic effects of cytotoxic agents based on the proposed trial designs and models conditioned on previous studies would be valuable.

Objectives: The aim of this study was to evaluate the ability of a semi-mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model for myelosuppression to predict the neutropenia observed in Phase I clinical studies, based on parameter estimates obtained from prior trials.

Methodology: Pharmacokinetic and neutropenia data from 5 clinical trials for diflomotecan and from 4 clinical trials for indisulam were used. Data were analyzed and simulations were performed using the population approach with NONMEM VI.
Parameter sets were firstly estimated under the following scenarios: (*i*) data from each trial independently, (*ii*) pooled data from all clinical trials and (*iii*) pooled data from trials performed before the tested trial. Then, model performance in each of the scenarios was evaluated by means of predictive (visual and numerical) checks.

Results and conclusions: The semi-mechanistic PK/PD model for neutropenia showed adequate predictive ability for both anti-cancer agents, diflomotecan and indisulam. When the model for each drug was conditioned on data from trials performed prior to a specific study, similar predictions of the drug related-neutropenia profiles and descriptors were obtained for the three estimation scenarios, indicating that neutropenic effects of cytoxic agents can be predicted from early clinical data applying semi-mechanistic PK/PD models.

Martin Fransson Pharmacokinetics of paclitaxel and its metabolites using a mechanism-based model

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Objectives: The influence of the genotypes of the metabolizing enzymes, CYP2C8 and CYP3A4 on the clearance of paclitaxel are still not fully established. To further investigate the impact of these enzymes on the metabolic pattern of paclitaxel *in vivo* this study aimed to expand a previously developed mechanism-based model for population pharmacokinetics of paclitaxel, where the solvent Cremophor EL explains the non-linear disposition [1], to also include the kinetics of its primary metabolites; 6α-hydroxypaclitaxel (6α) and p-3'-hydroxypaclitaxel (p3), and its secondary metabolite; 6α-, p-3'-dihydroxypaclitaxel (6α-p3), which is formed by further oxidization of the primary metabolites.

Methods: 33 women diagnosed with gynaecological cancer were treated with paclitaxel in combination with carboplatin during a 3-h infusion at a dose of 175 mg/m2 (n=30) or 135 mg/m2 (n=3). Genotypes were determined for CYP2C8, CYP3A4 and ABCB1/mdr-1 variants along with CYP3A4 activity. Population pharmacokinetic analysis of plasma samples was performed using NONMEM. The PRIOR subroutine with prior information from literature was used to support lack of data for unbound concentrations of paclitaxel [1] and concentrations of Cremophor EL [2].

Results: Model building was based on 1156 samples; 345 from paclitaxel, 332 from 6α, 336 from p3 and 143 from 6α-p3. Parameters for paclitaxel were close to prior values. Estimated unbound metabolite concentrations were best fitted using a one compartment model. Total 6α and p3 concentrations were both found to be dependent on Cremophor EL concentrations, and were best fitted using a Hill equation with an additive Cremophor EL component. No association between total 6α-p3 and Cremophor EL was found. Clearance/fm of 6α was significantly bidirectional correlated with the mdr-1 tri allele G2677T/A on a level of $P < 0.05$.

Conclusion: Paclitaxel metabolite kinetics seems to be highly influenced by Cremophor EL concentrations. The mdr-1 tri allele G2677T/A may affect clearance of the paclitaxel metabolite 6α-hydroxypaclitaxel. No correlation between population variability in the metabolism of paclitaxel and genotype variants of metabolizing enzymes could be identified.

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Maria Garrido Population pharmacokinetic modelling of unbound and total plasma concentrations of oxaliplatin administered by hepatic arterial infusion to patients with liver-metastases.

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Background: Oxaliplatin, a third generation platinum (Pt) complex, is active in metastatic colorectal cancer. The pharmacokinetic profile of ultrafilterable oxaliplatin has been investigated by several authors, and was described by a three or two compartment open models, depending on the sampling time and the analytical method to Pt quantification [1]. Although in many of these studies Pt levels have been measured as total and free plasma levels, the pharmacokinetic analyses of total and free levels have been performed separately [2]. Therefore, the aim of this study was to develop a population pharmacokinetic model describing simultaneously unbound and total plasma concentrations of oxaliplatin after intra-hepatic administration in patients with metastatic cancer.

Methods: Seventeen patients with liver metastases were treated with 100 mg/m^2 of oxaliplatin administered by the hepatic artery in 3-h infusion, followed by 500 mg/m^2 cetuximab intravenously infused for 2-h, and oral capecitabine administered every 12h for a week with dose escalation schedule depending on prior-dose-level toxicity. Blood samples were collected according to a sparse sampling with 3-4 samples per cycle and during 1 o 2 cycles.
Population pharmacokinetic analysis using log-transformation data, was performed with the first-order conditional estimation (FOCE) method with interaction in NONMEM program (version VI) [3]. Graphical diagnostics, representations and generation of simulation were done with the programs Xpose 4 and S-PLUS 6.2. [4].

Results: Total and free oxaliplatin plasma concentrations could be described by a two compartment model incorporating a non-linear plasma protein bindingh. Estimates for B_{MAX}, maximal binding capacity, and K_D, the concentration at half-maximal binding, were 4.4 (0.03) and 0.15 (0.18) mg/L, respectively. The values for other population parameters such as CL, total plasma clearance and V1, apparent central volume distribution, were according to those previously reported in the literature [1,5]. Interindividual variability could be estimated on V_1 and K_D and was 21 and 51 %, respectively. Although body mass index, age, hematocrit and capecitabine dose were selected from the GAM approach as significant covariates, none of these were found to have a significant effect on the PK characteristics once they were incorporated in the NONMEM model (P> 0.01).

Conclusion: This study shows that time profiles of total and unbound oxaliplatin plasma concentrations could be simultaneously described with a two compartment model associated with a non-linear binding to plasma components.

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Kimberley Jackson A Novel PKPD Model to Describe the Interaction of Drug Response of Combination Therapy: An Application in Preclinical Oncology.

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Objectives: Combination drug therapy clinical trials, especially in the field of oncology, are extremely prevalent. In order to evaluate the potential response of combination therapy, the effects of each drug alone and when co-administered need to be evaluated. In the current analysis, a semi-mechanistic PKPD model has been developed to describe the interaction between a targeted therapy (Drug A) and a cytotoxic agent (Drug B) on tumour growth response using murine xenograft data.

Methods: Efficacy studies were conducted for Drugs A and B alone and in combination. PK and biomarker effect data were also available for the targeted agent (Drug A) but due to constraints in blood volume in mice, no blood was available for PK analysis of Drug B. Analyses were performed using the population approach with NONMEM VI. The following three steps were followed to develop the integrated PKPD model: i) modelling of the time course of tumour inhibition caused by the cytotoxic agent; ii) modelling of the biomarker effects of drug A and iii) modelling of the tumour growth inhibition effects when Drugs A and B were co-administered.

Results: The following three models were developed to describe the interaction of two drugs with differing mechanisms of action: i) a modified version of the Gompertz model as described previously (1) successfully described the tumour growth effects of Drug B. Due to the lack of pharmacokinetic data for Drug B, the K-PD approach (2) (in which a virtual compartment is used to represent the biophase where the concentration is in equilibrium with the observed effect) was used to describe drug input to the model; ii) a two-compartment PK model linked to an indirect inhibition of degradation response PD model was used to describe the time course of the biomarker effects of Drug A and iii) a drug interaction model was developed to describe the effects on tumour growth response where it was assumed that Drug A reduces the efficiency of the tumour cell mechanisms to repair Drug B induced DNA damage, thereby enhancing the effect of the cytotoxic drug.

Conclusions: A novel semi-mechanistic model was developed to describe the interaction between combination therapy with a targeted therapy and a cytotoxic agent on tumour growth response using preclinical xenograft data. This approach was able to differentiate the tumour growth response of each drug given alone and combination.

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Fredrik Jonsson A Longitudinal Tumor Growth Inhibition Model Based on Serum M-Protein Levels in Patients With Multiple Myeloma Treated by Dexamethasone

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Objectives: The aim of this study was to develop and asses a tumor growth inhibition model based on changes in serum M-Protein, a tumor marker, in patients with multiple myeloma.

Methods: M-Protein measurements with time were pooled from 346 patients included in the dexamethasone arms of two pivotal phase 3 registration studies of lenalidomide plus dexamethasone vs. dexamethasone (MM009 (1), MM010 (2)). We developed a longitudinal exposure-response tumor growth inhibition model of drug effect on tumor growth dynamics (3) based on M-Protein level (taken as a marker of tumor size). The predictive performance of the model was evaluated using a posterior predictive check (PPC) based on 500 simulated replicates of the studies.

Results: The model is composed of sub-models for tumor growth dynamics (K_L), drug effect (K_D) and drug resistance (l). Patient-specific random effects are implemented on all of the model parameters. Drug effect is driven by drug dose over time in a virtual biophase compartment (K_P). Data did not support estimation of K_P and optimal value (K_P: 20 $week^{-1}$) was determined by log-likelihood profiling. No clinically relevant covariate effects were identified.

	Parameter Estimate	**RSE* (%)**	**Inter-individual variance**	**RSE* (%)**
KL (wk -1)	0.0264	8.6	0.76	15
KD (wk -1 per mg dexamethasone)	0.0134	6.0	0.44	13
Lambda (wk -1)	0.158	8.9	0.34	34
Sigma1 (additive residual error, g/l)	1.90	10.6		
Sigma2 (proportional residual error)	0.102	33.5		

*RSE: relative standard error of parameter estimates

The model is qualified to simulate relative change from baseline of M-Protein level at the end of cycle 2 (week 8). Observed results (25^{th}, 50^{th}, and 75^{th} percentiles) were consistent with the predictive distributions of the model.

Conclusions: This model enables the use of the change in M-Protein level as a continuous longitudinal biomarker for drug effect in multiple myeloma studies. This model will be part of a modeling framework to simulate expected survival of new investigational treatments and to support end-of-Phase 2 decisions and design of Phase 3 studies (4).

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Ron Keizer Evaluation of clinical dosing of E7820 from preclinical and clinical data using a biomarker

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Introduction

The novel anti-cancer agent E7820 inhibits angiogenesis by inhibition of mRNA expression of α_2-integrin.[1] It has shown to induce tumor remission in preclinical experiments[2], and is now tested in phase I.[3] It was hypothesized that the inhibition of α_2-integrin measured on platelets would provide a measure of pharmacological target modulation, and thereby a possible biomarker for drug efficacy.

Objectives

- establish target levels of α_2-integrin inhibition correlated with tumor stasis in mice
- to investigate if the dose regimen proposed from the phase I study (based on acceptable toxicity) would result in sufficient inhibition of α_2-integrin expression to reach this target

Methods

Tumor growth experiments were performed in 25 mice bearing a transplanted pancreatic KP-1 tumor, studying dosing at 0- 25 mg/kg over a period of 21 days. In the clinical study, E7820 was administered daily for 28 days, followed by a washout period of 7 days prior to starting subsequent cycles. Both in preclinical and clinical experiments, α_2-integrin levels were measured on platelets by FITC-conjugated anti-integrin staining in combination with flow cytometry. PK-PD models were developed in NONMEM VI, using FOCE-I. Modeling and simulation was performed according to a pre-specified analysis plan, and construction of the PK-PD model was performed sequentially. First, the E7820 plasma concentrations were correlated to the inhibition of α_2-integrin expression. Next, a tumor growth model based on unperturbed tumor growth experiments was fitted. The parameter estimates for the α_2-integrin model were then fixed, and the model predicted expression levels were used to drive the tumor growth model.

Preclinical modeling

Longitudinal description of the α_2-integrin expression level on platelets was modeled as a turnover model with an inhibitory effect on input rate (k_{in}) of E7820 plasma concentration, described by a linear equation or by the Hill equation. An inhibitory effect of plasma exposure on k_{in} was considered a mechanistically more plausible model than a stimulatory effect on k_{out}, as the pharmacological effect of E7820 is mediated through the inhibition of mRNA expression.

Several tumor growth models were evaluated including exponentials models, Gompertz models [4], and a tumor growth model introduced by Simeoni et al.[5] First, unperturbed growth was described,

after which it was attempted to describe the effect of inhibition of α_2-integrin. The effect of inhibition of α_2-integrin expression on one of the relevant growth rate parameters in the tumor growth models was incorporated as linear or E_{max} relationships. For both the model for α_2-integrin and the tumor growth model, it was evaluated if the available data supported the estimation of between-mice variation of the parameters. The incorporation of effect compartments to delay the effects of drug on α_2-integrin, or α_2-integrin on tumor growth inhibition, and the development of resistance to drug were also evaluated. For both the α_2-integrin and the tumor growth model, an exponential residual error model was used.

As at all dose levels tumor growth was observed despite initial remission, achieving a tumor size at t = 21 days lower or equal than the tumor size at baseline was defined as tumor stasis. To allow for discrepancies in tumor sensitivity between cell lines, two targets were set at 50% and 90% of mice achieving tumor stasis. Using the combined preclinical model, the relative inhibition of α_2-integrin expression at steady state that correlated with these targets ($I_{inh,50}$, $I_{inh,90}$) were calculated using simulations over a dose range of 50 to 200 mg/kg bid.

Clinical modeling
A PK model for E7820 in patients had been constructed earlier. Briefly, this consisted of a one compartment model, with first-order elimination and absorption.[6] This model was then linked to a turnover model describing the inhibition of α_2-integrin expression in patients. Next, simulations of profiles of α_2-integrin expression from the clinical PK-PD model evaluated the levels of inhibition of α_2-integrin expression that were achieved using these regimens. To evaluate if efficacy can be expected from the clinical regimens, these inhibition levels were then compared to the α_2-integrin targets required for tumor stasis defined from the preclinical experiments.

Results
Preclinical modeling
From preclinical experiments, 119 α_2-integrin measurements and 210 tumor size measurements were available. An E_{max} model was used to describe the relationship between plasma concentration and the effect on the input rate in the α_2-integrin turnover model. An exponential tumor growth best described unperturbed tumor growth and growth inhibition in mice due to the inhibition of α_2-integrin expression. The exponential tumor growth model was extended with a term describing initial slow growth, possibly due to the transplanted tumor not being fully embedded in its surrounding tissue. The tumor growth equation thus was described by: $dT/dt = -\alpha \cdot (1\text{-}e^{\beta t}) \cdot T - E_I \cdot T$, with T describing tumor size in mm, t describing time in days, and α and β describing tumor growth rate and initial growth resistance rate. The factor E_I described the effect of inhibition of α_2-integrin expression on tumor growth and was described by a sigmoid E_{max} model. Both the α_2-integrin and tumor growth model provided good fit as judged by visual predictive checks. Simulations from the combined model for α_2-integrin inhibition and tumor growth resulted in values for $I_{inh,50}$ and $I_{inh,90}$ of 14.7% and 17.9%, respectively.

Clinical modeling
The clinical dataset consisted of 462 α_2-integrin level measurements at 209 unique time-points from 29 patients, collected from up to 9 treatment cycles. Although considerable between patient variation was observed in baseline expression levels and response to drug, the observed α_2-integrin expression levels in patients and between patient variation could be described adequately using the turnover model. Simulation of clinical regimens from this PK-PD model showed that a dose of 100 mg qd, which was the maximum tolerable dose level in the phase I study, α_2-integrin expression was inhibited more strongly than the $I_{inh,50}$ in >95% of patients, and more strongly than the $I_{inh,90}$ in >50% of patients. Doses of 50 mg qd or lower resulted in ≤ 50% of patients expected to reach the $I_{inh,50}$.

Conclusion

The relative level of α_2-integrin inhibition that corresponded to tumor stasis in 50% or 90% of mice was only moderate ($_2$-integrin expression on platelets relative to baseline may be a valuable clinical biomarker for the drug effect on tumor growth, warranting further investigation.

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Cornelia Landersdorfer Pharmacodynamic (PD) Modelling of Anti-Proliferative Effects of Tetraiodothyroacetic Acid (Tetrac) on Human Cancer Cells

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Objectives: Tetraiodothyroacetic acid (tetrac), a deaminated analogue of L-thyroxine (T_4), competes with T_4 to bind to the integrin αvβ3 receptor on the cell surface and induces apoptosis and anti-proliferation in several kinds of cancer cells. We sought to develop a PD model to characterize these effects.

Methods: Human breast cancer MDA-MB-231 cells were treated with 7 different constant concentrations of tetrac in the perfusion bellows cell culture system for 19 days and similar experiments were conducted using human glioblastoma U87MG cells treated with 3 different concentrations of tetrac for 7 days. Human colon cancer Colo-205 cells were treated with 3 different concentrations of tetrac in flasks for 18 days. Total cell counts were obtained every 1 or 2 days. All data within each study were co-modelled in NONMEM VI. Simulation-estimation experiments were run using NONMEM and S-ADAPT (MC-PEM algorithm).

Results: A mechanism-based model adequately described the proliferation of cancer cells and inhibition of proliferation by tetrac. The action of tetrac on MDA-MB cells was best described as a dual effect with both inhibition of the rate of cell growth ($Imax_1$ 0.85, $IC50_1$ 5.1 μM) and inhibition of the probability of successful replication ($Imax_2$ 0.20, $IC50_2$ 0.087 μM). The effect of tetrac on colon cancer cells was modelled as inhibition of the probability of successful replication (Imax 0.17, IC50 0.020 μM). Average bias was +0.1% (+0.3%) for Imax and -5% (-6%) for IC50 from 50 replicate MC-PEM (FOCE) runs with an additive error of 0.05 on log_{10}-scale. Both effects on rate of cell growth ($Imax_1$ 0.57, $IC50_1$ 0.047 μM) and probability of successful replication ($Imax_2$ 0.92, $IC50_2$ 47.4 μM) were required to describe inhibition of cell proliferation of U87MG cells. Average bias was -5% (-3%) for $Imax_1$, +26% (+19%) for $IC50_1$, +0.01% (-3%) for $Imax_2$, and -0.4% (-4%) for $IC50_2$ in MC-PEM (FOCE) based on 50 replicates each with an additive error on log_{10}-scale of 0.1.

Conclusions: Modelling suggests the effect of tetrac on the probability of successful replication is most important for colon cancer cells in flasks, whereas both effects are necessary to describe tetrac effects on breast cancer and glioblastoma cells in the perfusion bellows system. The perfusion bellows system with PD modelling allows simulation of concentration time profiles expected in humans in an *in vitro* system and can support translation from *in vitro* to animal models and human clinical trials.

Jebabli Nadia Pharmacokinetic Modelling Of Methotrexate From Routine Clinical Data In Patients With Acute Lymphoblastic Leukemia

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Objectives: To develop population pharmacokinetic model for methotrexate (MTX) in patients with acute lymphoblastic leukaemia (ALL), receiving high-dose MTX followed by folinic acid rescue

Methods: Pharmacokinetic modelling was performed in NONMEM using a dataset including 273 patients (aged 2 to 23 years) who received high-dose MTX (5 g/m2 per course) in long-term treatment. 2582 methotrexate plasma concentrations were performed by fluorescence polarisation immunoassay (FPIA).

Results: A threecompartment open model with elimination from the central compartment described the pharmacokinetics of methotrexate. The most important covariates affecting the disposition of methotrexate were age (AGE, year), body weight (BW, Kg), and creatinine clearance (CLR, lh-1). The final model with exponential disposition of MTX was clearance (CL, lh-1) = (6.11 + WT*6.7310-2)+(1.0810-4*CLR)*EXP(1.9510-1) , (V, l)= 10,8+(AGE * 9.310-2) * EXP(9.110-1) , Q(lh-1) = 2.0410-3 * WT. Pharmacokinetic parameters (%CV) in this study were CL, 8.72 lh-1 (44 %); V1, 17.49 l (95%); V2, 6.048 l (56%); V3, 0.015 l (52%) . The model predictions in the qualification group were found to have no bias and satisfactory precision

Conclusions: The MTX population pharmacokinetics in patient with ALL is well described by this investigation. Substantial interpatient variability is explained by incorporating patient specific data into regression equations predicting pharmacokinetic parameters.

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Valerie Nock Leukopenia following high-dose chemotherapy with autologous stem cell retransfusion in patients with testicular cell cancer

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Objectives: Myelosuppression is one of the most important dose-limiting adverse events in many anticancer regimens. In a clinical study 19 patients received a combination therapy of carboplatin, etoposide and thiotepa/ifosfamid including stem cell reinfusion. The current data analysis describes the leukopenic effect in this regimen using PK/PD modelling.

Methods: Data from 17 patients receiving carboplatin, etoposid and thiotepa at doses up to 1500, 2400, 750 mg/m², respectively, and data from 2 patients receiving 10000 mg/m² ifosfamide instead of thiotepa were available for data analyses (drug and leukocyte concentrations) as well as additional data on stem cell reinfusion on day 7 for 18 IDs. Sampling resulted in a median of 25.9, 20.7, 18.5 and 4.4 data points for leukocytes, carboplatin, etoposide and thiotepa per patient, respectively. Leukocyte concentrations before therapy, at nadir as well as time to nadir and time until recovery to grade 1 leukopenia were investigated. Modelling and simulation activities were performed using NONMEMTM VI, statistical analyses using R 2.10.

Results: The median leukocyte count before therapy was 3.97x109 cells/L (range: 1.75-14.75x109 cells/L). Median nadir counts of 0.08 x109 cells/L (range 0.02-0.14x109 cells/L) were reached after 236 h (±39 h), reflecting a grade 4 leukopenia. Recovery to a leukocyte count above 3x109 cells/L was observed after a median time of 408 h (±75 h) for patients receiving stem cell retransfusion. In total a mean of 3.5x108 mononuclear cells (range 2.1x108- 3.2x1010), 2.9x106 CD34+ cells (range 0.10-1.38x107) and 1.82x105 CFU-GM (range 31.0x-4.49x105) were retransfused. First modelling of the concentration-time profiles of the three drugs suggested disposition pharmacokinetic parameters in line with previous knowledge. The time course of leukocytes after nadir revealed a steep increase in concentration followed by a pronounced rebound after retransfusion of stem cells.

Conclusions: Due to the rich data situation and results from statistical analyses, individual drug concentration-time profiles will be generated. These results will be used in a sequential modelling approach to describe leukopenia with a semi-mechanistic model [1], including PK profiles and information about the stem cell retransfusions mentioned above.

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Benjamin Ribba Combined analysis of tumor size data and histological biomarkers drives the development of a semi-mechanistic model of the effect of the antiangiogenic drug Sunitinib in mice

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Objectives: One difficulty in antiangiogenic drug development is the proper evaluation of drug efficacy. In preclinical research, biomarkers from histological analysis are extensively used, however, the information they provide is incomplete. Preclinical development of antiangiogenic drug may beneficiate from drug-disease modeling approaches incorporating histological data indicative of cytostatic action. In this study, we developed a semi-mechanistic model of the effect of the antiangiogenic drug Sunitinib in mice combining tumor size data and histological biomarkers.

Methods: Human colorectal cancer cells HT-29 were implanted in 45 athymic mice. When tumor volume reached 200-300 mm3, mice were randomized in two treatment groups. In the first group (n=15), mice received a single oral dose of 40 mg/kg of Sunitinib. In the second group (n=30), mice received the same dose daily, for twelve days. Tumor diameters were periodically recorded for each animal. Mice were randomly euthanized at different time points following the drug administration and tumors were analyzed: Intratumoral blood vessel density and diameter as well as the percentage of hypoxic and necrotic tissue were assessed. Monolix 2.4 was used to estimate the parameters of the mixed-effect models. Model selection was based on standard errors of the estimates, goodness of fit plots, visual predictive check as well as shrinkages.

Results: Tumor size data were first analyzed alone (single-output model). We adapted a model formerly developed by Hahnfeldt and colleagues [1]. In this model, the limiting size for the tumor is controlled by a time-dependent variable, namely K, or carrying capacity, which increases as tumor grows to account for the process of angiogenesis. Sunitinib action was modeled using a kinetic-pharmacodynamic (K-PD) formulation [2] and assuming the antiangiogenic drug to induce a decline in the tumor carrying capacity K, and consequently tumor growth inhibition and eventually shrinkage. We sequentially extended this model to account for the histological data. In this semi-mechanistic (four-output) model, necrotic tissue forms as a result of hypoxia as the tumor reaches its limiting size K.

Conclusions: The main innovation of this semi-mechanistic model lies in its ability to integrate classical histological biomarkers such as those commonly retrieved in preclinical studies. The model provides insights into the mechanisms of tumor growth inhibition and shrinkage following antiangiogenic drug administration and in this respect, may help the development of such compounds in preclinical stages.

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Hauke Ruehs Homocysteine as biomarker in a semi-mechanistic PK/PD model of methotrexate

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Objectives: Elevated homocysteine concentrations have been associated with neurotoxic symptoms upon chemotherapy with methotrexate (MTX). The aim of this study was to develop a PK/PD model based on plasma MTX and homocysteine concentrations measured in patients with acute lymphoblastic leukemia (ALL) as a basis for the development of improved dosing regimens with a lower risk of neurotoxicity.

Methods: Based on methotrexate and homocysteine plasma concentration data from 388 ALL patients of the TOTAL XV study [1] a PK-PD model was built with NONMEM 7.1 using the FOCE interaction method. Several compartmental and indirect response models [2] were investigated to describe the PK/PD relationship. Body size, age, sex and renal function were investigated as potential covariates on the model.

Results: The PK of MTX could be described by a two-compartmental model, parameterized by CL, V1, Q and V2. Considering the wide range of age (1-18 years) and the heterogeneous degree of maturation in the population an allometric scaling was included. Creatinine clearance was positively related to MTX CL ($p < 0.001$). The relationship between MTX and homocysteine concentrations could be described by fitting an indirect response model with impaired elimination of homocysteine. A lower elimination rate constant for homocysteine (kout) was positively associated with MTX concentrations ($p < 0.001$) using an inhibitory Emax model [2].

Conclusions: Our semi-mechanistic PK-PD model describes the methotrexate and homocysteine concentrations of young ALL patients. The model is currently evaluated.

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Alexandre Sostelly Modelling the interaction between Irinotecan and efflux transporters inhibitors: A KPD tumour growth inhibition model including interaction components.

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Introduction:

ATP Binding Cassette (ABC) transporters are known to play an important role in drug absorption and distribution, normal tissue protection and anticancer drug resistance.

Although efforts to reverse drug resistance using P-glycoprotein inhibitors failed in the past, the use of other ABC transporter inhibitors in clinic has never been tested.

Breast Cancer Resistance Protein (BCRP) is an ABC transporter involved in the efflux of a wide range of substrates, such as, SN38, the active metabolite of irinotecan (CPT-11). BCRP inhibitors have been newly designed and optimized based on acridone derivatives. For instance, MBLI87 has shown high activity against BCRP efflux in *in vitro* studies with the advantage of not inhibiting P-glycoprotein [1]. A proof of concept study has been carried out in xenografted mice and has demonstrated the efficiency of this new drug against CPT-11 BCRP mediated resistance [2].

In order to optimize the therapeutic regimen and effects of this new drug combination, a model is necessary to predict the effect on tumour growth given both drug exposures.

Objectives:

To model the interaction between MBLI87 and irinotecan (CPT-11) in Severe Combined ImmunoDefiency (SCID) mice with either CPT-11 resistant or non CPT-11 resistant xenografts and to compare the effect of MBLI87 with the reference BCRP inhibitor, gefitinib. Our model includes a KPD component which accounts for drug kinetics when pharmacokinetics information is not available and the interaction of both BCPR inhibitors on CPT-11 cytotoxic effect.

Data:

Animals: 60 SCID mice were inoculated with either CPT-11 resistant tumour cells or non CPT-11 resistant tumour cells. Each mouse was implanted on the left and right flanks with the same cells. Mice were spread into 10 treatment arms: Water, CPT-11, Gefitinib, Ethanol (Gefitinib vehicle), MBLI87, Nano-Particles (MBLI87 vehicle), CPT-11+Gefitinib and CPT-11+MBLI87.

CPT-11 was administered by intra-peritoneal route at 30 $mg.kg^{-1}$ 3 days a week during 2 consecutive weeks followed by a 15 days rest period. Gefitinib was administered at 15 $mg.mL^{-1}$ in water by gavage for a total of 75 mg.kg-1 following the same schedule as CPT-11. MBLI87 was administered by intra-peritoneal route as a 2.4 $mg.kg^{-1}$ dose for 5 days a week during 2 consecutive weeks followed by a 15 days rest period.

The 2-week period of drug administration plus its 15 days rest period were considered as one therapy cycle. Mice thus received 2 cycles over 8 weeks. Tumour-bearing mice were randomized before receiving drugs, the day after cells implantation. Tumour measurements (length and width) were assessed every two days after the first drug administration. If the volume of one tumour exceeded 1800 mm^3, the entire group was euthanized at the same time, for ethical reasons.

Data: At each day of measurements, the geometric mean of the four measures (length and width of tumours at right and left flanks) of each mouse was calculated to summarize information.
When CPT-11 was administered alone or in combination to mice with non CPT-11 resistant tumours, the tumour was not measurable. These data were not analysed.
There was no significant difference (based on analysis of variance for repeated measurements) between water group, *i.e.* the control group, and other vehicles treaments groups. Consequently these 3 groups (water, ethanol and nano-particles) were lumped in a single control treatment group.
Thus 45 mice were spread into 6 cohorts: control (N=18), CPT-11 (N=9), Gefitinib (N=6), MBLI87 (N=6), CPT-11+Gefitinib (N=3) and CPT-11+MBLI87 (N=3).

Methods:
Different kinds of models were tested to model longitudinal tumour growth measurements. Since two drugs were administered, we first used the surface response model proposed by Minto and colleagues [3]. Then we used a sigmoid effect model considering an additive effect to describe the interaction. We also modelled directly tumour growth profiles using 3 tumour growth models: exponential tumour growth model, tumour growth inhibition model proposed by Claret and colleagues [4] and the one proposed by Simeoni and colleagues called the modified-Gompertz model [5] with some modifications. These modifications concerned the use of a KPD model [6] for describing drug kinetics, since no pharmacokinetic information was available in those animals. Consequently drug effects were dependant on the amount in this compartment. An interaction parameter was introduced to quantify the action of BCRP inhibitors on CPT-11 cytotoxic effect.
Models parameters were estimated by the FOCE method implemented in NONMEM VI software.
For fitting growth curves, a sequential approach was chosen. First, the control and monotherapy data have been modelled separately. Final estimates from this analysis were used as initial estimates, in a second step, where all the cohorts were modelled simultaneously.
At each step of the model building process, goodness-of-fit plots, individual plots based on posthoc distribution, parameters confidence intervals and OFV value guided the choice of the best model. Once the final model had been established, simulation based diagnostics were performed.

Results:
In our study, only one dose level was administered therefore, we were not able to describe the surface response and Minto's model has been rejected. Sigmoid effect model has been also rejected because it was not able to describe our tumour growth profiles. Moreover, these two models appeared to be overparametrised. Among the tumour growth models, the modified-Gompertz model from Simeoni and colleagues has been preferred to the Claret and exponential ones according to OFV and Bayesian Information Criteria values.
Model Specification: The final model was a tumour growth inhibition model with KPD and interaction components, the CPT-11 effect was related to the amount of the drug in the kinetic compartment. In case of joint administration, the CPT-11 effect was related to both the amount of CPT-11 present and of BCRP inhibitors. The final model is written as follows:

$$dA_{CPT\text{-}11}/dt = -K_{e\ CPT\text{-}11} * A_{CPT\text{-}11}$$

$$dA_{gefitinib}/dt = -K_{e\ gefitinib} * A_{gefitinib}$$

$$dA_{MBLI87}/dt = -K_{e\ MBLI87} * A_{MBLI87}$$

$$d\Phi_{tumour}/dt = [L_0 * \Phi_{tumour}/(1+(L_0 * \Phi_{tumour}/L_1)^{\Psi})^{1/\Psi}] - [K_{2\ X} * DR_X * \Phi_{tumour}]$$

With:
$DR_X = K_{e\ X} * A_X$
X = CPT-11, Gefitinib, MBLI87
In case of joint administration, K_2 parameter accounted for the effect of MBLI87 and gefitinib on CPT-11 cytotoxic effect:

$$K_{2\ CPT\text{-}11} = K' + K'' * DR_{inhibitors}$$

inhibitors = Gefitinib, MBLI87

Where:

- A is the amount of drug with a constant elimination rate K_e
- L_0, L_1 are the modified Gompertz model parameters which describe unperturbed tumour growth
- Ψ is the parameter allowing exponential to linear growth phase switch
- K_2 is the drug potency
- K" is the parameter describing the interaction

Only tumour growth parameters, L_0 and L_1 were described to the individual level, all the others parameters were fixed effects in the population model.
Discussion: Exponential growth parameter was estimated at 0.06 day^{-1} and linear growth parameter at 0.2 $mg.day^{-1}$. These values were in accordance with values reported by Simeoni and colleagues [5]. Potency of BCRP inhibitors were estimated at 10^{-2} mg^{-1}. These two molecules didn't have any effect on cell growth. Their effect only consisted in reversing CPT-11 BCRP mediated resistance. CPT-11 is still active on CPT-11 resistant xenografts; its potency has been estimated at 0.3 mg^{-1}.
A significant synergistic effect was found between MBLI87 and CPT-11 (K"=5.3) whereas none was found between gefitinib and CPT-11 (K"=10^{-2}). Although there was no difference in tumour size kinetics between both cohorts, the interaction model confirmed that interaction was the strongest with MBLI87.

Conclusion:
A modified tumour growth model including interaction and KPD components was built on pre-clinical data for a new BCRP inhibitor, MBLI87, and irinotecan. Our results showed that MBLI87 was able to revert CPT-11 resistance at a 20-fold lower dose compared to gefitinib. The model was accepted thanks to standard procedures. Future use of the model will be firstly optimizing a dose finding study in mice and secondly simulating effects of this new drugs combination in humans in order to prepare the design a phase 1 study.

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Herbert Struemper Analysis of Biomarker Responses in Phase I Study of rhIL-18 in Combination with Rituximab in Non-Hodgkin's Lymphoma to Support Phase 2 Dose Selection

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Objectives: The safety and biological activity of the combination of recombinant human interleukin-18 (rhIL-18) in combination with rituximab is currently being evaluated in a Phase 1 study in patients with CD20+ B cell non-Hodgkin's lymphoma. IL-18 has the potential to augment the cytotoxic effects of rituximab, (i) by directly enhancing antibody-dependent cell-mediated cytotoxicity (ADCC) through NK cell and monocyte activation and (ii) by inducing a sustained tumor-antigen-specific T cell and antibody response through its stimulatory effects on the adaptive immune response [1]. The objective of the biomarker response analysis presented here is to support dose selection for a future Phase 2 study in the absence of dose-limiting toxicities.

Methods: An extensive panel of potential biomarkers including cell counts (total lymphocytes, B cells, CD4+ and CD8+ T cells, and NK cells), cell surface markers (CD69 and other markers of activation) and cytokine/chemokine levels was collected at various time points during the study. The timing of dosing and biomarker measurements was designed to assess the individual contributions of rhIL-18 and rituximab effects to biological and clinical effects. Emax curves for biomarker exposure response relationships were fit using S-Plus and prioritized according to their statistical and biological relevance.

Results: Biomarker samples were measured in a total of 18 subjects, 3 in each of 6 rhIL-18 dose groups (1, 3, 10, 20, 30, and 100 μg/kg qw). The presence of a definitive exposure response pattern depended on the type of biomarker as well as the time point of the measurement. Clear exposure response patterns were observed for NK and CD8+ T cell counts (likely indicating extravasation from the central circulation), for markers of NK cell activation and for select cytokine and chemokine levels. Several biomarkers showed a robust response at the lowest tested dose (1 μg/kg). Near maximal responses for the prioritized biomarker measurements were achieved at 20 μg/kg qw or above.

Conclusions: Dose selection for Phase 2 studies in oncology can be challenging based on Phase 1 studies with low subject numbers and without dose limiting toxicities. In the current Phase 1 study the biomarker analysis prioritized and quantified the biological activities affected by repeated rhIL-18 administration and provided crucial support for the dose selection for a future Phase 2 study.

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Hoai Thu Thai A mechanism-based model for the population pharmacokinetics of aflibercept in healthy subjects

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Objectives: Aflibercept (VEGF-Trap), a novel antiangiogenic agent that binds to VEGF, has been investigated for the treatment of cancer [1,2]. The aim of this study was to develop a mechanism-based pharmacokinetic model for aflibercept to characterize its binding to VEGF and its pharmacokinetic properties in healthy subjects.

Methods: Data from two phase I clinical studies with aflibercept administered as a single intravenous infusion were included in the analysis. Free and bound aflibercept concentrations-time data were analyzed using a nonlinear mixed-effects modeling approach with MONOLIX 3.1.

Results: The best structural model involve two compartments for free aflibercept and one for bound aflibercept, with a Michaelis-Menten type binding of free aflibercept to VEGF from the peripheral compartment [3,4]. The typical estimated clearances for free and bound aflibercept were 0.88 L/day and 0.14 L/day, respectively. The central volume of distribution of free aflibercept was 5.05 L. The maximum binding capacity was 1.02 mg/day and the concentration of aflibercept corresponding to half of maximum binding capacity was 3.06 µg/mL.

Conclusions: The present pharmacokinetic model for aflibercept characterizes well the underlying mechanism of disposition of aflibercept and its nonlinear binding to VEGF.

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Mirjam Trame External Evaluation of a Population Pharmacokinetic Model for Dosing Busulfan in Children – Body Surface Area better than Body Weight

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Objectives: A previously developed population pharmacokinetic model to evaluate the best method for dosing busulfan in children was tested by external evaluation using pharmacokinetic data from children receiving a different schedule of administration.

Methods: The development dataset included plasma concentrations of 94 paediatric patients, aged 0.4 to 18.8 years (median age 9.2), receiving either oral or i.v. busulfan for four consecutive days before bone marrow transplantation. Out of the 94 children, 48 children received oral busulfan every 6 h. The dosing varied between 13 and 20 mg/kg with seven patients receiving a dose of 600 mg/m^2. The other 46 children received IV busulfan as 2 h infusions every 6 h in 15 doses of 0.7 to 1.0 mg/kg. The first infusion was given as a double dose over 4 h followed by the second infusion 12 h thereafter. The evaluation dataset consisted of 24 children who received IV busulfan as 3 h infusion once-daily for 4 consecutive days. By means of population pharmacokinetic modelling using nonlinear mixed-effects modelling (NONMEM) plasma concentration-time data of the development dataset were analysed. Several covariates such as age, body weight and body surface area (BSA) were tested on their effects on the pharmacokinetic parameters. The next step was to evaluate the developed one-compartment model by external evaluation.

Results: A one-compartment model with BSA as a covariate for clearance (Cl/F) and volume of distribution (V/F) described the busulfan kinetics of the development dataset sufficiently. The final population estimates of the development dataset were: Cl/F 4.23 l/h per m^2 ± 27%, V/F 19 l/m^2 ± 35% and ka 0.963 h^{-1} ± 91%. Interoccasion variability (IOV) for Cl/F (10%) and V/F (22%) was lower than interindividual variability. Prediction of the population parameters of the evaluation dataset on the basis of the developed one-compartment model resulted in very similar population values compared to the developed dataset. Furthermore, the precision and robustness of the model could be confirmed by comparison of the goodness-of-fit plots of the development and the evaluation dataset.

Conclusions: In the paediatric population, BSA, not body weight, is the best predictor for Cl/F and should be considered for dose adjustment. By external model evaluation we were able to confirm the findings and show robustness of the model with data from different dosing and schedule of administration.

Kellie Turner Cyclophosphamide, Methotrexate, and 5-Fluorouracil Population Pharmacokinetic Models with Pharmacogenetic Covariates

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Objectives: The purpose of this study was to evaluate the effect of single nucleotide polymorphisms (SNPs) in genes involved in the pharmacokinetics of cyclophosphamide, methotrexate, and 5-fluorouracil in women with breast cancer using a population pharmacokinetics approach. We examined candidate SNPs in cytochrome P450 (CYP) 2B6 (CYP2B6); CYP3A4/5; CYP2C19; nuclear receptor subfamily 1, group I, member 2 (NR1I2/PXR); NR1I3/CAR; solute carrier family 19 (folate transporter), member 1 (SLC19A1/RFC); ATP-binding cassette, sub-family G (WHITE), member 2 (ABCG2/BCRP); NAD(P)H dehydrogenase, quinone 2 (NQO2); and dihydropyrimidine dehydrogenase (DPYD).

Methods: DNA was extracted from formalin fixed paraffin-embedded biopsy tissue from 43 women, and genotyping was done by TaqMan SNP genotyping allelic discrimination and restriction fragment length polymorphism (RFLP) analysis. The following SNPs were evaluated: CYP2B6*5, CYP2B6*13, CYP2B6*4, CYP2C19*2A, CYP2C9*2, CYP2C9*3, CYP3A5*3, CAR 540C>T, PXR-131G>T, PXR -1135C>T, NQO2 F47L, ABCG2 421C>A, RFC 696A>G, RFC 1293+707G>T, DPYD*5, DPYD*9A, DPYD*2A. SNP genotypes were evaluated as covariates in population pharmacokinetic models using NONMEM software.

Results: Cyclophosphamide clearance was 28% lower in CYP2B6*5 heterozygotes and 14% lower in CYP2C19*2 heterozygotes compared to wild-type individuals. However, these SNPs were not significant covariates in the final model. The NQO2F47L polymorphism was a significant covariate for cyclophosphamide clearance [23% (95% confidence interval 10-36%) lower in heterozygotes compared to wild-type]. 5-FU clearance was 20% lower (95% confidence interval 3-39%) in DPYD*2A heterozygotes compared to wild-type.

Conclusions: Of the 17 SNPs evaluated in this study, only those in NQO2 and DPYD were significant covariates in the models for cyclophosphamide and 5-FU pharmacokinetics.

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Federico VERGA Modeling of the metastatic variability in cancer disease.

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Objectives: In cancer diseases the appearence of metastases is a very pejorative forecast. In a first time we shall show how our work could help to precise the stage of disease for each patient with respect of their metastatic risk. In a second time we aim to find the optimal number of chemotherapy cycles in order to minimize the occurence of new metastases on the long term.

Methods: We have developed a mathematical model [1] based on partial differential equations, governed by four parameters: two for describing the tumoral aggressiveness and two in order to take into account the metastatic colonization. This model permits to compute the evolution of the total metastases number produced from a given primary tumor, with respect to the time. We call this number the Metastatic Index (MI).

Results: At first we shall present the impact of the parameters variability on the metastatic distribution. In a retrospective tri al Koscielny et al. have defined in [2] the risk to develop metastases with respect to the initial tumor mass. These data have been compared to those computed by the model. The similarity of the computed results and the observed ones could confirm the ability of the model in predicting the risk of metastatic extension.
In a second time we shall include in this modeling a chemotherapy treatment in the case of the metastatic breast cancer and we shall describe the variability of the total metastases number with respect to the variability of the chemotherapy cycles number.

Conclusions: The previous results show that the computation of the MI could be a useful tool in order to precise the tumoral classification and moreover it could help to target the best treatment for each patient.

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Christian Woloch Population Pharmacokinetics of 5FU and its Major Metabolite 5-FDHU in Colorectal Cancer Patients

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Objectives: Develop a population pharmacokinetic model for both 5-fluorouracile (5FU) and 5-fluoro-5,6-dihydrouracil (5-FDHU) to explore mechanisms and factors affecting 5-FU metabolism. The key enzyme implied in this metabolism is the dihydropyrimidine deshydrogenase (DPD). DPD is probably associated with severe toxicities in DPD-deficient patients [1].

Methods: Data came from a retrospective study on 129 colorectal cancer patients who received 6 cycles of 5-FU 370 mg/m^2/day i.v. boluses (5 days every 4 weeks) and l-leucovorin 100 mg/m^2/day, one month later after chirurgical resection. Demographic and biological data (gender, age, weight, liver enzyme, PBMC-DPD activity ...) were recorded from patient files and considered as covariates. Individual plasma concentrations of 5-FU and 5-FDHU were determined on day 1 of the first cycle with a validated high performance liquid chromatography method. A simultaneous model for the 5FU/5-FDHU concentration-time data system was performed using the population approach implemented in NONMEM VI.

Results: The pharmacokinetic of 5FU and 5-FDHU was well described by a three compartment model. Central and peripheral compartment were associated with 5FU and a single compartment was associated with 5-FDHU. Inter-individual variability was described by exponential terms and residual variability by a proportional error model. The elimination from the central compartment of 5FU was best described by a nonlinear Michaelis-Menten process and that of 5-FDHU, by a first order linear process.

Parameters describing the model:

1. 5FU total clearance, CL,
2. 5FU inter-compartmental clearance, Q,
3. 5FU distribution volume of the central compartment, V1,
4. 5FU distribution volume of the peripheral compartment, V2,
5. 5FU metabolism rate, Vmax,
6. 5FU Michaelis-Menten constant, Km,
7. 5-FDHU volume of distribution, Vm,
8. 5-FDHU clearance, CLm

Structural hypotheses:

- V2=3xV1,

- Vm=V1,
- interindividual variability of Q was fixed at 70% for which the objective function was the lower.

The table summarizes results of the population analysis.

Parameter	Typical Value (RSE %)	Interindividual variability (%) (RSE %)
CL (L/h)	33.6 (11.8)	41.7 (11.3)
Q (L/h)	5.81 (7.8)	-
V1 (L)	21.6 (4.3)	49.8 (15.8)
Vmax (mg/h)	396 (25.2)	67.0 (20.1)
Km (mg/L)	24.5 (13.1)	65.2 (27.8)
CLm (L/h)	15.6 (6.0)	68.6 (10.8)

Residual variability for the 5FU and 5-FDHU kinetic profiles was 14.7% (16.1%) and 19.7% (13.3%), respectively. The covariance matrix was obtained and post hoc estimates were obtained without shrinkage. Covariates included in the final model, were weight on V1, body surface area on CL and Vmax. No covariates were found to explain the interindividual variability of CLm.

Conclusions: This population PK model is the first one which integrates a nonlinear process describing the metabolism of 5FU to 5-FDHU. It could be used to assess relationships between exposures of both 5FU and 5-FDHU and related toxicities or efficacy.

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Gudrun Wuerthwein Population Pharmacokinetics of Liposomal Amphotericin B, Caspofungin and the Combination of Both in Allogeneic Hematopoietic Stem Cell Recipients

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Objectives: Caspofungin (CAS), liposomal amphotericin B (LAMB) and the combination of both (CASLAMB) are used for management of invasive fungal infections in allogeneic hematopoietic stem cell (aHSCT) recipients. Little is known, however, about the disposition of both agents and their combination in this special population.

Methods: The population pharmacokinetics and interactions of CAS and LAMB were investigated within a risk-stratified, randomized, multicenter phase II trial in 53 adult, cyclosporine-immunosuppressed aHSCT patients in the setting of granulocytopenia and refractory fever. Patients received either CAS (50 mg QD; d 1:70 mg), LAMB (3 mg/kg QD) or the combination of both until defervescence and granulocyte recovery. Pharmacokinetic sampling was mainly performed on days 1 and 4. Drug concentrations in plasma (LAMB: 405, CAS: 458 samples) were quantified by HPLC.

Results: CAS concentration data fitted best to a two-compartment model with proportional error model and interindividual variability (IIV) on clearance (CL) and central volume (V1) (CL: 0.426 L/h ± 24 %, V1: 9.25 L ± 29 %, intercompartimental clearance (Q): 0.823 L/h, peripheral volume (V2): 3.06 L). Concentration data of LAMB fitted best to a two-compartment model with combined error model and IIV on all parameters (CL: 0.786 L/h ± 69 %, V1: 18.6 L ± 42 %, Q: 2.86 L/h ± 56 %, V2: 81.7 L ± 60 %). Internal validation showed that both models adequately described the observed data. None of the covariates tested (LAMB- or CAS- comedication, respectively, sex, weight, age, bilirubin, creatinine clearance) further improved the models.

Conclusions: The disposition of LAMB and CAS was best described by two compartment models. Drugs exposures in aHSCT patients were comparable to those in other populations, and no pharmacokinetic interactions were observed between the two compounds.

Alena Zhang Evaluating the Extent of Chemotherapeutic Contamination from Central Venous Catheters in Children with Cancer and Providing Guidance for Accurate Reporting of PK Parameters

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Objectives: To support the use of a clearing procedure that minimizes catheter contamination when a single central venous line (CVL) is used to administer and sample chemotherapy in children, modeling and simulation (M&S) strategies have been employed to estimate the magnitude of residual bias, develop an algorithm to ensure the accurate reporting of PK results and evaluate the efficiency of the process for an ongoing BPCA trial with Actinomycin-D (AMD) and vincristine (VCR) in pediatric cancer patients.

Methods: An *in vivo* evaluation of the proposed catheter clearance procedure (four blood-draw return cycles) was performed in 3 pediatric cancer patients receiving AMD and VCR. Paired PK samples were obtained from CVL and peripheral IV (PIV) from 5 min to 24 hr post infusion. Using a 3 CPM structural model for AMD and combining our dataset with the published studies [1], three approaches were evaluated to assess the effects of catheter contamination on drug PK: (1) catheter type as a covariate on PK parameters; (2) CVL contamination as a fixed baseline effect on drug concentration response; (3) catheter binding compartment and blood-draw return cycle-dependent rate constant as components of drug input function. All M&S were performed using NONMEM VI. Comparison of model performance was conducted by objective function and goodness of fit diagnostics, predictive checks and via simulation with the clinical trial design serving as the primary metric of evaluation for the proposed correction algorithm.

Results: AMD dataset combined three pediatric studies containing 36 patients and 199 plasma concentrations. Covariate analysis yielded the best model when CVL sampling catheter was applied as a power function on central volume (0.84) and clearance (0.37). Sensitivity analyses based on time and concentration indicated that a baseline drug contamination factor in an exponential function (THETA=16.4 ng/mL, ETA=0.28) should be applied to individual prediction when CVL plasma concentration $\geq$ 25 ng/mL. The mechanism-based working model for catheter drug binding leveraged parameter estimates from the *in vitro* study, including initial percentage of drug adsorption, drug dissociation constants in the presence or absence of blood-draw return cycles. Further model refinement is ongoing.

Conclusions: Catheter clearance procedures can efficiently reduce AMD and VCR contamination during PK sampling from a single central catheter. M&S approaches support their use in prospective pediatric trials where PIV sampling is often a deterrent to enrollment.

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Claire Ambery Leveraging biomarker exposure-response in drug development

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Introduction: GSKxxx is a potent and selective compound being developed for the treatment of asthma.

Objectives: The objective of this work was to help select doses of GSKxxx for a Phase IIb asthma patient study.

Methods: A concentration-biomarker relationship was obtained using an inhibitory Emax model to link concentration to biomarker and enable definition of IC50. Subsequently simulations of the relationship between dose and biomarker inhibition associated with Cav were performed in Berkeley Madonna software. The PK parameters were provided by estimates from a human study.

Results: Parameters of the relationship between concentrations and biomarker were estimated with reasonable precision and the model fitted the data adequately. IC50 was estimated from the concentration biomarker relationship. For the simulations an inter-subject variability in IC50 of 10% was used to reflect potential variability in biomarker response. For the simulations an inter-subject variability in Cav of 50% was used to reflect potential variability in concentration. Doses of Drug A were selected based on the proportion of subjects predicted to exceed the IC50 for Cav.

Conclusions: Simulation of the biomarker exposure-response relationship facilitated the selection of doses to be investigated in a Phase IIb dose ranging study in asthma patients.

Jacqueline Anderson PK modelling of organophosphorus poisoning in humans

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Objectives: Organophosphorus (OP) pesticide poisoning is an important problem in South Asia, acute poisoning from OP's in Sri Lanka resulted in 853 deaths in 2007 with the incidence increasing1. Characterization of the dose-concentration-response relationship would be useful to understand the time-course of acute poisoning. However, accurate information on dose amount and time of ingestion is generally lacking. We therefore aimed to develop PK and PKPD models of OP's in acute poisoning.

Methods: A PK model for one OP, chlorpyrifos (CPF) and its metabolties was developed using NONMEM VI. The model was derived from acute poisoning data from patients (n = 75; 7 Female, age 15-65 years, 2-8 samples per subject). The reported volumes ingested ranged from 10 to 350 ml. CPF, chlorpyrifos oxon (CPO).

Results: A 2-compartment model for CPF with first order absorption kinetics and a one compartment disposition for the active metabolite CPO best described the data. Dose uncertainty was accounted for by allowing each individual's dose to deviate from the median dose of 57.5mls using the reported volume intake as a covariate on the relative bioavailability parameter. For CHL Ka was fixed to 1.64 (Hr), Cl was 0.9 (L/hr) SE 0.109, Vd 7.39 (L) SE 1.3, Vp 33.9 (L) SE 7.54 and Q was 1.65 SE 0.293. A proportional residual error was estimated to 37%. The estimated dose range was on average 30mls less than reported.

Conclusions: The PK model developed characterised the observed concentrations of 0.1 – 19 nM well with reasonable estimates of the dose range. Future investigations are planned to incorporate PD data including cholinesterase inhibition, an important biomarker, and survival data. We hope this model will help us to better understand acute and chronic chlorpyrifos poisoning toxicology, the relationship between dose and PD outcomes and potential treatment options.

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Abbreviations: AChE, acetylcholinesterase (EC 3.1.1.7); BChE, butyrylcholinesterase (EC 3.1.1.8); CPF, chlorpyrifos; CPO, chlorpyrifos oxon; RBC, red blood cells; Vp, peripheral compartment volume.

Massoud Boroujerdi Joint model for dropout in longitudinal trials in COPD patients

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Objectives: Long term longitudinal studies often have large dropout rates. The dropout is termed informative if it is related to the primary variable used for the assessment of efficacy in clinical trials. Forced exhaled volume in one second (FEV1) is commonly used for the assessment of disease severity and progression in chronic obstructive pulmonary disease (COPD). The objective of this study was to assess the joint model methodology for the simulation of individual hazard of dropping out in clinical trials.

Results: Data from 1356 COPD patients from a 52-week study treated with placebo were evaluated. A two level mixed model was used to describe the FEV1 over time. The time to dropout was modelled with Cox regression with basal FEV1 as covariate. The Cox model provides a mean estimate for changing basal hazard with time. The random components of two-level model for FEV1 indicating individual differences in initial FEV1 (intercept) and the rate of change (slope) were used as driver for the proportional hazard model. The risk of dropping out was computed as the accumulation of hazard with the survival being the exponentiated risk. Simulations were then performed to describe predicted dropout rate. The mean simulation of survivals closely resembles the Kaplan-Meier survival probability estimates. An application of this parametric approach is shown for the purposes of clinical trial simulation.

Conclusions: The Cox proportional hazard model with the addition of random effects to account for between-subject variability provides the basis for the simulation of survival in placebo treated COPD patients. Our simulations suggest that not only differences in baseline, but also changes in FEV1 over time contribute to the hazard or survival during the trial.

Karl Brendel Using Modelling & Simulation techniques to optimise the design of a paediatric PK/PD study

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Objectives: European Paediatric Regulations in force since January 2007 specify that, when applying for a new indication or new route of administration in adults, a corresponding Paediatric Investigation Plan (PIP) must be submitted to the Paediatric Committee. A development plan for use of Servier drug X in the paediatric population is, therefore, underway. The study being planned is a dose-finding PK/PD study which involves a single i.v. bolus administration of the compound to children in the target population. Modelling & Simulation techniques are playing a key role in designing this study to ensure that the ideal dose is identified as early as possible and that blood samples are being taken at optimum times.

Methods: As an adult physiologically-based (PB) PK model has previously been developed for this compound, this existing model was adapted and used to simulate the plasma concentration-time profiles which would result from an intravenous bolus dose of 0.1 mg/kg in children from 2 to18 years. A population PK model fitting both parent and metabolite concentrations, was built on these plasma concentration-time data and linked to a population PD model previously developed in adult, in order to simulate response-time profiles at different doses and in several age classes over the range being considered. According to pharmacological results obtained in juvenile animals and given the mode of action of this compound, it is expected that the PK/PD relationship will not differ greatly from that observed in adults. This PD model is an agonist Emax model with an effect compartment taking into account the activity of both the parent drug and its active metabolite.

According to biomarker baseline values as well as to response and safety targets, 4 age subsets were determined.For each envisaged dose and each subset of age, the proportion of subjects predicted to have a PD response between the efficacy target value and the safety threshold value, were calculated from simulated profiles, at various experimental times after the i.v. bolus.

Results: From PBPK simulations, children are slightly less exposed to the drug than adults. A three compartments-model for the parent and a one compartment-model for the metabolite were used to fit the simulated concentration-time data. Weight effects were applied and estimated on clearances and volumes of distribution. Simulations of the PD response and calculations of the *a priori* distribution of response rates for each age class end with a range of doses to be tested higher in children than in adults.

Conclusions: Based on this Modelling & Simulation approach, a starting dose and a range of doses to be tested, which comply with requirements both in terms of efficacy and safety can be chosen for each age class.

Karl Brendel Population pharmacokinetics-pharmacodynamics modeling of the QTc prolongation of Moxiflovoxacin and Levofloxacin in healthy volunteers: selection of the positive control in mandatory QT/QTc studies

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Objectives: Several classes of non-antiarrhythmic drugs induce lengthening of the QT interval. QT interval length is considered as a biomarker of ventricular tachiarrhythmia (Torsade de pointe). Regulatory agencies require QT/QTc studies to evaluate cardiac safety of non anti-arrhythmic drugs [1]. Because of multiple sources of variability in QTcI intervals for the investigation of any potential drug effect, population pharmacokinetics/pharmacodynamics (PK/PD) modelling approach is more and more used in order to split the overall variability into components [2]. Moxifloxacin and levofloxacin are often used as positive control to validate the sensitivity of the QT/QTc studies. The positive control should have an effect on the mean QT/QTc interval of about 5ms.
The aim is to help to the choice of the positive control and the dose to be administered in thorough QT/QTc study, in comparing population QTc PKPD model parameter estimates after moxifloxacin and levofloxacin administrations.

Methods: QTc data coming from two phase I studies (moxifloxacin 400mg and levofloxacin 1000 or 1500mg) including a total of 160 healthy volunteers under placebo were used to build the population model for the QTc. ECGs were recorded during 24h with an average 10 records per period and per subject. Estimation of the population parameters characterizing the QTc baseline was performed using NONMEM VI with the FOCE-I method. Then several models were investigated to evaluate any potential drug effect. Simulations will be performed to determine the optimal dose of moxifloxacine and/or levofloxacin allowing to have the best positive control in QT/QTc studies.

Results: The circadian QTc rhythm was modeled as a mesor and a sum of three cosine terms (one amplitude and one lag-time per cosine term), representing three periods of 24, 12 and 6 h. Thus, the population model consisted of 7 fixed-effect parameters with inter-individual variability parameters and a proportional residual error model. The lag-time of the second cosine term was fixed to zero in the model. Moxifloxacin and levofloxacin effects were modeled as linear effects. In this model, the effect of mean moxifloxacin (400mg) predicted maximum concentration (mean Cmax=2.5mg/L) corresponded to a change of QTcI from baseline of 11.8ms. For Levofloxacin (mean Cmax=9.6mg/L for dose 1000mg and 13mg/L for 1500mg), the change of QTcI were 3.7 and 5ms, respectively.

Conclusions: This population PK/PD analyses allowed us to characterize the effects of moxifloxacin 400mg and levofloxacin 1000 or 1500mg on the QTc baseline. Simulations will be the next step to determine both the optimal dose and the number of subjects to assure a mean QT/QTc interval of about 5ms with each positive control.

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Sophie Callies Integration of preclinical data to support the design of the first in-man study of LY2181308, a second generation antisense oligonucleotide.

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Goals: Using preclinical data, the analysis aimed at predicting the concentration and target inhibition profile of the survivin-inhibitor and antisense oligonucleotide (ASO) LY2181308 in humans.

Methods: An indirect pharmacodynamic (PD) model describing survivin mRNA and protein inhibition in humans following LY2181308 dosing was built using preclinical target inhibition and tumor growth delay data from murine xenografts. Plasma and tissue pharmacokinetic (PK) data from monkey were analysed by non-linear mixed effect modeling technique (NONMEM V). Allometric scaling was used to predict PK parameters in humans. Clinical PK/PD profiles were simulated (Monte-Carlo simulations).

Results: The pre-clinical PK/PD model predicted LY2181308 tumor concentrations ranging from 18.8 to 54 µg/g and target inhibition from 50 to 90 % inhibition (5th-95th percentiles) following 750 mg of LY2181308 in humans. The clinical data showed LY2181308 tumor concentrations ranging from 13.9 to 52.8 µg/g (n=4 patients at 750 mg), with a median survivin mRNA and protein inhibition of 20 % +/- 34 (SD) (n=9) and 23 % +/- 63 (SD) (n=10), respectively. The human multi-compartmental PK parameters were: central Vd, 4.09 L (SEE 8.95%); distribution clearances, 2.54 (4.06%), 0.0608 (29.6%) and 1.67 (23.8%) L/h; Peripheral Vds, 25900 (16.3%), 0.936 (22.5%) and 2.51 (11.6%) L; mean elimination clearance 23.1 L/h; mean terminal half-life, 32.7 days (range 22-52 days). Although the PD effect was over-estimated, the PK parameters were well predicted (median difference between observed and predicted PK parameters value of 20 % range (1 to 55 %).

Conclusion: The integration of preclinical PK/PD data can help predict with reasonable accuracy the appropriate dose and dosing regimen of ASOs in humans.

Roosmarijn De Cock Predicting glomerular filtration rate using clearance of amikacin

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Objectives: Throughout childhood many physiological changes occur. In addition, renal function is influenced by physiological changes resulting in differences in glomerular filtration rate (GFR) and tubular secretion/absorption processes at different stages of development. However exact quantification of the renal function to predict the clearance of drugs eliminated by the renal route is lacking. The aim of this study is therefore to describe the population pharmacokinetics (PK) of amikacin, an antibiotic which is almost entirely eliminated by the kidney, in order to quantify age-related developmental changes in glomerular filtration rate (GFR) (1) in neonates.

Methods: The population PK analysis was performed using the non-linear mixed effects modeling software NONMEM version 6.2. in 715 neonates (postmenstrual age 24-43 weeks, postnatal age 1-30 days) (2). The influence of the following covariates was investigated: birth and current weight, postmenstrual (PMA), postnatal (PNA), and gestational age (GA), creatinaemia, coadminstration of ibuprofen and dopamine, growth restriction, positive blood culture, mechanical ventilation and prenatal exposure to betamethasone.

Results: A one compartment model best described the data. Birth weight was identified as the most important covariate for clearance. Additionally, PNA was identified as a second covariate for clearance, thereby quantifying maturation after birth. The predictive value of PMA proved to be limited in the studied population with a large variation in gestational age and postnatal age, because this measure does not distinguish between pre-natal and post-natal maturation. Current weight was found to be the most important covariate for volume of distribution.

Conclusions: Variability in amikacin clearance in neonates can be partly explained by birth weight and postnatal age, indicating that birth itself has an impact on magnitude and maturation of renal clearance. To further identify and quantify the influence of these covariates on the glomerular filtration rate, the study will be extended to older age ranges (extrapolation study) and other drugs like netilmicin, tobramycin, gentamycin and vancomycin (cross validation study). By using the maturation rates of clearance values of all these different drugs, it is anticipated to describe the influence of maturation on GFR and finally develop a maturational model for GFR throughout pediatric life until adults.

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Oleg Demin Jr Can systems modeling approach be used to understand complex PK-PD relationships? A case study of 5-lipoxygenase inhibition by zileuton

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Motivation: Systems modeling approaches are seen as the next step in the evolution of mechanism-based pharmacokinetic-pharmacodynamic (PKPD) modeling. However, while some recent publications have highlighted development of such models, few examples exist in literature on the successful application of this novel methodology within the drug development setting. We report the exploration of the hypothesis that complex literature-based systems models can be developed and applied during drug discovery and development of 5-lipoxygenase (5LO) inhibitors for asthma. Our initial interest focused on the human dose/time/effect (FEV1) relationship of a marketed 5LO inhibitor (Zileuton).

Objectives:

1. To develop a minimal systems model of 5LO inhibition and FEV1 regulation using literature data.
2. To evaluate the possible mechanisms underlying the observed complex relationship between the PK and PD (FEV1) of Zileuton.
3. Use the model to test alternate medical hypotheses.

Methods: A systems model was developed integrating all known in vitro, in vivo and clinical data on the relevant components of 5LO-mediated inflammatory patho-physiology and possible regulatory mechanisms involved in the response at the intracellular, cellular and organism levels. This mathematical model contained the following components (i) cell dynamics model of eosinphil (EO) maturation, migration, activation and death, (ii) detailed biochemical model of 5-LO operation, (iii) semi-mechanistic model of leukotriene (LT) biosynthesis in leukocytes, (iv) biophysical model of bronchoconstriction, and (v) PK model of Zileuton and its inhibition of the intracellular 5LO pathway. All model parameters were estimated on the basis of available literature data.

Results: Multiple hypotheses were generated using the model to explain the observed delayed dose-response to zileuton administration in asthmatic subjects. Simulations using the model indicated that:

1. Acute bronchodilation after zileuton administration was due to direct inhibition of LT synthesis. Doses of 400 and 600 mg maximally achieved this inhibition hence no dose-response is observed.

2. In the asthmatic state high levels of activated Inflammatory cells in the lung are driven by two positive feedback mechanisms via LT activation of EO and IL-5 induced cellular proliferation and activation.
3. Sustained high levels of inhibition of LT synthesis (>85%) are required to interrupt these positive feedback mechanisms and so reduce the number of resident inflammatory cells. Thus leading to reduced bronchodilatory stimuli (LT and non LT such as histamine) and subsequent chronic bronchodilation at doses greater than 400 mg.
4. The delay in the observation of dose-response is characteristic of EO cell lifespan in the airways.
5. As observed in literature, model predicts that 5LO inhibition has inherently higher efficacy potential than LT receptor antagonism.

Conclusions: A systems model of the 5LO pathway and its role in asthma pathophysiology was developed and was successful in helping to understand the complex PK-PD relationship of zileuton. The model can be used in the discovery setting to better understand the role of various therapeutic interventions in asthma and potentially impact the design of early clinical studies of new candidates.

Pinky Dua SB-773812: Correlation between in-silico and in-vivo metabolism

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Background: Schizophrenia is a severe, debilitating, and usually chronic condition that affects about 1% of the adult population worldwide. SB-773812 is a molecule in development for schizophrenia and has been specifically designed to target antagonism at those receptors believed to be associated with antipsychotic efficacy (D2, D3, 5-HT2A, 5-HT2C, 5-HT6) while designing out affinity at receptors suggested to be linked to the side effects (H1, muscarinic M1-4, D1, adrenergic 1B, adrenergic 1-3) of current antipsychotics. Ideally an antipsychotic drug, used for chronic treatment, should have minimal drug-drug interaction (DDI) liability. The in-vitro data indicated that SB-773812 is metabolised predominantly by CYP3A4 enzyme. To determine the extent to which the inhibition of the 3A4 metabolic pathway could affect the metabolism of SB-773812, Ketoconazole a potent CYP3A4 inhibitor, was co-administered with SB-773812.

Objective: The aim of this work was to predict the extent of DDI by developing in-silico model in SimCYP^{TM} and then using the model predictions to guide the study design.

Methods: An in-silico model for co-administration of SB-773812 and Ketoconazole was developed in SimCYP^{TM} and model predictions were compared with the clinical data. The model was used to further guide and amend the clinical study part-way through in order to more accurately assess the maximum effect of Ketoconazole. Two groups of Ketaconazole dosing durations were examined, a total of 20 subjects in group 1 (original study) and 16 subjects in group 2 (amended study) were included in the study. Model predictions from SimCYP^{TM} for the amended study were also matched against the clinical data.

Results: SimCYP^{TM} model predictions matched well with the in-vivo data from the original study (group 1). An interim PK check was conducted to understand the extent of interactions of SB-773812 and Ketoconazole. The interim analysis indicated that extending the co-administration of Ketoconazole was necessary for assessing the extent of interaction. The in-vivo results from the amended study (group 2) were also in good agreement with in-silico predictions from SimCYP^{TM}.

Conclusions: This study was carried out to analyze the interaction of Ketoconazole co-administration on the pharmacokinetics of SB-773812. In-silico modelling tools such as SimCYP^{TM} are widely and increasingly being used to explore and characterize DDIs. This work illustrates the importance of using in-silico modelling for reliably predicting in-vivo metabolism and DDIs.

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Anne Dubois Model-based bioequivalence analysis of recombinant human growth hormone using the SAEM algorithm: liquid or lyophilized formulations of Omnitrope® versus original lyophilized Genotropin®

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Objectives: To assess pharmacokinetic (PK) bioequivalence, tests are usually performed on the area under the curve (AUC) and the maximal concentration (C_{max}) computed by a non-compartmental approach (NCA) as recommended by the guidelines [1,2]. Recently, bioequivalence tests based on nonlinear mixed effects models (NLMEM) have been developed [3,4,5]. Our objective is to illustrate model-based bioequivalence tests on a crossover trial studying three formulations of recombinant human growth hormone.

Methods: To transpose the standard bioequivalence analysis to NLMEM, we use a statistical model taking into account treatment, period and sequence effects on all PK parameters. We also include between-subject and within-subject variability on all PK parameters. We estimate the NLMEM parameters by the SAEM algorithm implemented in MONOLIX 2.4 [6,7]. Bioequivalence Wald tests are then performed on the treatment effect of AUC and C_{max}. Due to the exponential covariate model, for linear PK, tests on AUC are equivalent to tests on clearance. Since C_{max} is a secondary parameter of the model, its treatment effect and the corresponding standard error are computed by the delta method [8] or simulations. To illustrate model-based bioequivalence tests on sparse data, we sparsify the given dataset. To optimize the sparse design, we use an approach based on the population Fisher information matrix implemented in the R package PFIM 3.2 [9].

We apply this methodology to a randomized, double-blind, 3-way crossover trial. This study was conduced to compare the PK parameters of Omnitrope® powder, Omnitrope® solution and Genotropin® powder after a single subcutaneous dose of 5 mg. Thirty-six healthy volunteers were recruited.

Results: A one compartment model with first order absorption with a lag time and first order elimination adequately describes the data. The statistical model includes 40 fixed effects and 10 variance parameters. Standard errors are judged satisfactory for all parameters. Bioequivalence criteria were met for AUC and C_{max} and confirmed the results obtained by the NCA.

Conclusions: Contrary to NCA, the use of NLMEM allows the sparse sampling in bioequivalence assessments. This is an important improvement for studies in patients where rich sampling is difficult to implement. Models can also lead to better understanding of the biological system than a fully empirical approach and therefore help to interpret ambiguous results.

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Iñaki F. Trocóniz Population PK/PD model of the sedative effects of Flibanserin in healthy volunteers

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Background and objectives: Flibanserin (BIMT 17 BS) is being developed for the treatment of the hypoactive sexual desire disorder in females. Sedative effects have been found to be the main problematic adverse events after flibanserin administration.
The objective of the current evaluation was to establish a population PK/PD model for the sedative effects of flibanserin administered orally as an immediate release tablet to healthy volunteers.

Methods: Data were obtained from 24 healthy volunteers (14 males and 10 females) receiving flibanserin as a single oral dose of 100 mg.
Each subject was studied during two study days. During the first day the sedative effects were measured at each measuring time point using the Visual Analogue Scale (VAS) for "drowsiness" (0 cm="not in existence" to 10cm ="very strong"). In the second day the VAS response was also recorded, flibanserine was administered, and blood samples for pharmacokinetic were taken during 48 hours.
To better characterize the disposition of flibanserin in plasma, pharmacokinetic data from a clinical study where flibanserin was administered to 12 healthy male volunteers by a 30 min intravenous infusion were also included.
Three steps were followed during the population analysis performed with NONMEM VI: (i) step 1, modeling the VAS vs time profile during study day 1, (ii) step 2, pharmacokinetic analysis, and (iii) step 3, PK/PD model of the VAS effects incorporating the models developed in steps 1 and 2, plus the flibanserin effect model.

Results and conclusions:
Step 1. The time course of VAS data during the first study day ($VAS_{Baseline}$) was modelled empirically using linear splines with three breakpoints located at equally spaced clock times (6.65, 10.77, and 21.1 h).
Step 2. Disposition of flibanserin was best described with a three compartment model. Absorption characteristics of flibanserin were best described with a transit compartment model. Absolute bioavailability was 52%.
Step 3. Drug effects were incorporated in the model as it is shown in equation 1, where ckt refers to clock time, C_P, represents the predicted drug plasma concentration, C_{50}, is the value of C_P at half of maximum VAS response [$10-VAS_{Baseline(ckt)}$], and n the parameter governing the steepness of the VAS vs C_P curve.

$$VAS_{ckt} = VAS_{baseline,\ ckt} + (10-VAS_{baseline,\ ckt}) \times [(C^n_{P,ckt}) /(C^n_{P,ckt} + C^n_{50})] \quad \text{equation 1}$$

The VAS vs C_P relationship resulted to be very steep, supporting the concept of a threshold concentration (~200 ng/mL) below which plasma concentration has hardly any impact on the VAS scale. Model-based simulations showed that 20% of the subject population would show a VAS change from baseline ≥ 2 cm for a level of flibanserin in plasma of 225 ng/mL.

Martin Fink Phase I trials: Model-based assessment to identify a clinical relevant change in heart rate

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Objectives: The primary objective of this work was to ascertain, through an integrated PK/PD model-based approach, what measure of change in heart-rate (HR) should be considered as clinically relevant in phase I trials. Interindividual and between-study variability of circadian variations of HR demand a more sophisticated approach than simple baseline-correction, when attempting to distinguish drug effects from usual changes in HR.

Methods: Placebo and pre-dose heart rate data from 24-h holter monitoring from 7 phase I clinical studies were pooled (n=405, >700 full days of recordings). The basic mathematical model consisted of a sum of five cosine functions to replicate the circadian variations (with periods of 24, 12, 8, 6, and 4.8 hours, respectively). Study, sex, and weight were tested during the covariate building of a non-linear mixed effects model as well as the placebo effect compared to pre-dose.

Results: HR over the day ranged from 60 to 80 bpm (in a typical male). Gender differences could be found for the mesor (>5 bpm), but no study dependence was noted. The placebo effect (observed mainly) on the mesor was smaller than the gender difference. Study dependence was much more often found on the phase shifts than on the amplitude of the cosine functions - and the latter in general denoted for changes of less than 2 bpm for the typical subjects. Nonetheless, due to the phase shifts the maximum time-wise differences between studies were larger than 10 bpm.

Discussion: Not all the effects found to be statistically significantly different during model building could also be considered clinically relevant, especially the study dependent effects on the amplitude parameters. However, overall gender and study dependent effects influenced the circadian changes of HR of the typical subject more than what is considered to be a clinically relevant drug effect.

Conclusions: Due to the high variability in HR over the day and the large study and gender dependencies, it is recommended to consider a model based approach when estimating any potential drug effect compared to baseline and placebo during clinical trials.

Nils Ove Hoem A population PK model of EPA and DHA after intake in phospholipid as well as in triglyceride form.

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Objectives: The objective of this work was to establish a population (pharmaco) kinetic model of the plasma and phospholipid fractions of the two omega-3 fatty acids eicosapenatenoic acid (EPA) and docosehexaenoic acid (DHA), after administration in both phospholipid and triglyceride form.

Methods: Concentration time profiles of the two essential fatty acids EPA and DHA were assessed in 36 human volunteers. The experiment was conducted under strict control of food intake during a 12 day cross over study. Subject's acceptance of informed consent, planning, conduct and reporting of the study were performed in accordance with current ICH guidelines in a phase 1 clinic. Dense sampling of plasma was made for each subject during four 72 hour dosing intervals. Freshly frozen plasma samples were assayed for omega-3 fatty acids by a standard a GC-FID method.

Results: A population PK method was elaborated describing the endogenous as well as the exogenous variation in plasma as well as plasma phospholipids levels of EPA and DHA. The model incorporated dual input from both phospholipids and triglyceride sources and incorporated loss from and interaction between total plasma and the plasma phospholipids fraction. The modelling was performed in NONMEM v. 7

Conclusions: A population PK model was established that describe exogenous and endogenous loss and interchange of the omega 3 fatty acids EPA and DHA from and between plasma and plasma phospholipids.

Ibrahim Ince Critical illness is a major determinant for midazolam and metabolite clearance in children

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Objectives: The specific CYP3A4/5 substrate midazolam, is often used for sedation in pediatric intensive care units. However, the exact influence of severity of illness and developmental changes throughout childhood on the PK of CYP3A substrates has not been quantified. We aimed to estimate midazolam and metabolite disposition in relatively healthy and critically ill children from 1 month to 17 years of age and to study possible underlying mechanisms for variation.

Methods: Midazolam and metabolite data from three different studies were used; 24 previously healthy children receiving midazolam iv bolus and infusion postoperatively after elective craniofacial surgery [1], 18 pediatric oncology patients without hepatic or renal organ failure receiving midazolam iv infusion before undergoing an invasive procedure [2] and 13 critically ill patients receiving midazolam iv bolus and infusion for conscious sedation [3]. The datasets were merged in R and population PK modeling was performed using NONMEM 6.2. The influence of age and body weight was investigated for the PK of midazolam, 1-OH-midazolam and 1-OH-midazolam-glucuronide. In addition, we used SimCYP® to study the possible effect of liver flow, CYP3A4/5 activity and protein binding on PK variability.

Results: Population PK analysis showed that critically ill patients have a 80% to 90% lower CYP3A (midazolam to 1-OH-midazolam) and UGT (1-OH-midazolam to 1-OH-midazolam glucuronide) mediated clearance. No influence of age or body weight on the CYP3A4 mediated clearance was found. Body weight as a covariate for the UGT mediated clearance, significantly improved the model. Different scenario simulations with SimCYP® showed major impact of liver bloodflow and a combination of CYP3A4 & CYP3A5 abundance on the total clearance of midazolam.

Conclusions: From infancy to adolescence, critical illness shows to be a major determinant of midazolam clearance. Most likely causes are decreased liver flow and/or combined CYP3A4 and CYP3A5 abundance. While no influence of developmental changes on CYP3A4 mediated clearance was found, we did find a bodyweight-related influence on the UGT mediated clearance. These findings suggest that severity of illness in stead of age or body weight should be considered for dosing of midazolam in children.

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Elke Krekels Paracetamol pharmacokinetics in term and preterm neonates.

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Objectives: Processes underlying drug disposition are continuously changing in the paediatric population, this is especially pronounced in neonates. Information on the influence of developmental changes on drug pharmacokinetics remains largely unidentified, but is essential for the development of rational dosing schemes. To describe the influence of the maturational changes on the pharmacokinetics of intravenous paracetamol in neonates, a population model was developed.

Methods: The analysis was based on a sparse dataset containing 457 paracetamol concentrations in blood and 154 paracetamol, 143 paracetamol glucuronide, and 154 paracetamol sulphate concentrations in urine from 70 preterm and term neonates who received intravenous propacetamol infusions [1-3]. The population pharmacokinetic model was developed using NONMEM VI and a systematic covariate analysis was performed to identify the best descriptor for the maturational changes in the pharmacokinetics of paracetamol.

Results: The time-course of paracetamol was best described with a one-compartment model and changes in the distribution volume were best described with a linear bodyweight-based equation. Renal excretion of unchanged paracetamol was found to remain constant in the first month of life whereas the metabolism of paracetamol was found to increase exponentially with bodyweight. Additionally during this first month a shift from sulphation towards glucuronidation was observed. Upon multiple paracetamol administrations total paracetamol clearance remained unchanged, however a shift towards glucuronidation was observed that could not be attributed to changes in bodyweight and age.

Conclusions: Many physiological changes take place within the first month of life and the influence of these changes on paracetamol PK has now been described. The obtained covariate relationships imply that the traditional dosing regimen of paracetamol in mg/kg is suboptimal. How the observed maturational changes extrapolate beyond the neonatal period is part of future investigations.

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Yoon Jung Lee Model-based evaluation of DAS28 as a potential surrogate for ACR20 to establish the dose-response relationship for disease modifying anti-rheumatic drugs. A case study using tasocitinib (CP-690,550), an oral JAK inhibitor.

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Background: Tasocitinib (CP-690,550), a selective inhibitor of the Janus kinase (JAK) family, is being developed for the treatment of several autoimmune diseases such as rheumatoid arthritis (RA) and prevention of allograft rejection. The primary clinical endpoint for the response of RA to treatment is American College of Rheumatology response criterion of 20% improvement (ACR20) by which a patient is considered a responder or non-responder. Disease Active Score measured by 28 tender and swollen joint assessments (DAS28-3(CRP)), developed as a clinical index of RA to objectively evaluate a patient's response, has a continuous scale ranging from 0 to 9.4, reflecting the extent of underlying inflammation [1], [2]. Using DAS28 as a simplified notation for DAS28-3(CRP), the modeling hypothesis is that the continuous DAS28 may provide more precise dose-response curves than the binary ACR20, thus potentially improving the efficiency of dose response studies with new therapies.

Objectives: This study assesses the feasibility of using DAS28 as a more efficient measure than ACR20 for establishing dose-response of tasocitinib.

Methods: Data were obtained from a parallel, randomized, double-blinded, and placebo-controlled phase 2a study of CP-690,550 [3]. This 6-week study consisted of 4 dose arms, 0 (placebo), 5, 15 and 30mg bid, given orally in 252 patients with RA. Drug effects were assessed by ACR20 and DAS28 at baseline and at weeks 1, 2, 4, and 6, with ACR20 measured as a binary and DAS28 as a continuous variable. Both types of data were analyzed using NONMEM 7 within a mixed-effect model framework. For ACR20, using a logistic regression, the logit of the probability of ACR20 response was modeled as a sum of the latent variable threshold, placebo effect, and "pure" drug effect [4], [5]. Similarly for DAS28, the observed score was modeled as a sum of baseline, placebo effect, and pure drug effect. Model parameters were estimated sequentially in two steps as this approach estimated model parameters better than the simultaneous estimation of placebo and drug parameters. At the first step, placebo parameters were estimated from placebo group data only. Then, drug parameters were estimated from treatment group data by fixing placebo parameters at their estimates obtained at the first step. Dose-response information derived from DAS28 and ACR20 were compared using a time-averaged standard error of the model prediction normalized by the estimate (TASE, %). In addition, the percent change in DAS28 from baseline (DDAS) translatable to 30% difference from placebo for ACR20 (DACR) was estimated as follows. In Step 1, P30, the probability of DACR > 30%, was computed using the normal approximation. In Step 2, DDAS satisfying Prob($t \geq Tx$) = P30 was

computed using the t-distribution, with Tx being the t-statistic corresponding to a certain value of DDAS.

Results: The placebo effect was best described by a monotone increasing exponential function for ACR20 and an inverse Bateman function for DAS28. The drug effect was described as an inhibitory indirect response model to account for an inhibitory drug effect on the inflammatory RA process. Overall, the model represented the data well. For doses of 0, 5, 15 and 30 mg, TASE (%) estimates were 26.5, 12.1, 8.3 and 7.2% for the probability of being a responder according to ACR20, and 7.5, 4.8, 4.4 and 4.4% for DDAS, indicating ACR20 yields more variation and wider confidence intervals at all doses as compared to DAS28. The estimated DACR and DDAS increased with dose, ranging from 21 to 54% and from 16 to 41%, respectively, with DDAS being smaller than DACR at the same dose level. DDAS translatable to 30% of DACR was estimated to be 22%, which was obtained by regressing the estimates of DACR from all weeks and doses on those of DDAS.

Conclusion: These findings support that a continuous DAS28 endpoint may provide more precise dose-response curve estimates than the binary ACR20 response measure, thus offering the potential of achieving a similar level of precision in the effect size of clinically useful doses at lower sample sizes. To validate the above results, further analyses will be necessary, which will include the assessment of DAS28 for data from other studies with the same agent and other DMARDs in the same or different class. Further work would be to assess not just the precision but also the accuracy (reliability) of predicting doses that will ultimately be evaluated in Phase 3 studies on the ACR scale. In addition, covariate effects that might influence DAS28 variation will also be assessed.

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Ivan Matthews PKPD Modeling of Dose-Response & Time Course of B-Cell Depletion in Cynomolgus Monkeys

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Objectives: The pharmaceutical industry has a poor record of selecting the correct dose at the time of drug registration. The trend is that the frequency of dose changes (usually a reduction) post-registration has increased in recent years. In the wake of increased sensitivity to safety aspects of new drugs, Health Authorities have recently been asking for evidence of the minimum effective dose. This poster reports on a model-based estimation of dose response using B-cell counts following rituximab treatment in monkeys. B-cell depletion is a biomarker on the causal path for efficacy readouts for oncology indications which represents the first approved use of rituximab therapy.

Methods: A sequential population PKPD model was built in NONMEM using data from two pre-clinical monkey studies. Study A was a 4-week, weekly IV administration toxicity study at 20 mg/kg. Study B was a single dose IV administration at 0.06, 0.2 or 5 mg/kg with PKPD assessments for 4 weeks. One- and two-compartment PK models were fit to rituximab concentration data. A turnover model with stimulation of B cell removal linked to rituximab concentrations was fit to B-cell count data. Time course of drug effect was modeled using a parameterization involving the rate of B cell removal (Kout), baseline B-cell count (Base), maximum stimulatory effect of the drug on Kout (Smax) and the drug concentration that produces 50% of the maximum response (SC50). Identification of parameter variability and influence of potential covariates was examined, and the model was subjected to standard goodness of fit diagnostics.

Results: PK was adequately described by a two compartment disposition model. Influential covariates on population typical parameters were: weight on CL, Q, V1 and V2, high dose group on CL (20mg/kg doses have a lower CL) and high dose group on V1 (20mg/kg doses have a larger V1). Rituximab PD was adequately described with the turnover model that had a stimulatory effect on the removal of B cells (Kout). The stimulatory effect is non-linear with respect to drug concentration in the plasma and can be described using a sigmoid Emax type model. No influential covariates on population typical PD parameters were found.

Conclusions: This model based analysis was able to characterize the time course of drug effect for animals receiving different doses. Simulations from the model guided the clinical team to select among drug candidates to optimize attainment of pre-specified target levels of B cell reduction. The approach can be extended to inform decisions regarding sampling and trial duration – the challenge is to further extend this approach to use the analysis of animal data to inform human clinical dose–response.

Flora Musuamba-Tshinanu An optimal designed study for population pharmacokinetic modeling and Bayesian estimation of Mycophenolic acid and Tacrolimus early after renal transplantation

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Objectives: Mycophenolic acid (MPA) and Tacrolimus (TAC) are immunosuppressive drugs used in combination with corticosteroids to prevent graft rejection after solid organ transplantation. Their pharmacokinetics (PK) are characterized by a very high unexplained variability particularly in the earlier period after transplantation. The main objective of the present work was to design a study based on D-optimality criterion to describe the PK of MPA and TAC with good precision and accuracy and to explain their variability by means of patients' demographics, biochemical tests results and physiological characteristics. Subsenquently, the study aimed to develop limited sampling models and optimal designed Bayesian estimators for simultaneous therapeutic drug monitoring (TDM) of the 2 immunosuppressants.

Methods: PK profiles of MPA and TAC were obtained from 65 stable renal allograft recipients on a single occasion at day 15 after transplantation. A D-optimal sampling schedulethe was selected using popED software based on previously published studies parameters values for MPA and TAC. Population PK models were developped for TAC and MPA using NONMEM and subsequently limited sampling formulas and Bayesian estimators were developped for the simultaneous TDM of these drugs.

Results: Optimal samplig times were estimated to be at , 0.02, 0.24, 0.64, 0.98 1.37, 2.38 and 11 h after oral drugs intake. The best population PK models to describe MPA and TAC concentrations were two compartment models with first order elimination. A first order absorption with lag time and a transit comparment model best described TAC and MPA absorption respectively. Prameters were estimated with good precision and accuracy. Whilst hematocrit lebels and CYP3A5 genetic polymorphism significantly influenced TAC clearance, the pharmaceutical formulation(mofetil ester or enteric coated sodium salt) and MPR2 polymorphism were found to influence MPA absorption and elimination respectively. Limited sampling formulas and Bayesian estimators including optimal sampling times were subsequently developped and validated by bootstrapping and external validation.

Conclusions: The prospective use of simulteneous optimal design approach for MPA and TAC has allowed good estimation of their PK parameters in the early period after transplantation, wich is characterised by a very high unexplained variability. The influence of some covariates could be shown and limited sampling formulas and optimal designed Bayesian estimators could be devlopped for the simultaneous TDM of these drugs.

Jebabli Nadia Effect Of Clonidine On Bupivacaine Clearance In Tunisian Patients: Population Pharmacokinetic Investigation.

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Objectives: Combined lumbar and sciatic nerve blocks is associated with an increased plasmatic concentrations of bupivacaine, reaching sometimes toxic concentrations, with a large inter and intraindividual variability. Our team aimed to study the effects of clonidine, an α-2 mimetic known to affect systemic clearance, on bupivacaine pharmacokinetics when given as an adjuvant.

Methods: 62 patients with ASA scores I-II and aged between 18-102 years old were included in our study. Exclusion criteria were patients under 18 years and those contraindicated for plexus or nerve blocks. A dose of 120 mg of bupivacaine (for each nerve) was administered with 1 mcg/kg of clonidine (19 patients, group 1) or without clonidine (43 patients, group 2). We collected plasma samples, for each patient, before the blocks and 5, 10, 30, 45, 60, 120 and 240 minutes post-second injection. Time between both injection (lag time) was recorded. We used non linear mixed effects model (NONMEM) to analyse population pharmacokinetics of bupivacaine and determine the effect of clonidine association on bupivacaine absorption and systemic clearance.

Results: Time-concentration profiles were analyzed using a two compartments model with first order absorption, two input compartment, a central elimination and a flip-flop kinetic. We obtained a significant correlation between Bayesian-estimated and experimental observation (R^2 =0.7561, p< 0, 01). The most important covariates included body weight and age which affect respectively the volume of distribution and clearance. Moreover, our results show that clearance in the first group was significantly less than in group 2 (32.6 l/h and 60.74 l/h, respectively. p= 0.0429). No disparity in bupivacaine absorption was observed between two groups.

Conclusion: We have shown that bupivacaine absorption is fast in the two sites of injection, despite clonidine administration. Moreover, clonidine decreases bupivacaine clearance only. In fact, several studies have previously shown the effect of clonidine on local anaesthetics: Kopacz J (2001) reported that clonidine decrease lidocaine clearance *in vivo*, Mazoit JX (1996) demonstrated how clonidine decrases lignocaine peak plasma concentration when used as an adjuvant and Bruguerolle B (1996) detailed the decreasing effect of clonidine pre-treatment on bupivacaine metabolism in mice. Altogether, these data along with our results, shall allow us to better predict bupivacaine concentrations to administer in the presence or not of clonidine. Furthermore, our pharmacokinetic model will be used to determine an individual dosage for each patient and insure a better risk/benefit ratio.

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Michael Neely Pharmacogenomics and Individualized Dosage Regimens

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Objectives: To describe relationships between genetic testing and variations in gene expression over time, and how best to use this information to plan, monitor, and adjust maximally precise dosage regimens.

Methods: The structure of optimally precise Bayesian adaptive control is briefly reviewed, to set the context in which genetic/genomic information can be used.

Results: Population pharmacokinetic/dynamic models often have parameter distributions with significant genetically determined subpopulations such as fast and slower metabolizers. Normal or lognormal distributions may not be present.
Pharmacogenetics, from the 1950's, examines monogenic variations in drug behavior. Pharmacogenomics, from the 1990's, uses high throughput omics technologies [1]. It describes mulltigene or genome wide variations. Association studies correlate genomic and drug effect variation in individuals and populations. However, only about 3% of published human genomics studies presently focus beyond discovery-oriented applications [2].
Pharmacogenomic variation must be integrated into nonparametric population modeling and stochastic Bayesian adaptive control, to permit conversion of raw data into maximally precise individualized dosage regimens. Pharmacogenetics, pharmacogenomics, nonparametric population modeling, and optimal Bayesian adaptive control approaches have not yet meshed. Current covariates should be reconsidered in light of genomic variations. In addition, most genetic variation appears to be determined by individual variation, not race [3].

Conclusions: Optimally precise Bayesian adaptive control sets the structure to include human genetic/genomic information to optimize therapy [4]. As these fisld are now coalescing, there is much to be learned by all.

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Chiara Piana Once Daily Pharmacokinetics Of Lamivudine In HIV-Infected Children

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Objectives: The use of antiretroviral (ARV) drugs in children imposes careful considerations regarding dosing frequency and patient compliance. There may be considerable benefits for both children and caregivers if dosing frequency can be reduced to once daily for all drugs used during the course of therapy. The objective of this investigation was to assess whether once daily dosing provides similar exposure to lamivudine (3TC), as compared to the recommended b.i.d. regimen in HIV-infected children between 3 months and 12 years old.

Methods: Simulation scenarios were explored using a pharmacokinetic one-compartment model previously developed to describe drug disposition in the paediatric population. In the model body weight was found to have an effect on clearance and volume of distribution. The simulated population consisted of a cohort of 180 patients, aged between 3 months and 12 years old. 500 replicates were simulated, in which the use of solution and tablets was considered taking into account the wide age range. To ensure appropriate representation of different age groups, the WHO weight-for-age tables were used as reference for the correlation between age and body weight. Systemic exposure (AUC) and maximum peak concentration (Cmax) were derived as primary parameters of interest. In addition to median and percentiles, parameter distributions were also presented and compared to previous clinical trial data following once daily dosing. NONMEM VI was used to perform the simulations and R was used for the graphical and statistical summary of the results.

Results: The simulations show that once daily dosing of lamivudine yields comparable exposure (AUC) to historical values observed in children on a twice daily regimen of lamivudine, as well as in adults receiving lamivudine once or twice daily, both for solution and tablet administration. Given the change in dose frequency, higher Cmax are observed, but the observed values do not exceed tolerability limits.

Conclusions: Administration of lamivudine according to a once daily dosing regimen provides appropriate exposure in children aged from 3 months to 12 years. Our findings strongly suggest that the reduction in the dosing frequency to once daily may represent an improvement in treatment acceptability and adherence. Increased adherence may result in increased efficacy particularly in resource limited settings.

Didier Renard A trial simulation example to support the design and model-based analysis of a new dose and regimen finding study

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Objectives: Use trial simulation as a general tool to make informed recommendations on the following aspects of a new dose and regimen finding study protocol:

- trial design (Stage I),
- sample size (Stage II),
- analysis methodology (Stage III).

Methods: Trial simulations were performed in three stages. In Stage I, the primary objective was to facilitate trial design decisions regarding the use of a modeling approach instead of a traditional method (ANCOVA) and the choice of some design features (e.g. parallel or crossover, dose levels, study visits). The median absolute deviation from true value for quantities of interest (comparisons of active doses or placebo-corrected responses) was utilized as a measure to compare efficiencies of different design attributes. In Stage II simulations were conducted to determine sample size. In Stage III simulations were conducted to evaluate the proposed model-based analysis approach which was articulated along 4 key principles:

1. The dose-response relationship is of Emax type.
2. The totality of data is included in the analysis, not just the end-point.
3. Several candidate models, deemed a priori reasonable to describe the data, are considered.
4. Model averaging [1] is employed to achieve more robust inference.

Simulations were performed to reflect current knowledge and uncertainty based on available data. Key metrics were bias as well as length and coverage of confidence intervals to compare model-based and ANCOVA methods.

Results: Stage I: Simulations revealed that considerable improvements in precision can be expected from using the model-based approach over the traditional endpoint analysis. The choice of analysis method (model-based vs. ANCOVA) was the most discriminative feature among those investigated. Other design attributes such as parallel groups vs. crossover resulted in net efficiency gains one order of magnitude lower.

Stage II: Not further discussed here.

Stage III: Model averaging revealed good properties, with a favorable trade-off between bias and precision resulting in less variability overall. In particular, significant gains in efficiency remained over

ANCOVA with greater benefits seen when comparing active doses. The procedure was found to be slightly conservative when examining coverage probability.

Conclusions: Stage I and II of trial simulations allowed to determine key design features for the new study. The choice of a model-based method over ANCOVA was the primary factor to be considered in order to improve the overall study efficiency. The proposed analysis methodology was shown to be robust and efficient, with a favorable trade-off between bias and precision resulting in less variability overall. Greater benefits should be anticipated in comparisons of active doses rather placebo-corrected responses, which is of particular importance when it comes to contrasting doses at the dose selection stage. The procedure was found to be on the conservative side which should not be regarded negatively, at least within a regulatory context.

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Jan-Stefan van der Walt A population model describing the pharmacokinetics of iv esomeprazole in patients aged 0 to 17 years, inclusive

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Objectives: A population pharmacokinetic analysis was conducted to describe the steady-state pharmacokinetics of iv esomeprazole and its 5-hydroxy and sulphone metabolites, when given to patients 0 to 17 years old, inclusive.

Methods: Data collected following esomeprazole injection with doses of 0.5mg/kg (age 0-1 month, N=6), 1.0mg/kg (age 1-11 months, N=7), 10mg (age 1-5 years, N=7 and 6-11 years, N=8), 20mg (age 6-11 years, N=8 and 12-17 years, N=6) and 40mg (age 12-17 years, N=8) were used. Blood sampling (1-8 samples) for esomeprazole and its sulphone and 5-hydroxy metabolites were collected in the time window prior to the last dose and until 8.5h after the last dose. Population pharmacokinetic modelling was undertaken in NONMEM VI (FOCE INTER) with emphasis on characterizing the elimination of esomeprazole and metabolites via CYP3A4 and CYP2C19.

Results: The final model consisted of two esomeprazole disposition compartments, and one disposition compartment each for the sulphone and 5-hydroxy metabolites, all with first-order elimination. Post-conceptional age was a significant covariate on the clearance of the sulphone metabolite via CYP2C19 and was modelled as a maturation function (starting at conception and asymptoting in a sigmoidal manner) reaching an adult value at an age of 3-4 years. The CYP3A4 activity was estimated to contribute with 33% to the total clearance of esomeprazole which is in accordance with previous findings (Andersson, 2001). Additional covariates (including body surface area, serum albumin, presence of gastroesophageal reflux disease, arterial vs venous sampling or age/dose group) did not improve the model fit or the predictive performance of the model. The model evaluation by nonparametric bootstrap and visual predictive checks confirmed the model to be robust and to perform well with regard to simulation.

Conclusion: The population pharmacokinetics of iv esomeprazole was well described by the population model and found to be weight- and age-dependent across the age range of 0-17 years, inclusive.

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Johan Wallin Internal and external validation with sparse, adaptive-design data for evaluating the predictive performance of a population pharmacokinetic model of tacrolimus

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Introduction: Tacrolimus is a potent immunosuppressant agent used to prevent and treat rejection in paediatric liver transplantation. Tacrolimus has a narrow therapeutic window and displays considerable between and within-subject pharmacokinetic (PK) variability. The PK of tacrolimus change markedly in the immediate post-transplant period. We have previously developed a population PK model of tacrolimus with the intent of capturing this process(1). Commonly used simulation based diagnostics are unsuitable when using adaptive design data, but visual evaluation of the predictive performance can be performed with prediction corrected VPC (pcVPC), where observed and simulated observations are normalized based on the population prediction (2). This model has been used to suggest a revised initial dosing schedule and forms the basis for a dose adaptation tool.

Objectives: To evaluate the predictive performance of the model in comparison to two previously published models by Sam et al (3) and Staatz et al (4), by simulation based diagnostics as well as by prediction of data collected from an independent group of paediatric liver patients.

Methods: pcVPC:s were constructed using all available data and the three models. PK data from the first two weeks following liver transplantation was collected retrospectively from the medical records of 12 paediatric patients. Population and individual predicted drug concentrations were compared to measured concentrations. To evaluate the models' potential for Bayesian forecasting in dose adaptation, individual predicted drug concentrations based on one or three prior measurements were evaluated. Predictive performance was compared by calculation of MPE and RMSE.

Results: The graphical diagnostics (pcVPCs) indicated a strong over-prediction of typical plasma concentrations for the Sam model, while the Staatz model exhibited a pronounced under-prediction during the early post operative time. The proposed model demonstrated overall satisfactory predictive performance with only a marginal and quickly transient initial over prediction. Accuracy and precision in external validation was significantly better for the proposed model compared to prior models, indicating the possibility of using the model for dose schedule development and Bayesian forecasting.

Conclusions: The proposed PK model predicted the validation data reasonably well, and was superior to the previously published models in the early post-transplantation phase.

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Chenguang Wang Scaling clearance of propofol from preterm neonates to adults using an allometric model with a bodyweight-dependent maturational exponent

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Objectives: For propofol clearance, allometric scaling has been applied successfully for between species scaling and for scaling within a certain human weight range [1,2]. However, in neonates and infants, predictions of clearance based on both the 0.75 fixed or 0.78 estimated allometric model are systematically higher and lower than the observed values, respectively [3]. In this study, different covariate models for the influence of bodyweight on clearance of propofol were studied in a full age span from preterm and term neonates, infants, toddlers, adolescents to adults.

Methods: Datasets from six different propofol studies (body weight: 0.68-80kg, age: 0.002-57 yrs) [4,5,6,7,8,9] were included in the analysis using NONMEM VI. The influence of bodyweight on clearance was investigated in 4 ways: i) a single exponent allometric scaling model, ii) a mixture model with different allometric exponents for two subgroups, iii) a bodyweight-cutting-point separated model with two different allometric exponents, iv) an allometric scaling model with a bodyweight-dependent maturational exponent according to equation:

$$Exponent_{BW} = Exponent_0 - (Exponent_{max} * BW^{\gamma})/(EBW_{50}^{\gamma} + BW^{\gamma})$$

in which BW is bodyweight, $Exponent_{BW}$ is the exponent for a bodyweight BW, $Exponent_0$ is the exponent for a bodyweight of 0, $Exponent_{max}$ is the maximum decrease in exponent with increasing bodyweight, EBW_{50} is the bodyweight at 50% of the maximum decrease in exponent and γ is the hill coefficient.

Results: The allometric scaling model with a single estimated exponent of 0.7 proved to be inadequate for individuals whose bodyweights were less than 20 kg. The mixture model resulted in a decrease in objective function of 11.5 points ($P<0.01$) compared to the single exponent allometric model, and comprised of one subpopulation (24.4%) with an estimated exponent of 2.01 and another subpopulation (76.6%) with an estimated exponent of 0.65. The bodyweight-cutting-point separated allometric model further improved the description of the data with a drop in objective function of 14.5 points ($p<0.05$) compared to the mixture model, and consisted of an exponent of 1.45 for bodyweights lower than 16 kg and an exponent of 0.68 for bodyweights higher than 16 kg. The bodyweight-dependent maturational exponent model best described the data, especially in the younger age range, with a 205 ($p<0.001$) points drop in objective function. Values for the equation describing the change of the exponent with

bodyweight were 1.35, 0.784 and 3.74 for $Exponent_0$, $Exponent_{max}$, EBW_{50}, respectively, resulting in a gradual change in exponent from 1.35 in neonates to 0.566 in adults.

Conclusions: Of the studied covariate models, both the mixture model and the bodyweight-cutting-point separated model show that the scaling exponent is larger in neonates and toddlers than in older children and adults. This larger exponent was identified before for morphine glucuronidation in children under the age of three years old [10]. The bodyweight-dependent maturational exponent model was found to best describe the maturation of propofol clearance in a population varying from preterm neonates to adults. The change in the scaling exponent is a potential indicator of the physiological maturation process during ontogeny in children.

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Jeff Barrett A SAS-based Solution for NONMEM run management and post-processing

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Objectives: While the NONMEM algorithm remains the centerpiece of population analysis workflow, data assembly, pre and post processing are functions typically handled outside of NONMEM. Although SAS offers an excellent platform for these tasks, it has often been excluded from such analyses because the user community is not as invested with SAS, cost, and previously inferior graphics to other algorithms. We have created a SAS-based environment to assemble NONMEM datasets from template input files, perform data checking, manage NONMEM runs, summarize run output within and across projects, and provide flexible post-processing including the management of scripts written in other 4th generation languages and compilers (R, FORTRAN, etc)

Methods: SAS scripts create NONMEM ready datasets for single and multiple analytes, and various input regimens. Templates for fixed format input files are created to import data into the SAS script. The NM_SAS script runs NONMEM and performs the user-specified post-processing (compatible with NONMEM 5, 6 or 7). Users must define environment variables including the path of the NONMEM executable. The script changes the directory as specified using the X command. The PIPE command and FILENAME is used in SAS to run NONMEM. The PIPE command writes the output from the command prompt into the SAS log to aid debugging NONMEM. Upon successful NONMEM execution, all relevant tab files are created in this directory.

CWRES calculation in NONMEM 6 is accomplished by calling R within SAS; the COMP.R script (Xpose) calculates the CWRES tab file assuming the NONMEM 6 control stream contains the necessary arrays (HH, GG etc) to output the CWTAB.est or derive file (not required in NONMEM 7). The runs are managed within user-defined folder structure. The control stream is saved in the main folder and copied into the specific RUN folder by SAS. A Runlog is created using the RUNLOG.for file (Metrum Institute). With the new ODS graphics features in SAS 9.2 panel plots, matrix plots etc are easily generated. Templates can be created so two or three plots can be placed in rows or columns. The script can be changed by advanced SAS users as they deem fit. Diagnostic plots can be output as JPG, EMF or PDF files. Development and testing has been conducted on a Windows XP environment, but this solution is easily ported to LINUX-based machines and server environments.

Results: Representative output from NM_SAS post-processing including diagnostic plots, run log summaries, Q-Q plots for CWRES, histograms of ETA distributions, co-plots (matrix layout) and observation density within sampling windows will be shown. A demo notebook will be available to observe real-time operation.

Conclusions: This SAS-based solution provides a viable option to the pre-and post-processing requirements for analysis of data with the NONMEM algorithm. This solution is provided to the

pharmacometrics community (http://www.med.upenn.edu/kmas/code) in the hope that its future development and functionality will be expanded.

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Mike Dunlavey Derivation of SAEM C-matrix in Phoenix

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Objectives: In SAEM, the C matrix encodes the relationship between random effects and fixed effects, including covariate effects. The objective is to derive this matrix from a language-based description of the mixed-effect model.

Methods: The method used in Phoenix is to examine the "stparm" statements (statements that define the calculation of structural parameters) and, via symbolic differentiation, determine the relationship between the various fixed effects and the random effects. If the relationship cannot be represented in the restricted form of the C matrix, then use of SAEM is automatically ruled out.

Results: The algorithm for performing this analysis is given.

Conclusions: The method is effective for a wide variety of structural parameter models, including various forms of covariate effects. It is not necessary for a model to be written in a special way in order to be used by SAEM.

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Marc Gastonguay Comparison of MCMC simulation results using NONMEM 7 or WinBUGS with the BUGSModelLibrary

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Objectives: To compare the relative performance of the NONMEM 7 [1] BAYES MCMC method with WinBUGS [2] plus the BUGSModelLibrary [3] by applying them to simulated data for a range of PK and PKPD models.

Methods: For each of the following test cases, 100 data sets were simulated using NONMEM 6 (n = # subjects, nobs = # observations/subject): 1 compartment IV, n = 100, nobs = 10 (ad1tr2); 1 compartment IV, 2 sub-populations, n = 300, nobs = 8 (ad1tr2mixture); 1 compartment IV, inter-occasion variation, n = 250, nobs = 15 (ad1tr2occ); 1 compartment PO, n = 200, nobs = 3 (ad2tr2); 2 compartment IV, n = 100, nobs = 12 (ad3tr4); 2 compartment IV, CL & V1 dependent on age and gender, n = 400, nobs = 5 (ad3tr4covariate); 2 compartment IV, n = 1000, nobs = 2 (ad3tr4sparse); 2 compartment PO, n = 250, nobs = 3 (ad4tr4); 3 compartment IV, n = 200, nobs = 10 (ad11tr4); 1 compartment PO, binary PD, n = 72, nobs = 16 (fflag); Each set was analyzed with NONMEM 7 and WinBUGS using 3 chains of 10,000 MCMC iterations. The first 5,000 iterations from each chain were discarded. Results were compared w.r.t. summary statistics of the MCMC samples, computation time and "effective N", i.e., an approximate estimate of the equivalent number of independent samples from the posterior distribution [4,5].

Results: Summary statistics of NONMEM 7 and WinBUGS generated MCMC samples were generally comparable, an exception being ad11tr4 where WinBUGS over-estimated the inter-individual variances. For most examples effective N for the residual standard deviation was greater for NONMEM 7. NONMEM 7 also resulted in greater effective N for several parameters in the ad2tr2, ad3tr4covariate, ad3tr4sparse, ad4tr4, fflag and ad11tr4 examples. WinBUGS resulted in a greater effective N for the inter-occasion variance in the ad1tr2occ. The median NONMEM 7/WinBUGS ratios of computation times were 0.654, 1.91, 5.94, 1.08, 0.783, 1.90, 2.06, 0.729, 1.01 and 2.37 for ad11tr4, ad1tr2, ad1tr2mixture, ad1tr2occ, ad2tr2, ad3tr4, ad3tr4covariate, ad3tr4sparse, ad4tr4 and fflag, respectively.

Conclusions: MCMC simulations using NONMEM 7 and WinBUGS produce results with comparable accuracy. NONMEM 7 produced less auto-correlated residual standard deviation samples. WinBUGS required much less computation time to produce comparable MCMC results for a mixture model (ad1tr2mixture), and about half the computation time for the ad1tr2, ad3tr4, ad3tr4covariate and fflag examples. WinBUGS required more time to produce less precise results for the first order absorption model cases ad2tr2 and at4tr4.

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Leonid Gibiansky Bias and Precision of Parameter Estimates: Comparison of Nonmem 7 Estimation Methods and PFIM 3.2 Predictions on the Example of Quasi-Steady-State Approximation of the Two-Target Target-Mediated Drug Disposition Model

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Purpose: To compare performance of Nonmem 7 FOCEI, IMP, IMPMAP, SAEM, and BAYES methods on the simulated example of a complex pharmacokinetic system with rich sampling, and to compare precision of Nonmem parameter estimates with those predicted by PFIM 3.2 optimal design software.

Methods: The Target-Mediated Drug Disposition (TMDD) equations and the Quasi-Steady-State (QSS) approximation of these equations were extended [1] to describe drugs that can bind to multiple targets. This system was used to simulate a population data set for a monoclonal antibody that binds to both soluble (S) and membrane-bound (M) targets (3250 unbound drug and 3305 total S-target concentrations from 224 subjects; rich sampling; IV doses 100-600 nmol; SC doses 1000 nmol). It was assumed that the unbound drug concentrations and the total S-target concentrations are measured while the M-target is not observable. The true model (started from various initial conditions) was used to fit the simulated data using FOCEI, SAEM, BAYES, IMP, and IMPMAP methods as implemented in Nonmem 7.1.0. All models were MU-modeled with MUs being linear functions of THETAs; FOCEI model was also run without MU-modeling transformation. PFIM 3.2 optimal design software [2] was used to predict precision of the parameter estimates. The parameter estimates and their relative standard errors (RSE) obtained by different Nonmem methods were compared with each other, with the true values, and with PFIM predictions. All models used ADVAN13, TOL=9, INTER, NSIG=3, and SIGL=9. The other used options were: NBURN=15000, NITER=1000, and ISAMPLE=3 for SAEM, NITER=3000 and ISAMPLE=300 for IMP and IMPMAP, and NBURN=10000 or 20000 and NITER=5000 for BAYES.

Results: All estimation methods except IMP (that diverged) provided parameter estimates. Population and individual predictions of all methods were very similar. FOCEI did not converge exceeding the maximum number of function evaluations. $COV step failed with the default options but provided standard error estimates with MATRIX=S. For the fixed-effect parameters, FOCEI with MU-modeling (on the log scale of parameters) provided the best results with the maximum bias of 9%. The FOCEI method on the original parameter scale, SAEM, and BAYES were generally similar with the bias under 10% for all but 2, 2, and 4 fixed-effect parameters, respectively. IMPMAP was not able to estimate parameters of the M-target and generally had larger bias for the other fixed-effect parameters. The variances of the random effects were estimated with the larger bias, but overall, FOCEI and SAEM had the least bias followed by BAYES and IMPMAP. Estimates of RSE for the fixed effects and residual variability were in a good-to-perfect agreement between all Nonmem methods and PFIM predictions. For the variances of the random effects, FOCEI and BAYES provided RSE similar to PFIM while for IMPMAP and SAEM (with the covariance step performed by IMP) RSE estimates were higher than

those predicted by PFIM. Surprisingly, for BAYES method increase of NBURN from 10,000 to 20,000 resulted in increase of the bias for most parameters.

Conclusions: For the simulated example of the TMDD model with two targets and rich sampling design, FOCEI, SAEM and BAYES estimation methods of Nonmem 7 performed similarly, both in terms of bias and precision of the parameter estimates. IMP method diverged while IMPMAP parameter estimates were more biased and less precise. FOCEI implemented in log-transformed parameter space overall performed better than all the other estimation methods. PFIM was shown to provide reliable estimates of the expected precision of the parameter estimates.

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Åsa Johansson New Estimation Methods in NONMEM 7: Evaluation of Bias and Precision

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Objectives: The aim was to investigate the performance with respect to bias and precision of all estimation methods available in NONMEM 7 for a diverse set of PKPD models.

Methods: Five PKPD models with different types of PD data: continuous (1), binary (2), ordered categorical (3), repeated time-to-event (4) and count (5) were used in the study. The estimation methods investigated were: BAYES, IMP, IMPMAP, ITS, SAEM, FOCE (for model 1) and LAPLACE (for models 2-5). The options for the estimation methods were kept as default except that a convergence test was applied if available. Stochastic Simulations and Estimations (SSE) using PsN (http://psn.sf.net) were utilized to compare the methods: for each model, 500 datasets were simulated and then reanalyzed with the different methods. Relative root mean squared error (RMSE) ($100*\text{sqrt}(\text{mean}[(\theta_{Est}-\theta_{True})^2]) /\theta_{True}$) in estimates were evaluated for each parameter. A score based on ranks according to RMSE was attributed to each method for each model.

Results: The average fraction of runs for which the minimization completed successfully differed between the methods; 100% with SAEM and FOCE, 43% with ITS and between 81% and 95% for the other methods. The average rank scores resulted in the following ranking of the methods: SAEM (2.2), IMP (2.6), IMPMAP (2.8), ITS (3.2), FOCE/LAPLACE (4.2) and BAYES (5.8). SAEM performed best for models 1, 2 and 3, whereas IMPMAP was the best method for model 4 and IMP for model 5, followed by ITS. The BAYES method had the lowest ranking for all models, except model 3 where it was ranked number 5 and for which ITS performed worst. The average ranking scores for the fixed effects were similar to the total ranking scores, whereas for the random effects best ranking score was shared with FOCE/LAPLACE and IMPMAP. The FOCE/LAPLACE methods performed well with model 1, 2 and 5, whereas IMPMAP performed well with model 3, 4 and 5. The BAYES method performed worst regarding the random effects and had the lowest rank with all models.

Marc Lavielle The SAEM algorithm for Non-Linear Mixed Effects Models with Stochastic Differential Equations

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Objectives: The use of stochastic differential equations in non linear mixed effects models enables the decomposition of the intra-patient variability into some residual errors and some dynamical system variability. Several authors already addressed this problem and proposed an approximation method based on the First Order Conditional Estimation (FOCE) method used in non-linear mixed effects models, with the Kalman Filter used for SDEs (see [1], [2], [3]). In [4], the authors propose a stochastic EM algorithm where the diffusion process of the SDE is considered as a component of the non observed data and is simulated at each iteration. This procedure has some appealing theoretical properties but the computational effort is prohibitive for practical applications.
The objective of this contribution is to present a new maximum likelihood estimation procedure which is computationally tractable in practical situations and which avoids the linearization of the model.

Methods: We propose a new algorithm based on the Stochastic Approximation EM (SAEM) method with the Kalman Filter for linear SDE systems.
We show that a linear SDE system is not relevant when the components of the stochastic system are known to be positive, which is usually the case in a biological perspective. Assuming that the diffusion process randomly perturbs the coefficients of the associated ODE system is more realistic but the SDE system is not linear any more. The extended Kalman filter for non linear SDE systems can be used in such situations.
This methodology was implemented in a working version of MONOLIX and tested on several simulated PK examples.

Results: We show with these simulated examples that the proposed method does not reduce to consider some correlated residual errors. Indeed, we show the ability of the method to properly decompose the intra-patient variability into several components.

Conclusions: A new maximum likelihood estimation method for non linear mixed effects models governed by a system of stochastic differential equations is now implemented in a working version of MONOLIX.
For nonlinear SDE systems, we aim to develop in a next future a new SAEM based method using a particle filter instead of the extended Kalman filter. This method is expected to exhibit better theoretical and practical properties.

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Robert Leary Quasi-Monte Carlo EM Methods for NLME Analysis

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Pharsight

Problem and Methodology: The classical EM method incorporates an E-step which requires the evaluation of often analytically intractable intergrals. In the context of PK/PD NLME estimation, the integrals of interest are the normalizing factor for the posterior density of the random effects for each subject, as well as the first and second moments of this density.

The Monte-Carlo EM (MCEM) method proposed by Wei and Tanner[1] replaces these integrals with empirical averages using random draws from the distribution of interest. Often this distribution cannot be sampled directly, and techniques such as MCMC (as in the SAEM algorithms in MONOLIX and NM7) and importance sampling (as in the MCPEM algorithm in NM7) are used. The accuracy of the required integrals is controlled by the number of samples N, and typically the theoretical asymptotic error behavior is O(1/sqrt(N)). While often rapid progress can be made in early iterations of MCEM even with low accuracy integrals and small sample sizes, the accuracy requirements increase in the later stage iterations, and very large sample sizes may be required. Thus a significant improvement in efficiency may be obtained in the later stages by lowering the sample size required to achieve the required accuracy.

Here we consider the use of quasi-random (QR) draws using low discrepancy Sobol sequences, as originally proposed for the PK/PD NLME context in the PEM algorithm of Leary et al. [2] The advantage of QR relative to random draws is that the theroretical asymptotic error behavior is now approximately O(1/N), a very significant improvement. A new implementation of PEM based on importance sampling has been developed for the Pharsight Phoenix NLME platform, which utilizes recent enhancements of the QR technique with the scrambling techniques of Owen [3]. This implementation allows the direct comparison of random and QR versions, as well as adaptive error monitoring.

Results: Numerous PK/PD NLME test problems have been compared with random vs. QR importance sampling. Generally the theoretical O(1/N) vs O(1/sqrt(N)) advantage of the QR technique has been confirmed in practice. Improvements in speed of nearly 2 orders of magnitude have been observed for some posterior density integrals where high accuracy is requred, with the sampling requirements being reduced from tens of thousands of points to several hundred. We note that this also confirms a similar QR vs. random draw efficiency improvement obtained by Jank [4] in a MCEM application to a geostatistical generalized linear mixed model.

Conclusions: We have demonstrated that quasirandom integration offers significant practical efficiency advantages relative to the random integration techniques employed in purely stochastic MCEM methods using importance sampling. It is still an open question and an area of active research

in the statistical community whether the efficiency advantages of the QR methodology, in conjunction with scrambling, can be extended to MCMC methods such as SAEM.

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Hafedh Marouani Nonparametric Approach using Gaussian Kernels Estimates Multivariate Probability Densities in Population Pharmacokinetics

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Objectives: Describe the interindividual variability (interIV) by means of a multivariate probability density function (pdf) using a two-stage nonparametric procedure. Our proposal enables incorporating intraindividual variability (intraIV) and out-performs the traditional two-stage method, which ignores intraIV and overestimates random effects.

Methods: In the first stage of this procedure, covariates are recorded and individual parameters x_i are estimated by using the maximum likelihood principle. Because the maximum likelihood is asymptotically Gaussian, precisions of estimates P_i are computable and quantify the intraIV. In second stage, the nonparametric kernel approach compiles the n available training data x_i and P_i to reliably estimate the underlying pdf:

$$f(x,h) = (nh)^{-1} \Sigma K[(x-x_i)/h]$$

with K the Gaussian kernel and h the bandwidth. We propose to individualize h by incorporating the intraIV so as $h_i = sP_i^{½}$. The choice of the new bandwidth s in the above relationship is typically critical in terms of performance when implementing kernel smoothers [1].

Results: The feasibility of the proposed procedure is illustrated by a simulation study. The raw data were "prewhitened" to scale equally in all directions in the parameter space. Several approaches for selecting the "optimal bandwidth" are studied [2]. Performances of this procedure were evaluated by establishing consistency of estimates and rate of convergence for bandwidth selection. This procedure is used to obtain nonparametric conditional pdf of the kinetic parameters given the individual covariates. We show how to use this conditional pdf as prior information in Bayesian estimation.

Conclusion: Both intraIV and interIV are incorporated in the proposed nonparametric procedure. The optimal bandwidth in the kernel pdf estimator is computed. This procedure does not require the structural model between covariates and kinetic parameters but it establishes conditional distribution between them. The method is easy to implement and quick for data processing.

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Ines Paule Estimation of Individual Parameters of a Mixed–Effects Dose-Toxicity Model for Ordinal Data

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Objectives: This work addresses the issue of estimating the individual effects (empirical Bayes estimates (EBEs)) of mixed-effects models for ordered categorical data (e.g. undesirable effects).

Methods: Different algorithms for estimating the EBEs were compared by a simulation study: 2 local optimizers: the quasi-Newton method (as implemented in NONMEM software) and the simplex; a global optimization method Recursive Random Search (RRS) and the estimation of full posterior distribution by MCMC sampling (in WinBUGS). The first three methods provide single maximum a posteriori (MAP) point estimates (modes), which were compared to means of the posterior distributions given by MCMC sampling. The comparison is made in terms of accuracy and precision of point estimates, as well as approximate run time. The model used in this simulation study is a kinetic-pharmacodynamic (KPD) mixed-effects proportional odds Markov model for ordinal data [1]. A sensitivity analysis investigated the impact of the richness of data, of the extent of variability of the random effects, and of the strength of the relationship between the outcome (toxicity grades) and the explanatory variable (dose).

Results: All tested optimisation algorithms gave similar results (those of the RRS and the simplex were almost identical, with the simplex being 60 times faster). The EBEs had some bias and quite low precision. Means of posterior distributions were more accurate estimates than modes. Sensitivity analysis showed a significant impact of data richness and especially of the identifiability of the model, that is a weak relationship between the outcome (toxicity grade) and the explanatory variable (drug dose) impedes the correct estimation of EBEs.

Conclusions: Correct EBEs of categorical data models may be obtained only in particularly informative conditions and only for individuals having some toxicity, and the quality of estimates is insensitive to the estimation method used. In those conditions, the simplex gives as good results as a global optimizer, and is much faster.

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Elodie Plan Nonlinear Mixed Effects Estimation Algorithms: A Performance Comparison for Continuous Pharmacodynamic Population Models

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Background: Nonlinear mixed-effects modelling has enabled substantial advances in the learning-and-confirming process during drug development. It has been accompanied by considerable improvements of the statistical softwares. Although algorithms were tested with PD data for categorical [1] and count models [2,3], and communications done for continuous models [4,5], a thorough study remains to be performed.

Objectives: To compare estimation performances of FOCE in NONMEM VII and R 2.9.1 nlme (FOCE_NM and FOCE_R), LAPLACE in NONMEM VII and SAS 9.2 (LAP_NM and LAP_SAS), adaptive Gaussian quadrature in SAS 9.2 (AGQ_SAS), and SAEM in NONMEM VII and MONOLIX 3.1 (SAEM_NM and SAEM_MLX) for a set of PD models.

Methods: Six models were considered, all derived from a sigmoid Emax model including baseline, multiplicative interindividual variability (IIV) on each parameter and correlation between Emax and ED50. The Hill factor successively was 1, 2 and 3 and the residual error was either additive or proportional. The design adopted for the datasets counted 100 individuals having an observation at 4 dose levels.
This stochastic simulations-estimation study was performed as follows, 100 datasets were generated in NONMEM and subsequently analyzed using each of the 7 algorithms. All algorithms started from initial estimates set to, firstly, the values used to simulate parameters, secondly, values set far away from the truth (higher fixed effects, lower random effects).
Results were examined through relative root mean square error (RRMSE) of the 100 estimates, in order to assess both accuracy and variability. A rank based on RRMSE was attributed to each algorithm for each parameter within each model; these ranks were then averaged across models, to allow the algorithms to be ordered.

Results: Parameter estimates could be obtained for all data sets with all algorithms, except FOCE_R. Considering all population parameters, from the best RRMSEs to the poorest, results were SAEM_NM (2.28), AGQ_SAS (3.13), LAP_SAS (3.65), LAP_NM (3.91), FOCE_NM (4.02), SAEM_MLX (4.15), and FOCE_R (6.83). For the parameter of interest ED50 (IIV), the average RRMSE was around 13.5 % (28.5 %) for all algorithms except FOCE_R: 30 % (70.5 %). Altering initial conditions made the picture more complex as properties did not change in a parallel manner for all algorithms.

Conclusions: All algorithms but FOCE_R performed with bias and precision of reasonable order of magnitude for these settings. Runtimes and the impact of the design are currently under study.

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Sebastian Ueckert New Estimation Methods in NONMEM 7: Evaluation of Robustness and Runtimes

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Background: NONMEM is the most widely used software for population PKPD analyses. The latest version, NONMEM 7 (NM7), includes several new sampling-based estimation algorithms in addition to the classical methods. Besides the recently evaluated accuracy and precision inherent in these methods [1], time to complete estimation and sensitivity with respect to initial values might be critical in practice.

Objectives: To investigate the runtimes and robustness of the FOCE, LAPLACE, ITS, IMP, IMPMAP, SAEM and BAYES methods in NM7.

Methods: Five models representing different types of PKPD data handling, continuous, binary, count, ordered categorical (OC), repeated time-to-event (RTTE), were used to simulate 100 datasets that were subsequently reestimated using NM7 through PsN 3.1.8 (http://psn.sf.net). All datasets were analyzed twice, (A) starting with initial estimates set to the simulation values and (B) starting at values randomly generated using the CHAIN option. For the latter, fixed effects were sampled from a uniform distribution to $[0;2\theta_{TRUE}]$ (IACCEPT=1); for the random effects, a Wishart density of variance ω_{TRUE} with 20 degrees of freedom was used. All estimation methods were used with their default settings and a test for convergence if available.
Average estimation time for each method was calculated from runtimes reported by NM7 (running on similar, dedicated machines). Median absolute deviation in final estimates between approach A and B was computed.

Results: Across models LAPLACE (FOCE for the continuous model) had the shortest runtimes, followed by ITS with runtimes equal to LAPLACE for the OC model and approx. half as fast for the remaining models. Runtimes for SAEM were between 20 and 40 times longer than for LAPLACE, but always faster than IMP and IMPMAP (40-60 times slower than LAPLACE). For all models BAYES was slowest (up to 250 times LAPLACE).
In general, sensitivity w.r.t. initial values was higher for random than for fixed effects and differed considerably between methods, models and parameters. However, the BAYES method showed the highest sensitivity in all scenarios. Furthermore, FOCE/LAPLACE had the lowest sensitivity across parameters for all but the OC model, where the IMP method performed best. For the continuous, binary, count and RTTE models, ordering of methods by increasing sensitivity yielded in: FOCE/LAPLACE, ITS, IMP, IMPMAP, SAEM, BAYES. For the OC the same ranking gave: IMP, IMPMAP, SAEM, ITS, LAPLACE, BAYES.

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Caroline Bazzoli New features for population design evaluation and optimisation using PFIM3.2: illustration on warfarin pharmacokinetics - pharmacodynamics

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Objectives: We developed the free R function PFIM [1] for population design evaluation and optimisation. Here, we illustrate the use of PFIM 3.2 that we recently launched.

Methods: Compared to PFIM 3.0 [2], PFIM 3.2 includes several new features in terms of model specification and expression of the Fisher information matrix (M_F). The library of pharmacokinetic (PK) models has been completed. Furthermore, a library of pharmacodynamic (PD) models is now available. PFIM 3.2 can handle a block diagonal M_F or a complete one. It is now also possible to use models including fixed effects for the influence of discrete covariates on the parameters [3], and/or inter-occasion variability (IOV) [4]. The predicted power of the Wald test for comparison or equivalence tests, as well as the number of subjects needed to achieve a given power can be computed.

Results: We use the standard example of warfarin PKPD. Warfarin is administered as a single oral dose to 32 subjects. Plasma concentration and effect on prothrombin complex activity (PCA) are measured. A one compartment PK model with first order absorption and elimination is used and the effect on PCA is described by a turnover model with inhibition of the input. First, we evaluated the empirical rich design and compared it to a design optimised using the Fedorov-Wynn algorithm. With 2.1 less samples than the empirical design, the optimal design provides similar predicted standard errors for the fixed effects. Then, as CYP2C9 is involved in warfarin metabolism, we wanted to evaluate designs with this genetic covariate effect on clearance. With the optimal design and a clearance assumed to decrease by 50% for patients with a mutant genotype, only 8 subjects are needed to obtain a power of 90% for the comparison test detecting the genetic effect. Finally, we planned a crossover PK study to assess the absence of interaction of drug X on warfarin absorption rate-constant (k_a). We assume some IOV on k_a. With the empirical PK design, the expected power is 46% to assess the absence of interaction on k_a. To achieve a power of 90% for this equivalence test, 116 subjects would be needed.

Conclusions: We illustrated the use of PFIM 3.2 showing the consequence of the design and of the number of patients on the power of the Wald test for discrete covariate. PFIM 3.2 is a great tool to evaluate and/or optimise designs and to control expected power of the Wald test for comparison or equivalence tests.

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Chao Chen Test Of Concept By Simulation: Comparing Response-Rate Findings Between Parallel And Titration Designs

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Background. Between-subject variability (BSV) in dose-response for efficacy (E) and toxicity (T) leads to difference in optimal dose among patients. Therefore parallel group trials (PRL) conducted at fixed doses are likely to underestimate the true response rate (R) due to over-dosing some patients while under-dosing some others at each tested dose. In drug development, early knowledge of a clinically meaningful R helps establish a realistic expectation for the potential medicine and facilitates crucial investment decisions. A titration design (TRN) that mimics clinical practice would help achieve this. Conceivably, the difference between the R estimated from these two designs can be influenced by factors such as therapeutic window, dose selection, measurement error for both E and T, and co-variance for E and T. Expected outcome can be simulated for both designs in scenarios defined in these aspects.

Objective. The objective of this work is to compare the response rate and the robustness and efficiency of its estimation, in terms of accuracy and precision, between PRL and TRN trials.

Methods. Trial data were simulated for hypothetical drugs whose E and T can each be described by a simple Emax model. Drugs with wide or narrow therapeutic index were tested at three dose levels. For TRN, dose was increased step-wise if E is lower than 0.5 and T is lower than 0.2. Subjects with E of at least 0.5 and T lower than 0.2 (at the final dose, in the case of TRN) were considered as responders. Simulations of PRL and TRN trials were conducted for various levels of BSV (25% to 75%) in the mean doses producing 50% of maximum E (ED50) and T (TD50). Impact of correlation (up to 0.9) between ED50 and TD50 was also considered. A small measurement error was included for both E and T. For each scenario and design, replicate trials of various sample sizes were simulated to obtain median and 90% confidence interval of R. Necessary sample size for achieving a desirable precision of R estimate at 90% confidence level was compared between the two designs. The R obtained using both designs were compared to the true value.

Results and Conclusion. Preliminary findings show that response rates estimated by TRN trials are up to twice that estimated by PRL trials, in the scenarios tested here. Further, lower sample size is generally required to achieve similar level of precision. These results support the preferential use of TRN where applicable.

Marylore Chenel Optimal design and QT-prolongation detection in oncology studies

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Objectives: QT interval prolongation is considered as a biomarker of *torsade de pointe* (TdP) in cardiac safety assessment in drug development. Thus, specific QT/QTc studies are usually performed in healthy volunteers, allowing an accurate estimation of such noisy data as QT interval length. This is however not possible in the specific context of oncology, where patients only can receive the drug. Population approach may help the description of PKPD relationship while taking into account all sources of variability (e.g. circadian rhythm, inter-individual variability, inter-occasion variability, residual error) [1], but the clinical constraints of phase I/II studies in oncology limit electrocardiogram (ECG) schedules.
Based on both known population PK and QT circadian rhythm models, assuming the PKPD relationship and testing different effect sizes, we propose a design strategy in order to assess cardiac safety by optimizing ECG sampling times.
Our aim is to propose a cardiac safety assessment method, based on both optimal sampling design and population PKPD modelling. The ultimate goal is to estimate the power of detection of any potential effect of SX compound on QT interval length.

Methods: First, a population PK model of drug SX was developed based on both oral and IV phase I studies (45 patients). This model was used to simulate the concentration of the drug based on the administration schedule of further studies.
Secondly, a population model describing the circadian rhythm of QTc was developed using data from two former QT/QTc phase I studies including a total of 160 healthy volunteers under placebo. Both model buildings were performed using NONMEM VI with the FOCE-I method.
Based on preliminary experience in PKPD of QT length, we assume a linear relationship between drug concentration and QTc effect. A range of values of the drug effect on QTc was tested (from 5 ms to 100 ms).
At last, the ECG record times planned in the trials to come were evaluated using PopDes 3.0 design evaluation feature and were compared to the optimal ones obtained by D-optimality criteria (with Fedorov exchange optimization algorithm) [2]. Planned ECG schedules are on days 1 (predose, 1h and 4h after 1st dose, 1h and 4h after 2nd dose), and on days 2, 4, 14 and 22 (predose and 1h after 1st dose each day). In parallel, the precision of estimation of the drug effect parameter was used in the computation of the power of detection of a significant drug effect.

Results: SX concentration-time data were fitted with a 3-compartment model with a first-order absorption. Inter-individual variability was added on clearance CL, bioavailability F, absorption rate Ka and on inter-compartmental constants Q2 and Q3. The residual error was multiplicative. The circadian rhythm of QTc was modelled as a mesor and a sum of three cosine terms (one amplitude and one lag-time per cosine term), representing three periods of 24, 12 and 6 h, with inter-individual variability on every parameter except the second amplitude term, and an additive residual error. The

drug effect is assumed to be proportional to the mesor.
The proposed design lead to a good estimation of every parameter of the model, according to the RSEs given by the population Fisher information matrix. Whatever the tested value of the drug effect, the statistical power of detection of a significant QT effect (i.e. that may cause a QT-prolongation adverse event) was found to be over 90 %. Comparison with optimal designs (under various time constraints) showed possible improvements for future studies.

Conclusions: This work proposes a modelling and simulation based strategy in order to make sure QT prolongation risk is correctly assessed in the context of clinical trials in oncology. Although the assumptions made on PKPD relationship is not negligible and will be assessed throughout further trials, the first results show a good power of detection of a QT-prolongation related adverse event with a feasible ECG recording design in oncology patients.

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Nicolas Frances Influence analysis explores heterogeneity in database before data processing by a parametric population method

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Objectives: How to proceed when heterogeneous population data are intended to be analyzed by means of a parametric population method like NONMEM. By means of an influence analysis, examine whether covariates are in the origin of this heterogeneity.

Methods: We previously developed a model describing tumor size dynamics in metastatic breast cancer treated by two drugs used in combination [1]. 222 patients received Docetaxel plus Capecitabine and have been monitored up to 50 weeks. The model includes K-PD components for the two drugs and resistance mechanism. Population analyses were performed using NONMEM v6 and simulation analyses, using Matlab v8a. Population analysis of these data results in high values of shrinkage for post hoc estimates. Therefore, Bayesian estimation procedure turns unreliable; the model can not be used to predict evolution disease or to individualize treatment. We attempted to partition the data in homogeneous groups which can be analyzed by a parametric method. Using the same model and the same database, three approaches controlling heterogeneity were applied: the live-one-out approach, the mixture model within NONMEM [2] and the non-parametric approach implemented within NONMEM [3].

Results: The live-one-out method shares the database in two groups. This result was confirmed by the mixture model. The non-parametric approach is under investigation. Administration and observation protocols did not explain the partition of data in two groups. No other covariates were available to explain this partition.

Conclusion: Influence analysis was applied to explore heterogeneity in the recorded database. It would be of interest to find covariates powerful to share patients in homogeneous groups before data processing. These covariates could be biologic markers (characteristics of tumor) or pharmacokinetic parameters (characteristics of drugs or individuals).

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Sergei Leonov Optimization of sampling times for PK/PD models: approximation of elemental Fisher information matrix

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Introduction: Optimal design of population PK and PD studies has seen an increasing interest over the last decade. In 2006, an annual Population Optimum Design of Experiments (PODE) workshop was initiated on the theory of optimal experimental design for nonlinear mixed effects models and its applications in drug development; see http://www.maths.qmul.ac.uk/~bb/PODE/PODE.html. A special session was organized at PODE 2007 to present different software tools for population PK/PD optimal designs. Presentations at this session were summarized at PAGE 2007 meeting, see Mentré et al. [3]; and a discussion of software tools continued at PODE 2009.

Methods and Objectives: The key component for constructing model-based optimal designs is the Fisher information matrix of a properly defined single observational unit; see Fedorov and Hackl [1]. In the context of PK/PD studies the elemental information matrix corresponds to a sequence of sampling times for an individual subject; e.g., see Gagnon and Leonov [2], Retout and Mentré [4]. In our presentation, we focus on certain options of calculating/approximating the information matrix which include different ways of modeling population variability; different orders of approximation of the mean response; regular scale of measurements vs log-scale for PK data.

Results: We present several examples, including (a) rather simple ones, where closed-form expressions may be obtained and, therefore, the comparison of different options becomes quite transparent, and (b) more complex models which are used in practice and which require Monte Carlo simulations to validate the results.

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Flora Musuamba-Tshinanu Evaluation of disease covariates in chronic obstructive pulmonary disease (COPD).

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Objectives: Prospective longitudinal studies in COPD often fail to clearly show improvement of the disease condition in patients under active vs. placebo arm. In addition to a potential lack of efficacy, this finding could be partly explained by the sensitivity of FEV1 (forced expiratory volume in one second) to patient demographics and disease-related inclusion criteria [1]. Thus far, the relevance of these factors on treatment effect size has not been assessed.

The aim of this exercise was to explore the influence of different patient demographics and disease-related factors on the outcome of clinical trials. A decline of FEV1of at least 50mL was considered to be clinically relevant for the purposes of this evaluation.

Methods: A KPD model was used to simulate the time course of treatment effect. Relevant continuous and categorical covariates were randomly sampled from a unique multivariate normal distribution constructed from the frequencies, distribution and correlations of these covariates in patients enrolled in three Phase III clinical studies [2]. Comparisons between simulated correlations and real patients were performed to assess the reliability of the estimated correlations. Subsequently, scenarios based on a typical placebo-controlled parallel group design were simulated with 100, 150 and 200 patients per treatment arm. The influence of relevant covariates on the treatment effect size (ΔFEV1) was explored by varying inclusion and exclusion criteria (i.e., reversibility to salbutamol/albuterol, disease severity, gender, smoking status, age and previous use of inhaled corticosteroids (PICS)). Each scenario consisted of at least 500 simulations. NONMEM v.6.2 and R were used in an integrated manner for data handling and subsequent statistical analysis. Statistical significance was assessed by hypothesis testing using analysis of covariance (ANCOVA).

Results: The proposed methodology enables generation of accurate summary statistics for covariates in the target population. In addition, demographic and disease-related factors were found to influence outcome not only in terms of magnitude of ΔFEV1 at completion of treatment, but also in terms of the onset of response. Whilst disease severity, reversibility, height, gender and age of patients seem correlated to each other, no significant association was observed between smoking status and PICS.

Conclusions: : Demographic and disease-related factors can affect the decline of FEV1 during the course of treatment in a clinical setting. Simulation scenarios can be used to quantify the implications of patient stratification and other relevant confounders on treatment outcome in COPD trials.

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Thu Thuy Nguyen Design evaluation and optimisation in crossover pharmacokinetic studies analyzed by nonlinear mixed effects models

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Objectives: Nonlinear mixed effects models (NLMEM) can be used to analyze crossover pharmacokinetic (PK) bioequivalence trials. Before modelling, it is important to define an appropriate design. The main approach for design evaluation and optimisation has been for a long time based on simulations but it is a cumbersome method. An alternative approach is based on the population Fisher information matrix (MF) which expression for NLMEM [1,2] was implemented in the R function PFIM [3,4,5]. We aim to propose an extension of the evaluation of MF for NLMEM in crossover trials and to apply this extension to design a future crossover PK study of amoxicillin in piglets.

Methods: We extended MF for NLMEM with inclusion of within subject variability, in addition to between subject variability, and with discrete covariates changing between periods. We used a linearization of the model around the random effects expectation. The power of the Wald test of comparison or equivalence was computed using the predicted standard error (SE). We evaluated these developments by simulations mimicking a crossover study with two periods, where piglets received amoxicillin and placebo at period 1 then amoxicillin and a product X at period 2. The objective of the trial is to show the absence of interaction of X on the PK of amoxicillin. Simulations were performed for a rich design as well as for an optimal sparse design derived from the rich one and with different values of treatment effect on amoxicillin clearance. We then used the extension of MF to plan a future study, with similar crossover design as the simulation study, based on results of a previous study of amoxicillin in piglets.

Results: For various simulated scenario, predictions of SE and powers by MF were close to the empirical ones obtained after fitting the simulated trials with the SAEM algorithm [6,7] in MONOLIX 2.4 [8]. The optimal sparse design had similar power as the rich design. These extensions were implemented in the new version 3.2 of PFIM, available since January 2010 [5]. For the application, from the expected SE computed by PFIM 3.2 for the future study, we predicted much more needed subjects than the previous study to show the absence of interaction of X on the PK of amoxicillin with good power.

Conclusions: This extension of MF for NLMEM is relevant. PK bioequivalence trials analyzed through NLMEM allow sparse designs and can be performed in patients. PFIM can be used to efficiently design these trials.

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Joakim Nyberg Global, exact and fast group size optimization with corresponding efficiency translation in optimal design

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Objectives: To increase the efficiency in various stages in drug development, optimal design has been used [1]. Group size optimization has been investigated previously by various techniques, e.g. within the Fedorov-Wynn algorithm [2], and implemented in software [2,3], however these search methods can be quite computer intensive.

The aim of this investigation is to develop and explore fast and accurate methods for optimizing the number of individuals in different design groups. A secondary objective is to use the method to translate the efficiency to a more interpretable number.

Methods: Two different methods were developed, 1) an exhaustive global search (GS) and 2) a faster approximation (FA) method.

For any group q of individuals the population fisher information matrix (FIM_q) is equal to the sum of the individual $FIM_{i,q}$ in the group. If individuals within a group have the same design and are indistinguishable then, for N_q individuals, $FIM_q=N_q*FIM_{i,q}$. The total population FIM is the sum of all the M design groups in a study $FIM=\Sigma FIM_q$. N_q can be varied within the limit for group q, $N_q \sim [N_{q.min}, N_{q,max}]$ and the sum of all individuals in the study can be varied between $[N_{tot,min}, N_{tot,max}]$. GS investigates every possible combination of N_q for all design groups M (only one calculation of $FIM_{i,q}$ per group is needed). An approximate, but much faster, solution (FA) can be found by sequentially assigning individuals to the most informative group.

The efficiency when comparing two designs, say A and B where A>B, can often be easily translated into the extra number of individuals that is needed in design B to reach the same information as design A. However, when e.g. D-efficiency is used, $D_{eff}=[det(A)/det(B)]^{1/p}$ and the number of design groups is >1 the determinant is nonlinear with respect to all N_q and it's not trivial to extract all N_q from the determinant. Instead the above search algorithms may be used to find the worst case scenario N_{max}, where additional individuals are added to design B in the group where they give the least amount of information, within restrictions $[N_{q.min}, N_{q,max}]$ and $[N_{tot,min}, N_{tot,max}]$. Similarly, $N_{min,}$ where the individuals are placed in an optimal way may be calculated.

Results: Group size algorithms 1) and 2) were successfully implemented into PopED (2.10) [3] and the efficiency translation is available as a graphical tool in PopED, contributing to a more intuitive understanding of efficiency. In general the GS and FA methods give similar results, however, the FA could not be used when the OFV (e.g. determinant) for a single matrix $FIM_{i,q}$ couldn't be calculated, e.g. when some rows/columns are zero. The optimization methods work with global optimal designs criterions as well as local designs criterions.

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Angelica Quartino Application of Optimal Design to Reduce the Sample Costs of a Dose-finding Study

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Objectives: A dose-finding study was planned with 3 treatment arms and 120 patients in each arm. To obtain an early readout of a pharmacodynamic effect, each patient was to receive one test dose as an immediate release tablet. For maintenance dosing an extended release tablet was to be given twice daily for 8 weeks. The planned PK sampling schedule consisted of 18 samples per patient (reference design) to assess the predictability in PK between the test dose and the repeated dosing.
The aim of the project was to optimize the PK sampling times and particularly to reduce the number of samples, without losing precision of the parameter estimates.

Methods: Based on data from Phase I-IIa studies a 3-compartment model had been developed that included transit compartments describing the absorption process. Non-linearities were identified and characterized for absorption and distribution. Day-to-day variability (IOV) was included in clearance. Several scenarios were optimized based on the relatively complex PK model. The number of samples was fixed to 18, 16, 14, 12 or 10 samples per patient. For each sample size, the sampling times were optimized both with and without restrictions to the practical aspects of study conduct. The D-optimization was performed in PopED v. 2.10 (http://poped.sourceforge.net/).
Furthermore, simulations (n=40) and re-estimations were performed using NONMEM 6.2. The precision (RSE%) and mean absolute error (MAE) were calculated in order to evaluate the performance of the designs on parameter estimations.

Results: The optimized design for the 18 samples per patient scenario increased the efficiency with 70%, which may be translated into 150 fewer patients needed, compared to with the reference design. The proposed optimal design incorporating clinical restrictions had a similar efficiency as the reference design, but included only 14 samples per patient. Thereby the study cost could be reduced by ~100 000 Euro.
The simulations showed comparable RSE% on average per parameter as was predicted by the optimal design for both the reference and proposed design. The MAE was <20% on average per parameter and was similar between the two designs.

Conclusions: Optimal design theory allowed identification of a design for a complex population PK model that is more informative than the original design, despite fewer samples. Thereby, the study cost could be significantly reduced.

Sylvie Retout Bayesian modeling of a PK-PD relationship to support an adaptive dose-finding trial

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Context: An adaptive sequential, within patient, dose-escalation design is proposed for a phase I study (N=12) to establish the relationship between the concentrations of a drug and the effects on a biomarker. Adaptive decisions are planned to be guided by a Bayesian modeling of the PK-PD relationship.

Objective: To investigate by simulation the feasibility and the efficiency of an adaptive dose-finding trial using Bayesian modeling of the PK-PD relationship.

Method: Twelve individuals, split into 4 cohorts of 3 patients, are planned to be treated with 3 sequentially escalating IV doses. The study starts from a predefined sequence of 3 doses. PK and PD measurements are collected for each dose. After each new cohort, Bayesian estimation is used to derive the posterior distribution of each population PK-PD parameters. Based on the medians of those posterior distributions, we estimate the dose - response curve as well as the doses at which 25%, 50% and 75% inhibition is reached. Those 3 doses, rounded to the nearest possible doses, define the new dose sequence for the next cohort.
We assume a two compartment first order elimination for the PK model, and an indirect response model for the PD, with inhibition of the production rate of response. Different scenarios are simulated based on possible values of IC_{50}, the concentration at which 50% of inhibition is reached, and k_{out}, the first order loss rate of response. We also investigate different sampling strategies, with either only one PD measurement per dose or two. For each scenario, we simulate 30 replications of the trial; the Bayesian estimation is performed using WinBUGS[1] via the R2WinBUGS library[2] of R[3].

Results: Whatever the scenario, two PD measurements per dose allow adequate estimation of IC_{50} (mean and inter-patients variability) at the end of the 4th cohort, whereas only one measurement per dose leads to an inaccurate estimation, and, as a consequence, to an inaccurate prediction of the time course of response. Regarding k_{out}, it is sometimes poorly estimated, especially for scenarios with low k_{out} value; however, it has less impact on the prediction of the time course of response.

Conclusion: That work demonstrates the feasibility and the efficiency of that adaptive dose-finding trial, increasing the chance to correctly estimate the PK-PD relationship early in the development of the drug, even on a few number of patients. It is expected to result in more streamlined Phase II/Phase III trial plan.

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Amit Taneja Optimisation of experimental design for drug screening in behavioural models of pain.

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Objectives: Recently, an optimal design technique was developed for the analysis of discrete variables[1]. We aimed to evaluate the feasibility of applying ED-optimality to screening of compounds taking model and parameter uncertainty into account. We illustrate these concepts using gabapentin as a paradigm compound .

Methods: The analysis consisted of two sequential steps: 1) model building & validation and 2) evaluation of a hypothetical screening experiment. Binary response in the logit space was used for optimisation of sampling times and dose levels under the assumption of known pharmacokinetic profile and expected potency range. Baseline/placebo effect, maximum effect and residual variability were assumed to be independent of treatment type and derived from historical data (n=45). We assumed drug potency (EC50) to be the parameter of interest. Optimisation scenarios were based on feasibility, with limits for sample size, dose levels and sampling times.Gabapentin concentrations were simulated for the selected range of doses and sampling times using a two-compartment pharmacokinetic model (V2=0.18 L, V3=3.8L, Cl=0.03 L/h, Ka=0.6 h-1, Q=78 L/h, F=0.83). The estimated EC50 was 198 ng/ml. Validation of the optimised design included simulation of response and refitting of the data to the same logistic model. For the prospective use of the method, optimisation factors were reassessed by testing a range of EC50 values for a hypothetical compound with similar pharmacokinetic profile. Response profiles based on candidate designs were then simulated and data analysed using a logistic model. In addition to parameter estimates, dose response curves are also presented. A Monte Carlo (MC) integration technique was used to integrate the FIM with Latin hypercube (LH) sampling. POPED 2.10/ MATLAB 7.9 were used for the optimal design. Simulations were performed in NONMEM 6.

Results: Preliminary results show that dose selection is essential for accurate parameter estimation (i.e., low relative standard error) . Doses of 100 mg/kg or higher were identified for gabapentin, with variable sampling times for each dose level. Sampling windows ranged from 0 to 8.8 hrs post-dose. Relative standard errors in parameter estimates remain sensitive to group size, despite repeated sampling.

Conclusions: We show how optimality concepts can be used to assess drug potency in screening experiments using historical priors to support model parameter estimation.

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Donato Teutonico Development of a template for clinical trial simulations in COPD

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Objectives: The ability to quickly and easily simulate clinical trial scenarios is essential in drug development [1]. However, despite the choices of software available for modelling and simulation, none offer the possibility for systematic trial simulation and consequently for the evaluation of trial performance. The objective of this exercise is to evaluate the performance of a modular template to assess scenarios (design factors), run simulations (model predictions) and evaluate output (graphical and statistical summary).

Methods: The template was conceived in a modular manner using independent scripts and MSToolkit, an R library for clinical trial simulation [2]. The template generates *in silico* patients, simulate response and evaluate the efficacy of the candidate design. The user can specify the parameters of study design, flag, drop out model and missing observations. The trial population can be defined from user-defined patients with a pre-specified covariate distribution matrix or from actual demographics. Given that independent scripts are used, the template may integrate functionalities to perform simulations with different software, like NONMEM, WinBUGS and R. In this case, an automated call to NONMEM VI is used to generate FEV1 responses in a COPD trial. The results are managed by the template reporting features, which includes a series of graphical and statistical summaries.

Results: The template enables the generation of relevant scenarios in an automated manner. A series of graphical and statistical summaries are generated at the end of the simulations that highlight the changes relative to baseline (ΔFEV1) for each dose level compared to placebo, among other, plots such as FEV1 vs. time, ΔFEV1 vs. time and tables such as median and percentiles are produced and saved in a simulation folder specially created. The statistical power of the study was also correlated to the number of subjects and the effect of other parameters on the outcome was evaluated (dose, study duration, drop-out).

Conclusions: The combination of MSToolkit with modular R scripts has provided key components for the creation of design scenarios and enabled the execution, analysis and reporting of clinical trial simulation results. As this is part of an ongoing effort, it is anticipated that future functionality and versatility will also facilitate exchangeability between simulation software packages. The template can be easily adapted to suit other therapeutic applications and study design types.

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Sebastian Ueckert Comparison of Different Global Optimal Design Approximations

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Objectives: To compare Monte-Carlo integration and Laplace integral approximation for global optimal design in terms of precision, runtime and best study design. Furthermore, to explore the performance of a new algorithm using the Laplace approximation, but avoiding explicit calculation of 2nd order derivatives.

Methods: Calculation of globally optimal designs require the evaluation of an integral over the complete parameter space. In this work we compared the performance of the following four different numerical algorithms in computing ED optimal designs implemented in PopED [1]:

(I) Monte-Carlo integration with random sampling (MC-RS): integration is performed by sampling random parameter combinations, evaluating the integrand for those samples and averaging the results.
(II) Monte-Carlo integration with Latin hypercube sampling (MC-LHS): using stratified Latin hypercube instead of random samples.
(III) Laplace integral approximation (LAPLACE): integration is performed by finding the mode of the integrand and performing a second order Taylor expansion around this point [2].
(IV) Laplace integral approximation with BFGS Hessian (LAPLACE-BFGS): using the BFGS algorithm [3] to calculate an approximate Hessian during the maximization step of the LAPLACE.

A hypothetical experimental design for a drug following a simple one compartment model with IV bolus dosing, 20 individuals and 2 samples per individual was used for the comparison. Performance of the different methods was assessed in terms of optimal sampling points, runtime and objective function value. OFV obtained with MC-RS using 100,000 samples served as a reference for all methods. Variability of Monte-Carlo methods was evaluated by repeating computations for different number of random samples.

Results: Calculated OFV differed considerably between methods with the MC-LHS method being closer to the reference. Variability in OFV was higher for MC-RS than for MC-LHS and decreased with number of samples. However, optimal sampling points found by all methods were similar. In terms of runtime LAPLACE-BFGS performed best, followed by LAPLACE and the MC methods. For MC methods, runtime was proportional to number of random samples. Computations with MC-LHS were slightly slower than with MC-RS.

Conclusions: The LAPLACE method constitutes a fast alternative to computational intensive MC methods, however stability and application to non-normal priors has to be further investigated. Runtime of LAPLACE was further reduced by using an approximate BFGS Hessian.

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Venkata Pavan Kumar Vajjah Generalisation of T-optimality for discriminating between competing models - an application to paracetamol overdose

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Background and Objectives: The T-optimality criterion for model discrimination were introduced by Atkinson and Fedorov [1]. Application of this method required the condition that one of the competing models is correct. We term this criterion local T-optimality. In addition, T-optimal designs are generally not efficient for parameter estimation [2, 3]. The aims of current work are (1) to develop and assess a robust T-optimal method that relaxes the requirement that one of the candidate models is true and (2) to combine this robust T-optimal method with robust D-optimality for parameter estimation. The motivating example is paracetamol in overdose. Reports on the pharmacokinetics (PK) of paracetamol in overdose are conflicting with authors describing both linear [4] and nonlinear elimination [5] disposition. This has significant implications for the use of N-acetylcysteine as an antidote in treatment of patients who take an overdose of paracetamol.

Methods: The two competing models for the PK of paracetamol in overdose were; (1) a 2-compartment model with linear elimination (M1); (2) a 2-compartment model with Michaelis-Menten elimination (M2). The population PK parameters for M1 were available from the literature from paracetamol at therapeutic doses [6]. Simulations were conducted to find values of Vmax and Km values such that the PK profile of paracetamol using M2 looks similar to M1 at therapeutic doses (up to 2g/dose) but would yield different profiles after overdose (e.g. 30g). A HClnD-optimal design was obtained for both the models using WinPOPT [7]. Three hybrid DT [8] designs were constructed: (1) using local T-optimality assuming M1 to be correct (D1), (2) using local T-optimality assuming M2 to be correct (D2) and, (3) robust T-optimality where either M1 or M2 could be correct (D3). Using NONMEM VI, 100 data sets were simulated and estimated under each of D1, D2 and D3 assuming that either M1 or M2 were correct. The power was calculated as the proportion of times that the correct model was identified based on a likelihood ratio test. The number of subjects in each simulated data set was calibrated so that the power was close to 60% in order to see a signal from the different designs.

Results: The Vmax and Km values obtained in simulation study are 3540 mg/h and 200 mg/L, respectively. The Hybrid local DT-optimal designs D1 and D2 were not similar indicating that assuming either M1 or M2 is true could be misleading. The power of D1, D2 and D3 if M1 was correct was 70%, 40% and 52% respectively. The power of D1, D2 and D3 if M2 was correct was 13%, 87% and 87% respectively. The D3 design performed acceptably to either models being correct model.

Conclusions: The assumption inherent with local T-optimality, that one of the two competing models is true, may result in poor study power. A robust T-optimality method is described that relaxes this assumption which when combined using a hybrid DT-optimality had good power to distinguish between the models without assuming one of the two competing models is true.

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Coen van Hasselt Application of a semi-physiological model describing time-varying pharmacokinetics to support optimal clinical study design

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Introduction: Physiological changes during pregnancy can alter drug pharmacokinetics[1] (PK). Precise quantification of PK changes during pregnancy is therefore required if drugs are to be administered to expectant mothers, although design of such experiments can be difficult. D-optimal design is one method that can be used to identify sampling schedules that ensure precise parameter estimation. However, prior models that account for time-varying PK during pregnancy are unlikely to exist challenging the use of D-optimality.

Objectives: The objectives of this work were to a) develop a semi-physiological PK model from existing literature, which described the time-varying PK of enoxaparin during pregnancy; b) use this model to determine an informative sampling design for a prospective clinical study quantifying the PK of enoxaparin during pregnancy.

Methods: The physiological variables total body water and creatinine clearance were selected as predictors for pregnancy-related changes in volume of distribution and clearance. The mean change in these physiological variables was linked to a population PK model for enoxaparin in non-pregnant females.

The semi-physiological model was then used to simulate enoxaparin concentrations throughout pregnancy, which were compared concentrations simulated from an empirical model[2] that described the population PK of enoxaparin during pregnancy.

The semi-physiological model was then used to develop an optimal sampling design using WinPOPT[3], which was evaluated by means of simulation using the previously published empirical model[2] and subsequent re-estimation.

Results: The simulated concentration-time profiles from the semi-physiological model were comparable with the profiles of the previously published model[2]. A D-optimal design was successfully developed using the semi-physiological model. This design resulted in precise parameter estimation using data simulated from the true model. The need for a changing design over pregnancy was not evident, most likely due to the magnitude of change in PK parameters not being large enough.

Conclusions: This work demonstrates how relevant physiological variables published in the literature can be used to make informed predictions on the PK of enoxaparin during pregnancy. Moreover, we

have demonstrated that a literature based semi-physiological model can be used to support development of informative sampling designs.

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Paul Baverel Informativeness of Internal and External Validation Techniques in Various Simulation Settings

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Objectives: Internal (IV) and external (EV) validation procedures are two well-established statistical methods testing the predictability of a model. Selection of the appropriate model-based diagnostic is essential, both techniques presenting limitations in specific circumstances. The aim was to compare the predictive performance of IV and EV for similar sized learning datasets and in various simulation settings, a population (PV) validation scheme being used as reference.

Methods: An automated procedure was implemented in PsN [1] to operate series of stochastic simulations followed by estimations (SSE) in NONMEM 6.2, coupled to 3 distinct numerical predictive checks (NPC: corresponding to IV, EV, and PV) based on an oral one-compartment PK model. Random effects were included on all model parameters (30% CV) and residual variability was set to 10% CV. For IV and EV, simulated datasets were designed so that the number of individuals (IDs) ranged from 3 to 384, with an increment multiplication factor of 2 within each new SSE series (i.e. 3,6,,,...192,384). Each individual contributed to 3 sampling points obtained from a preceding optimization in PopED 2.0 [2]. For PV, a large number of individuals (1000) were simulated and symbolized the population pool from which IV and EV individual samples were drawn from. In such settings, from each set of SSE final parameter estimates, NPC was applied to initiate IV, EV, and PV. For IV, the same dataset was used for estimation and prediction, whereas for EV and PV, a new (validating) dataset of similar size as the learning was simulated. Finally, mean errors (MEs) and mean absolute errors (MAEs) of (IV-PV) and (EV-PV) NPC outcomes were computed as indicator of bias and imprecision respectively. [3]

Results: At the median of observations/predictions and across the range of data size investigated, both IV and EV were in good agreement with PV, no consistent bias and little imprecision being revealed. However, discrepancies occurred between IV and EV at the tail of the observations/predictions distribution (90% prediction interval): for small learning datasets (<48 IDs), IV predictions were more biased and imprecise than EV. As expected, increasing data size reduced bias and imprecision for both IV and EV.

Conclusions: Results suggest that when the dataset is small (<48 IDs), data splitting followed by EV is recommended, while when dataset is large, use of IV is advised. However, these outcomes are undoubtedly model and design dependent and cannot be generalized.

Ackowledgement: This work has previously been presented at ACoP 2009 conference.

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Roberto Bizzotto Multinomial logistic functions in Markov-chain models for modeling sleep architecture: external validation and covariate analysis

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Objectives: A mixed-effect Markov-chain model based on piecewise linear multinomial logistic functions has been recently proposed [1] to characterize the time course of transition probabilities between sleep stages in insomniac patients treated with placebo. The aims of this work were to further develop the model, explore the covariate effects, and perform the external validation of model structure and parameters estimates.

Methods: Polysomnography data were obtained from the first night after placebo administration to patients affected by primary insomnia and belonging to two different placebo-controlled, parallel studies (study A and study B with NA=116 and NB=81). Time courses of sleep stages (awake stage, stage 1, stage 2, slow-wave sleep and REM sleep) were assumed to be realizations of a Markov-chain process and modeled using multinomial logit functions, from which transition probabilities can be easily back-calculated [1]. In this work, a thorough investigation of the structure and predictors of the logit functions has been performed, including: a) the choice of ratios entering the logits, b) the estimation of significant correlation terms, c) the implementation of a longer memory for the Markov-chains, d) a different description of transitions during and after initial sleeplessness, e) a reduced parameterization of the logits time dependence. Model building was based on dataset A and guided by model adequacy criteria (log likelihood ratio test and Akaike Information Criteria) and visual predictive checks (presented in [3]). External validation of the final model was based on dataset B and relied on the evaluation of objective function value (OFV), empirical Bayes estimates (EBEs) distributions, and posterior predictive checks (PPCs). Finally, stepwise covariate analysis within NONMEM [2] was performed on dataset A.

Results: The changes introduced in the model before including covariates led to an increase of data likelihood, without significantly affecting runtimes and model size. Although sleep maintenance parameters resulted still slightly biased, the final PPC showed a definite improvement in the distributions of aggregated sleep parameters. When using dataset B, PPC provided very similar outcomes; moreover, OFV and EBEs distributions did not change substantially when parameters estimated from dataset A were plugged in. Finally, age, gender and BMI were found as statistically significant covariates affecting many transition probabilities in different night time intervals; however, their inclusion did not improve substantially PPC performance and provided limited reduction in inter-individual variability.

Conclusions: Previously proposed mixed-effect Markov-chain models for describing sleep architecture of insomniac patients treated with placebo [1,4] were further improved. External validation has shown that the developed framework provides not only an adequate sleep model but also reliable parameter estimates for a general population with similar sleep characteristics and study conditions. Some influential covariates have been detected whose clinical relevance deserves further exploration in a wider population of insomniac subjects.

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Roberto Bizzotto Multinomial logistic functions in Markov-chain models for modeling sleep architecture: internal validation based on VPCs

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Objectives: Simulation based diagnostics are increasingly used to illustrate model properties [1], especially in the context of categorical data. A multilogit Mixed-Effect Markov-chain model has been recently proposed for describing sleep architecture in primary insomnia patients [2,3]. The aim of the present work was to perform the internal validation of this model based on visual predictive checks (VPC) for categorical data [4].

Methods: Data were obtained from the first-night of polysomnographic (PSG) recordings from 116 subjects diagnosed with primary insomnia and belonging to the placebo arm of a PSG-parallel study. Each individual sequence of sleep stages (awake, stage1, stage2, slow-wave sleep and REM) was supposed to obey to a Markov-chain and each transition probability was modeled through a piecewise linear multinomial logistic function depending on time [2,3]. VPCs were performed to evaluate potential model misspecification and model robustness (uncertainty of model parameters estimates). Each VPC was based on 100 datasets simulated from point estimates of model parameters. Two types of VPCs were performed: a) the first one is based on simulated and observed data; b) the second one depends on model parameters re-estimated from the simulated data. In particular, a) transition frequencies and fractions of observations for each stage were calculated from raw data considering ten intervals of the night having equal width and compared to the 95% confidence interval derived from simulated datasets on the same intervals. Subsequently, b) typical transition probabilities and the 5% and 95% percentiles of individual transition probabilities distribution along the night were computed from model parameter estimates and compared to their corresponding simulation based 95% CI.

Results: The VPCs showed in general a good agreement between the statistics derived from raw and simulated data. Most of the transitions among sleep stages were well characterized in terms of parameters accuracy and precision. A slightly higher uncertainty was observed for the transitions from slow-wave sleep and REM sleep. This result is likely due to the limited occurrences of these transitions.

Conclusions: Model-based diagnostics are essential in the process of model development and validation: their application may become complex in case of categorical data. The model adequacy of our multinomial Markov-chain model of sleep architecture [3,4] was addressed by performing VPCs on transition\stages frequencies and model parameters. Overall, the application of VPCs allowed to conclude that parameters estimates were unbiased and precise and did not suggest model misspecification.

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Roberto Bizzotto PK-PD modeling of Wake after Sleep Onset time-course

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Objectives: Wake after Sleep Onset (WASO) quantifies the night time spent awake after falling in a persistent sleep state and is considered one of the key sleep parameters to characterize the effect of a hypnotic drug. SB-649868 is a potent orexin antagonist with demonstrated ability of decreasing such clinical endpoint. A pharmacokinetic-pharmacodynamic (PK-PD) model using total WASO (i.e., WASO on the whole night) has recently been developed [1]. The aim of this work is to model SB-649868 effect on WASO time course (i.e., WASO by hour), and to compare WASO time-course vs. total WASO model outcomes.

Methods: Pharmacokinetic (PK) and pharmacodynamic (PD) data were collected in a polysomnography randomized, double-blind, placebo-controlled, cross-over study. 52 subjects spent two nights in each arm of the study. Plasma concentrations data were analyzed using a non-linear mixed-effect approach as implemented in NONMEM VI. Modeled PK profiles were then used to characterize WASO time-course, i.e. the time spent awake in each hour of the night after falling asleep persistently at least once. The final PK-PD model was used for predicting both WASO time-course and total WASO after treatment with different doses using an improved formulation.

Results: A PK-PD model was developed assuming that each contribution to total WASO (observed at 1-hour intervals) was described by its own typical parameter, in the logit scale. The individual deviation from the typical logit value of a specific interval was assumed to belong to a normal distribution and correlated to the deviations of the same subject in the other intervals. A first night effect and a treatment effect were found to be statistically significant. A Weibull model was found to best describe the concentration-related effect. Statistically relevant differences among different night intervals were detected in certain parameters of the Weibull model. Visual predictive check (VPC) showed good performance of the model for both WASO time-course and total WASO. When comparing the new PK-PD model to the previous one on total WASO [1], similar outcomes were obtained on the VPC level, but residual unexplained variability was reduced. In the simulations using the improved formulation the residual variability dropped from 30% to 10% with the new approach.

Conclusions: A new PK-PD model has been developed for accurately assessing both the time-course and the total WASO, after treatment with SB-649868. Residual variability was lower considering the time-course model. This model is more appropriate to thoroughly characterize the potential effect of changes in doses and formulation.

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Emmanuelle Comets Using simulations-based metrics to detect model misspecifications

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Objectives: Model evaluation is an important part of model building, and has been the subject of regulatory guidelines. Weighted residuals have long been used for model diagnostics, but their computation is based on a linearisation of the model and their shortcomings have been demonstrated [1]. Prediction discrepancies (pd) and normalised prediction distribution errors (npde) have been proposed which take into account the full predictive distribution [2] and have better statistical properties [3]. In the present paper we present an alternative way to compute npde which avoids an approximation during the decorrelation step. We also illustrate the use of npde, pd, and VPC on several simulated datasets.

Methods: We will assume that a model MB has been built using a building dataset B. Our null hypothesis is that this model can be used to describe the data collected in a validation dataset V (which can be B in internal evaluation).

Visual Predictive Checks (VPC), prediction discrepancies (pd) and normalised prediction distribution errors (npde) all belong to the general class of posterior predictive check, whereby model MB is used to simulate data according to the design of V, and the metric computed on the real data in V is compared to the distribution of the same metric obtained through the simulations. Visual Predictive Checks are obtained by plotting prediction intervals over time. Prediction discrepancies are computed as the quantile of the observation in the corresponding predictive distribution, while npde are computed similarly but after decorrelating both simulated and observed data [4]. Scatterplots of pd and npde versus time or predicted concentrations can be used to evaluate different aspects of model misspecification.

Results: Prediction bands around selected percentiles can be obtained through repeated simulations under the model being tested, and their addition to VPC plots or plots of pd and npde versus time and predictions are useful to highlight model deficiencies. Finally, tests can be used to assess whether the npde follow their theoretical standard normal distribution, and provide a complement to graphs. Datasets were simulated under several conditions: a first dataset was simulated with the same model used to compute the metrics; three other datasets were simulated with different model misspecifications. Applying the different tests and graphs to the metrics computed for each dataset, we show how various model misspecifications can be detected.

Conclusions: Graphs with prediction bands were found to be especially useful and visually appealing, while tests based on the npde were able to detect model misspecification for the three simulated datasets.

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Didier Concordet A new solution to deal with eta-shrinkage: the Weighted EBEs!

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Objectives: Empirical Bayes Estimates (EBEs) of individual PK/PD parameters are given by all population PK/PD software. They are widely used for covariate model building and during model evaluation (via IPRED and IWRES). Unfortunately, they suffer from the shrinkage phenomenon that makes fuzzy the potential relationship between covariates and individual parameters and which may lead to the so-called 'perfect-fit' phenomenon [1]. Eta-shrinkages greater than 20-30% have been advocated to be 'lethal' for the use of EBEs [2], leaving the population PK analyst quite lonely with his job! However, globally high eta-shrinkage does not imply that all EBEs are shrunk: some individuals may have informative EBEs. We thus propose new weighted EBEs (WEBE) that allow the analyst to evidence the hidden relationship between covariates and individual PK/PD parameters by fully exploiting all information available on each individual.

Methods: The method we propose comes from the seminal work of Lange and Ryan [3] about linear mixed effects models. Currently, all individuals contribute with the same weight to all exploratory (e.g. EBEs vs. covariates) and diagnostic plots (e.g. IWRES vs. time, Q-Q plots of eta/epsilon), irrespective of the uncertainty on EBEs. The main idea of the present method relies on weighting EBE of an individual proportionally to its precision. Weighted plots and statistics (IWRES, ETAS …) are derived from these weighted EBEs. The performance of our method was assessed over a range of population PK and/or PD models.

Results: Our weighted plots showed good performances in detecting hidden relationships between individuals PK/PD parameters and covariates, even when eta-shrinkage was very high, provided rich data were available for some individuals. The corresponding statistics fully exploit these weights. Of course, our method does not create any information: forget it when all individuals are poorly documented!

Conclusions: We have developed a new method to reveal hidden relationships between individual PK parameters and covariates and to help in model validation. Its good theoretical properties were confirmed by several simulation studies using different PK and/or PD models.

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Paul Matthias Diderichsen A comparison of sequential and joint fitting of pain intensity and dropout hazard in acute pain studies

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Objectives: Subjects in acute pain studies not receiving adequate pain relief have a high risk of dropping out of the study. The non-random dropout necessitates the construction of appropriate dropout models in order to reproduce the observed data in simulation. For simplicity, such dropout models may be developed in a sequential manner, where a pain intensity (PI) model is developed and used to explain the observed dropout from an acute pain Phase 2 study (N=91). However, when dropout depends on unobserved data (between observations of PI), the dropout and PI should be modeled simultaneously. The objective of this work was to compare the estimates obtained from fitting PI and dropout data sequentially vs. simultaneously.

Methods: The PK and PI following administration of study drug were modeled as described in [1]. The risk of dropping out was modeled using an informed dropout model (ID [2]), where the hazard was defined as the product of a baseline hazard and an exponential function of the model-predicted PI, modified by a pain memory factor as described in [1]. Parameter values for the three models were estimated in NONMEM, initially using a sequential approach. The joint likelihood for observing the PI data (Y_O) and dropout data (T) is given by [2]:

$$P(Y_0,T)=\int P(T|Y_0,\eta)\, P(Y_0,\eta)\, P(\eta)d\eta$$

The conditional likelihood for the dropout data depends on the random effect, η, and should therefore be fit simultaneously with the PI data. In order to investigate the error made by fitting the ID model sequentially, the PI and dropout model parameters were fit simultaneously and compared to the results from the sequential analysis.

Results: Dropout model parameter estimates changed up to 14% when PI and dropout model parameters were fit simultaneously instead of sequentially, however no PI model parameter changed more than 4%.

Conclusions: In acute pain studies where dropout can be assumed to truly depend on PI, dropout data is expected to contain information about the underlying PI. Hence simultaneous fitting of PI & dropout data is expected to improve the fit of the PI and the PI dependent hazard. In the present analysis, jointly fitting the dropout and PI data using the ID model did not provide a visibly better fit compared to the sequential fit. This was possibly due to the intensive PKPD sampling which reduced the amount of additional pain intensity information contained in the underlying model as compared to observed data.

References:

[1] Diderichsen et al.: Modeling “Pain Memory” is Central to Characterizing the Hazard of Dropping Out in Acute Pain Studies, ACOP 2009 (poster)

[2] Hu and Sale: A Joint Model for Nonlinear Longitudinal Data with Informative Dropout, J Pharmacokinetics and Pharmacodynamics, 30, 2003

Paul Matthias Diderichsen Sufficiently high observation density justifies a sequential modeling approach of PKPD and dropout data

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Objectives: A common approach to modeling the exposure-dependent efficacy or safety outcome of a clinical trial is to first develop a model describing the pharmacokinetics (PK) of the drug, and subsequently explaining the observed efficacy using the mean or individually predicted PK as an independent variable in a pharmacodynamic (PD) model. A similar sequential approach may be used in the construction of hazard models for describing observed dropout, where the predicted PKPD is used to drive the hazard model. Unless the hazard is described using observed data only, the sequential approach to modeling the hazard is theoretically less preferable to a simultaneous approach where PKPD and hazard model parameters are estimated jointly. In this work, we investigate if sequential and simultaneous approaches result in similar parameter estimates for six simulated study scenarios with varying density of PKPD data.

Methods: The data for this study was simulated using a one-compartment PK model and an inhibitory PD model describing the effect (EFF) using parameter IC50. Dropout was simulated using a hazard proportional to the efficacy: HAZ=A*EFF. Six scenarios with increasing number of PD observations (from 2 to 24) were simulated. The hazard of dropping out was modeled using a random dropout model (RD [2]) based on observed data only, and an informed dropout model (ID [2]), that used the PD model to explain the hazard. The ID model was fit sequentially (SEQ-ID) and simultaneously (SIM-ID) with the PD data. PD and hazard model parameters were estimated for the 3 models using NONMEM.

The joint likelihood for observing the pain intensity data (Y_O) and dropout data (T) is given by [2]:

$$P(Y_0,T)=\int P(T|Y_0,\eta)\, P(Y_0,\eta)\, P(\eta)\mathrm{d}\eta$$

The conditional likelihood for the dropout data depends on the random effect, η, only in the ID models, which should therefore be estimated simultaneously with the PD data.

Results: The deviation from the true parameter value was estimated for A, IC50, the CV on IC50, and the error on EFF. The deviation in IC50, CV(IC50) and A decreased when the density of observed data was increased. While the hazard proportionality factor, A, was well estimated for both the SEQ-ID and SIM-ID methods in all six scenarios, IC50 was accurately estimated in sparse data scenarios only when the SIM-ID model was used.

Conclusions: The hazard model parameter was well described in all six scenarios with either of the SIM-ID and SEQ-ID approaches. The benefit of the joint analysis was a reduction in deviation of PD model parameter in sparse scenarios where the true effect had considerable fluctuations between observations. The benefit of a sequential analysis was a simplification of models and datasets and decreased model runtime. While the conclusion that sufficient density in the observed PD data allows for a sequential analysis holds for the present simulated dataset, other datasets require individual consideration as to whether sequential or joint analysis should be used.

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Julie Grenier Population Pharmacokinetic Meta Analysis: Inhibition by Quinidine of the First-Pass and Systemic Metabolism of Dextromethorphan to Dextrorphan

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Objectives: Zenvia is a combination product of Dextromethorphan (DM) and Quinidine (Q) where Q is used as an inhibitor of DM metabolism by CYP2D6 enzymes. The objectives of this study were to determine the population pharmacokinetic (PK) parameters of Q, DM and its metabolite dextrorphan (DX) in plasma after single and multiple doses of Zenvia and to identify the impact of demographic covariates on the population PK parameter estimates.

Methods: The results from a series of Phase I - III studies were pooled. Data from 133 subjects were analyzed using a total of 5730 data points for Q, DM and DX combined. The impact of covariates was assessed graphically. First, Q data were modeled and resulting PK parameters were then fixed for each individual so that predicted Q concentrations were used for the modeling of DM and DX plasma data with inhibition by Q of the metabolic conversion of DM to DX. Standardized visual predictive checks (SVPC) were evaluated for the internal and external validation of the final population PK models.[1] A set of 70 subjects from other studies were used for the external validation.

Results: The population PK model that best described the PK of Q in plasma was a 2-compartment model with linear absorption and elimination and a lag time for absorption. The population PK model that best described the PK of DM and DX in plasma was a model with 2 first-order constants of absorption with lag times, 2 compartments for DM and 1 compartment for DX. The metabolic conversion of DM to DX was described by a sigmoidal inhibition model related to Q concentrations, both at first-pass and systemically. The model discrimination and selection for DM/DX was based on data from extensive-metabolizers (EM) only. A maximum *a posteriori* Bayesian (MAPB) analyses was performed on data from one of the studies where there was an intermediate metabolizer (IM) and an ultra-metabolizer (UM). The model was adequate to fit these 2 subjects. A clear difference was seen in the inhibition curves between the different genotypes.

Conclusions: The PK of Q, DM and DX are well described by the population PK model developed. None of the available covariates were considered significantly correlated with any of the PK parameters. The external validation results show that the model predicts well the plasma PK of Q, DM and DX and can be used for the MAPB analysis of other sets of data or to predict the outcome of different dosing regimens for future clinical use.

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Julie Grenier Population Pharmacokinetic and Pharmacodynamic Meta Analysis of Zenvia: Modeling of QT Prolongation

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Objectives: Zenvia is a combination product of Dextromethorphan (DM) and Quinidine (Q) where Q is used at a subtherapeutic level as an inhibitor of DM metabolism by CYP2D6 enzymes. The objective of this study was to establish the relationship between the predicted plasma concentrations of Q, DM, and DX and the changes in QT intervals from baseline at 3 dose levels (including supratherapeutic).

Methods: Results from 2 thorough QT studies were pooled and included 82 subjects. A total of 7446 QT measurements were used for baseline assessment and 11,382 QT measurements were used for QT prolongation evaluation. Based on a previously developed population PK model[1], individually predicted Q, DM and DX concentrations were used for QT prolongation modeling. The first step was to model all baseline and placebo QT values, using actual time. Once the most appropriate model was selected, individual baseline QT interval parameters were fixed for the model discrimination of QT prolongation. Linear, Emax and sigmoidal Emax models were tested with and without a time-delay for Q, DM and DX separately. Additive PD models were also tested. The best PD model selected was then used to fit both baseline and QT prolongation at the same time. Standardized visual predictive checks (SVPC) were evaluated for the internal validation of the final population PD model.[2]

Results: The model that best fitted the baseline/placebo QT intervals used individual correction factor for RR intervals. Diurnal variations were modeled using a truncated Fourier series with 3 oscillators. Between-day variations were also fitted with a truncated Fourier series but with 2 oscillators and fitted periods. Placebo was not found to be different from baseline.[3] A sigmoidal Emax model dependant on Q concentrations only was the model that best described the observed QT prolongation. The best fit was obtained by fitting the baseline parameters at the same time. No covariate was deemed significantly correlated with any of the PD parameters.

Conclusions: The wide range of available Q concentrations allowed for the characterization of a sigmoidal model relating the prolongation of QT interval to Q concentrations. Although no definitive conclusion can be made about the potential of DM or DX to induce QT interval prolongation, the plasma Q concentrations are sufficient to explain the observed drug-induced QT interval prolongation following Zenvia administration.

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Mary Lor Modeling and Simulation of Drug X and its Metabolite in Plasma and Urine

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Objective: To construct a pharmacokinetic (PK) model using plasma and urine data from healthy subjects to characterize the PK of Drug X and its metabolite.

Methods: Single ascending oral doses of Drug X were administered to 3 groups (n=30) over 2 periods. Plasma and urine samples were collected over 72 hours. Concentrations of Drug X and its metabolite were analyzed using a validated LC/MS/MS method. Different models were developed and tested using ADAPT II[1] and a population analysis was performed using IT2S[2]. Simulations were performed to determine the length of time that a given plasma concentration was maintained following daily oral drug administration.

Results: The structural PK model that best characterized the PK of Drug X was a 2 compartment model with 2 absorption peaks; each associated with a lag time and a 1st order absorption rate constant. The best model selected for the metabolite concentrations was a 1 compartment model. Drug X was eliminated in urine, converted to the metabolite and eliminated by other pathways while the metabolite was eliminated in urine and other pathways. All eliminations were non-linear. Many subjects exhibited multiple peaks in the plasma concentration-time profiles which were most likely due to intra-subject variability in the absorption of Drug X from the gastrointestinal tract. In order to provide an adequate description of the observed data, the final PK model was integrated with 2 absorption rates and 2 delay constants.

Conclusion: Drug X was best described by a 2 compartment model with 2 absorption rates; each associated with a lag time and a 1st order absorption rate constant while the metabolite was best described by a 1 compartment model. Drug X and its metabolite both exhibit non-linear elimination. Clearance of Drug X appeared to be predominately non-renal in nature. The elimination t½ increased with increasing dose.

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Joakim Nyberg Investigations of the weighted residuals in NONMEM 7

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Objectives: Improving the calculations of the weighted residuals has proven to be of high importance; especially if the model is highly nonlinear in the random effects [1,2]. Various new and published methods for calculating the weighted residuals have been implemented in NONMEM 7 [3]. The aim of this project is to investigate these new methods.

Methods: A sigmoidal Emax-model (gamma=4.5) that showed the importance of using CWRES versus WRES was used to investigate the different residuals [1]. Emax and EC50 both had between subject variability (BSV) corresponding to ~71% CV. The study design was rich; 200 individuals with 25 observations each.
Five different scenarios were investigated with the true and a misspecified model (gamma=1): 1) Additive residual unexplained variability (RUV), 2) proportional RUV, 3) exponential RUV, 4) exponential BSV on the proportional RUV, 5) Between occasion variability on Emax with an additive RUV.
The residuals investigated were: NWRES (First order (FO) residuals without interaction), WRESI (FO residuals with interaction), CWRES (FO conditional residuals without interaction), CWRESI (FO conditional residuals with interaction), ECWRES (Monte Carlo calculated weighted residuals without interaction), EWRES (Monte Carlo calculated weighted residuals with interaction) and the NPDE (Normalised Prediction Distribution Errors). The simulation based residuals were calculated with the default number of samples (300) but in some cases a more intense sampling was also investigated (3000 samples). Interaction was always used in the estimation line, however MAXEVAL=0 or EONLY=1 was used to disable any population parameter estimation. All the residuals were calculated for 100 simulated data sets with the true and misspecified model and hypothesis tests for mean 0, variance 1 and normality were calculated.

Results: The CWRES and NPDE seem to outperform the other residual diagnostics. Furthermore the CWRES was, in general, better than the NPDE when the default number of samples was used. When more samples were used, either NPDE or CWRES could be better in different situations. When simulation from the model is not possible NPDE cannot be used. The other simulation based residuals (ECWRES, EWRES) didn't perform as well as the CWRES and NPDE. CWRESI didn't seem to be better than CWRES or NPDE even when the there was interaction in the model. As expected the NWRES and WRESI were not performing well in any of the investigated cases.

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Chiara Piana The Influence Of Covariate Distribution On The Prediction And Extrapolation Of Pharmacokinetic Data In Children.

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Objectives: The predictive performance of a model in which covariates have been identified should imply the ability not only to accurately describe the data used during model building, but also to make extrapolations to a population in which the covariate values differ from the original population. Extrapolation beyond the covariate range explored is particularly important for the purposes of pharmacokinetic bridging in paediatric indications. The aim of this simulation exercise is to assess model performance when covariate distribution and range of values differ from the original population used during model building.

Methods: A hypothetical drug with a one compartment model was used, in which weight has been linearly and exponentially correlated to clearance. Allometric scaling concepts were taken into account, but the exponents were explored with values higher and lower than 0.75. Plasma concentrations were simulated for a group of 43 children with a weight range between 7.43 and 61.3 Kg. A total of 8 observations per subject were simulated. In addition to full population, two subgroups were created. The first group comprised 20 children with weight between 10 and 15 kg, whilst the second group included 14 children with weight between 30 and 45 kg. The simulated plasma concentration data sets were subsequently fitted to a pharmacokinetic model according to standard model building criteria. Model performance was assessed by comparing the accuracy of AUC and Cmax estimates obtained for each subgroup, based 1) on a model derived from the overall population (n=43) and 2) by extrapolations to subgroup 2 (n=14), based on a model derived from subgroup 1 (n=20). NONMEM VI was used to perform model building and simulations and R for data manipulation and graphical summary of the results.

Results: PK parameters of interest could not be accurately predicted from a pharmacokinetic model obtained from a population with a different covariate range. Factoring the differences in the covariate distribution did not improve model performance. Predictions were accurate only when a model is used for the purposes of interpolation within the population. regarding results.

Conclusions: The use of pharmacokinetic modelling in paediatric research should be limited to interpolations within the range of values observed during model building. The covariate point estimate (from the overall population) must be kept in the model even when extrapolations refer to a subset of the original population.

Italo Poggesi Modeling a time-dependent absorption constant: a trick and some considerations

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Background: Simple first-order absorption models are often inadequate to describe the absorption processes. In addition, the inclusion of a lag-time parameter in the model typically results in difficulties in the parameter estimation. To overcome some of these problems, we found beneficial to describe the absorption rate constant (ka) as a time-dependent function using, for example, a sigmoidal Emax relationship [$ka(t)=ka*t^c/(t_{50}^c+t^c)$]. Alternative models, i.e. those considering single or double Weibull distributions, have been proposed in the literature [1, 2]. In general, all these models are implemented in NONMEM using differential equations (ADVAN6) [3]. Interestingly, we observed that they could also be directly implemented using the corresponding built-in PK models (e.g., ADVAN2/ADVAN4).

Objectives: In this communication we present the results obtained using the two approaches and we describe some practical considerations for their implementation in NONMEM.

Methods: The models including a) the Emax or b) the single Weibull distribution have been implemented for 1- and 2-compartment open models using either ADVAN6 or ADVAN2/ADVAN4 models in NONMEM (v. 6). The models have been fitted to real and simulated datasets.

Results: The simulated datasets obtained using either ADVAN6 or ADVAN2/ADVAN4 models were equivalent. Furthermore, the same model parameters were estimated by fitting the models to real or synthetic datasets. The implementation with ADVAN2/ADVAN4 resulted in considerably shorter run-times; sometimes it appeared less robust than the one based on differential equations in case of identifiability problems, likely due to the different parameterization. For both implementations, when a repeated-dose schedule is considered, caution should be taken to provide an appropriate number of datapoints over time (i.e. few missing observations for each dosing event) to allow NONMEM to correctly take into account the amount provided by all the individual doses.

Conclusions: Some atypical absorption processes can be implemented in NONMEM either using user-defined differential equations or the corresponding built-in pharmacokinetic models. In both cases, for repeated administration, an appropriate number of datapoints is required to allow the software to correctly handle the dosing events.

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Stephan Schmidt Implication of differences in model parameterisation in osteoporosis

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Objectives: The RANK-RANKL-OPG system was identified as a key player in the regulation of bone remodelling by osteoblasts (formation) and osteoclasts (resorption). Two models with partly conflicting RANK-RANKL-OPG parameterisations were proposed in the literature (Lemaire et al. (1) vs. Pivonka et al. (2)) to characterise osteoblast and osteoclast activity. The aim of our study was 1) to compare these two models and 2) to identify the parameterisation that best describes changes in bone turnover markers and bone mineral density (BMD).

Methods: Data from 767 healthy postmenopausal women, randomly assigned to treatment with tibolone (0.3, 0.625, 1.25, and 2.5mg) or placebo and supplemental calcium (500mg daily) (3), were analysed using a using a non-linear mixed effect modelling approach in NONMEM 6.2. Two mixture kinetic-pharmacodynamic (KPD) models with respective Lemaire and Pivonka RANK-RANKL-OPG parameterisations were fitted to the data. Bone-specific alkaline phosphatise, osteocalcin, urinary N-terminal collagen telopeptide and BMD in lumbar spine (L1-L4) and total hip were used as biomarker input. Model selection and validation were based on statistical and visual diagnostic criteria. Simulations (n = 500) using the final parameterisations of both models were performed at each dose level to evaluate the quality of the predictions for BMD in lumbar spine and total hip as the primary biomarkers.

Results: Both KPD models converged successfully and allowed for fitting of all bone turnover markers. While the parameterisation of the RANK-RANKL-OPG system required the incorporation of a mixture model to identify responders and non-responders to tibolone treatment, parameterisation according to Pivonka allowed using a simple regression model. Predictions from this latter model further indicated that poor response to treatment may be due to differences in maximum effect (I_{max}) rather than in concentrations necessary to reach the half-maximum effect (IC_{50}). In addition, simulations of BMD in lumbar spine and total hip provided similar results for both models.

Conclusion: Based on parsimony principles and on simulation outcome, our findings indicate that parameterisation of the RANK-RANKL-OPG system according to Pivonka is superior to that of Lemaire. Future research will 1) evaluate the performance of this model to describe the effect of drugs with different mechanisms of action and 2) relate short-term changes in biomarkers to long-term fracture risk.

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Steven Xu A Casual Graphic Goodness-of-fit Assessment for Markov Pharmacodynamic Models

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Background: Markov modeling is a powerful tool for analyzing longitudinal categorical response variables (i.e. chronic disease progression through discrete disease stages), and have gained increasing popularity recently, particularly in the field of population PK/PD modeling and simulation. The Goodness-of-fit assessment of Markov models remains an active on-going research topic[1, 2]. Simulation based model evaluation tools (i.e. visual predictive check, VPC) for Markov models has been used in recent PK/PD publications [3]. Gentleman proposed a goodness-of-fit approach by comparing observed and predicted prevalence, defined as counts/percentages of individuals occupying each state at a particular time, for a time-homogeneous Markov model [4].

Objectives: In PK/PD analysis, the time homogeneity of Markov models usually does not hold because of inclusion of time-dependent covariates. The objective of the analysis was to apply Gentleman's approach to PK/PD Markov models that include time-dependent covariates such as drug concentrations or biomarker levels.

Methods: The analysis was done by simulating a hypothetical chronic disease progression process for 200 subjects over 1000 days. Let us assume that the disease can be categorized and ordered with three states: stable, blast, and death. Thus, two types of transition are possible for this process: from stable stage to blast stage and from blast stage to death. It is assumed that there is a hypothetical biomarker for this disease, and can be used to predict the disease progression. For simplicity, we assume that the relationship between the transition rates and the levels of the biomarker follows an exponential growth function. Once the simulated data is fitted with a Markov model, the expected prevalence can be calculated as the product of the total number of subjects under observation at time t and the estimated transition probability $P_{1j}(0, t)$ assuming all subjects are at stable state at $t = 0$. For a time inhomogeneous Markov model, the transition probability, $P_{1j}(0, t)$, can be calculated by multiplying a number of individual transition probability matrices assuming the time-dependent covariate can be approximated as piecewise-constant. The goodness of fit can then be assessed by visually or numerically comparing the observed prevalence occupying a disease stage, $O(t)$, at time t with the expected number of subjects in that stage, $E(t)$, at time t.

Results: The simulated data was analyzed by Markov models implemented in NONMEM®. Two models were fitted: a base model without any covariate and a model with biomarker levels as the time-dependent covariate. Compared to the base model, the objective function value of the covariate model was 129 points smaller. The observed and predicted prevalence for each disease state were overlaid and plotted over time for each model to assess the goodness-of-fit. The uncertainty in the predicted prevalence over time was visualized by constructing 95% confidence intervals around the mean-

predicted profiles. The proposed goodness-of-fit plots for the models demonstrated that the base model underestimated the prevalence of subjects occupying the stable stage at early times, whereas overestimated the prevalence of subjects occupying the blast stage during this time interval. The biomarker level in this simulation was assumed to increase as the time increases. Without accounting for the time-dependent covariate, the base model prediction deviates from the data at early times. The prevalence plots clearly showed the superiority of the model with time-dependent covariate.

Conclusions: Gentleman's goodness-of-fit check for prevalence can be used as an alternative graphic assessment for PK/PD Markov models, in which concentrations or biomarker levels serve as time-dependent covariates. However, the statistical significance of the model deviation cannot be assessed formally.

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Margherita Bennetts Simulation Methodology for Quantitative Study Decision Making in a Dose Response Setting

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Objectives:
Tools & Methodology: Develop a framework for simulating study data based on current longitudinal models using R and NONMEM6. Obtain a table of Trial Performance Metrics that quantify study success in terms of how many times a correct decision is made.
Study: Quantify the expected performance of a designed Phase IIb dose-ranging study and probable Phase III dose by evaluating Decision Criteria for FEV_1 and Heart Rate endpoints.

Background: Decision criteria are rules to decide the course of action (a decision) prior to initiation or after completion of a clinical study. The performance of the drug compound and study are assessed against Target Values defined by the project team based on specific issues pertinent to the stage of drug development, such as clinical relevance or commercial viability. The true treatment effect DELTA is unknown, but can be estimated from the predictive distribution of DELTA, for a given model fitting the current state of knowledge about the drug effect, integrated across fixed and random effects. This estimate of the true effect, DELTA^, can be used to assess the technical success of a drug compound irrespective of study design. In contrast, T is an estimate of DELTA using data analytic models (the formal prospectively defined study data analysis methods). This estimate of the trial effect can be used to assess the success of the study design including elements such as sample size. In a simulation context Quantitative Decision Criteria allow us to evaluate the probability of DELTA^ and T achieving their Target Values for a given set of model parameters common to both estimates within paired replicates. The resulting table of Trial Performance Metrics enable the project team to assess the probability of Technical Success for the drug compound and the probability of making a correct Go/No Go decision given the study design. [1, 2, 3, 4]
The designed, 4 week, study consisted of 5 treatments (three dose levels of novel drug, placebo and active control) with 80 subjects/treatment group. Longitudinal FEV_1, PK and Heart Rate endpoints were to be measured on days 1 and 29.
The NONMEM Models for the endpoints were based on previous studies in the drug program. FEV_1 was a one-compartment, bio-phase kinetic/sigmoid E_{max} PD (KPD) model with baseline and circadian variation. Heart rate consisted of a PK model with complex absorption profile and high accumulation, and an E_{max} PD model including covariates for gender, baseline and circadian variation. [5]

Methods: Model parameter estimates, parameter uncertainty and random effects were extracted from the final NONMEM6 model estimation output files.
Trial input datasets specifying the structure of the study design were constructed for NONMEM6 simulation of FEV_1 using R. Truth input datasets were constructed with an identical design with only one subject per dose. Replicate-specific paired parameter Truth/Trial simulation control files were constructed by overwriting $THETA parameter values with ones drawn from the underlying multivariate normal distribution centred on the final model parameter estimates with associated

variance/covariance. The resulting study specific longitudinal FEV_1 tables read back into R for derivation of endpoints, analysis and application of Decision Criteria.
Once all simulations were complete, Truth and Trial success proportions were summarised to form Tables of Trial Performance Metrics.

Conclusions: A fit for purpose process was developed for simulations using R and NONMEM6 enabling the study team to make quantitative decisions regarding choice of study Decision Criteria and probable doses to manufacture for Phase III.

Discussion: The poster will discuss simulation and application of quantitative decision criteria in a dose response setting and issues encountered regarding appropriate simulation of Truth replicates for the FEV_1 and Heart Rate models.

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Martin Bergstrand Semi-mechanistic modeling of absorption from extended release formulations - linking in vitro to in vivo

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Background: The FDA guidance on extended release (ER) formulations (1) states that *"Whatever the method used to establish a Level A IVIVC, the model should predict the entire in vivo time course from the in vitro data."* Common methods for establishment of IVIVC do not utilize the available relevant information in order to do so. One example is information on regional absorption properties that is frequently obtained in drug development to guide development of ER formulations. A relatively new method for clinical assessment of tablet GI transit, regional absorption and *in vivo* drug release is Magnetic Marker Monitoring (MMM) (2).

Aim: A new framework to incorporate relevant clinical data and *in vitro* data to establish IVIVC.

Methods: Data from an ongoing drug development program has been used for development and testing of the suggested approach. The model building data consisted of *in vitro* data from a family of HPMC gel matrix tablets and *in vivo* data from: an MMM study with one solid formulation (tablet transit, *in vivo* drug release and plasma concentration) and plasma concentration data from other studies following local infusion in colon (Bioperm capsule), i.v. dosing and administration of oral solution. A model validation dataset included plasma concentrations for three formulations for which no *in vivo* data had been used during model building.
A model describing drug release as a function of experimental conditions (pH, RPM and ionic strength) and formulation characteristics (API, tablet size etc) was developed. The *in vitro* model was later applied to the *in vivo* drug release data from the MMM study together with prior knowledge on physiological properties throughout the GI tract and the observed tablet position. The model was used to estimate the extent of mechanic stress in different parts of the GI tract, expressed as corresponding RPM in the *in vitro* experiments. The drug release model was subsequently used as an input function for a PK model including regional absorption and disposition throughout the GI tract. The PK model and a Markov model describing tablet transit patterns for different regiments of concomitant food intake was constructed based on a previously described principle (2).

Results: Modeling of the *in vivo* drug release rendered estimates of regional mechanic stress; upper stomach 93 RPM, lower stomach 130 RPM, small intestine 63 RPM, colon 45 RPM. Furthermore it was found that the mechanic stress was significantly lower during the night (-55%). Differences in rate and extent of absorbed substance over the different parts of the GI tract were described with the PK model. A satisfying predictive performance was demonstrated for both drug release and plasma concentrations with respect to the formulation used for model building. Prospective prediction of

formulations not used for model building was in parts successful and in other parts informative on how the model could be further developed.

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Julie Bertrand Genetic effect on a complex parent-metabolite joint PK model developed with NONMEM and MONOLIX

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Objective: To investigate the influence of genetic covariates on the PK of an antipsychotic agent under development and its active metabolite. Here, we address the case where the active metabolite is back-transformed into the parent drug leading to identifiability problems and numerical difficulties [1].

Methods: We jointly modelled the plasma concentrations of both the parent drug and the metabolite collected in 101 patients on two occasions (after 4 and 8 weeks of treatment) at 1, 3, 6 and 24 hours (trough) following once a day administration. For each patient, genotypes were obtained for 5 *CYP2D6* and 2 *CYP2C19* polymorphisms.
Four different structural models were compared based on BIC [2], using the FOCE with interaction algorithm implemented in NONMEM 5 and 6 and the SAEM algorithm implemented in MONOLIX 2.4. Models were first written as ordinary differential equations (ODE) systems, but closed form (CF) solutions were subsequently derived to facilitate further analyses.
Once selected the structural model, addition of between- and within-subject variances was investigated using likelihood ratio tests. Genetic covariates were finally included following an ascendant selection using Wald test. A permutation approach was performed to assess the p-values of the covariates remaining in the final model [3].
External evaluation with normalized prediction discrepancies was performed using a study involving healthy volunteers [4].

Results: The model selection was similar using either NONMEM or MONOLIX and ODE or CF. The final PK model included two compartments with a back-transformation and a first-pass effect where a fraction F_P of the dose reaches the circulation as parent and a fraction $1-F_P$ reaches the circulation as metabolite. Volumes of parent drug and metabolite were set to be equal, and a dose-dependent decrease in bioavailability was taken into account. Five of the 8 model parameters had between-subject variances significantly different from 0, and only the clearance of the parent had a significantly non null within-subject variance. The clearance of the metabolite through processes other than back-transformation was decreased by 35% in *CYP2D6* poor metabolizers.

Conclusion: A similar model was selected in all configurations. Using the SAEM algorithm we could estimate all population parameters as well as between- and within-subject variabilities with standard errors for this rather complex model. *CYP2D6* polymorphisms appeared to affect the PK of the metabolite.

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Martin Boucher Imputation of missing variance data comparing Bayesian and Classical non- linear mixed effect modelling to enable a precision weighted meta-analysis.

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Objectives: When carrying out a meta-analysis of summary level data, the recommended approach is to weight each observation (e.g. arithmetic mean, treatment effect) by its associated precision. Often there are missing standard deviations in the literature and hence an attempt should be made to impute these missing values. The aim was to compare Classical and Bayesian methods of missing data imputation using a non linear mixed effects model.

Methods: Internal and external reports were searched to find randomised double blind placebo controlled studies where naproxen had been used to treat subjects with osteoarthritis (OA) pain for knee or hip. The endpoint of interest was mean WOMAC pain score which is typically measured at several time points post dose during a study, the desire being to model the time course for placebo and naproxen. However 30% of the WOMAC pain scores did not have a standard deviation reported.

The time course of standard deviations was described using a longitudinal mixed effects Emax model with parameters for baseline, maximum effect over baseline and the time to get to 50% of that maximum. A 2 stage approach was taken using both a Classical (maximum likelihood) and a Bayesian approach. This involved fitting a model to the standard deviations, using the model predictions to impute missing values and then merging these missing values to the original dataset prior to modelling WOMAC pain scores. A Bayesian approach was also used to simultaneously model standard deviations and WOMAC pain scores. The three approaches were then compared.

Results: A visual examination of the standard deviation data across studies revealed a non-linear relationship over time post dose. An Emax model was hence chosen as a suitable model. For the Bayesian and Classical two stage approaches, the resulting predicted standard deviations for the missing observations were almost identical. However for the simultaneous fit of standard deviation and WOMAC pain data, there was less agreement compared to the 2 stage approaches. This suggested that there might be feedback from the WOMAC pain model to the standard deviation model. The use of a ‘CUT' function in WinBUGS was successful in preventing this feedback. The parameter estimates for the WOMAC pain model were comparable across all three approaches.

Conclusions: Simultaneously modelling WOMAC pain score and standard deviations was an efficient way to impute missing data and carry out a meta analysis but care is needed in terms of feedback. The ‘CUT' function takes away this feedback but thought should be given to the reasons for this feedback (e.g. model misspecification). This work was done in a data rich situation where 70% of standard deviations were present. Future work should look into sparse data situations where the assumptions being made may be much greater. It would also be of interest to assess how these approaches compare

to other methods such as weighting by sample size or using a common imputed standard deviation across all missing observations.

Olivier Colomban Toxicogenomic dose-response model assessed by DNA chips on rats treated by flutamide

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Objectives: To fully characterize testicular toxicity in adult Wistar rats induced by flutamide (FLU), a potent antiandrogen, and to estimate the benchmark doses (BMD) modifying gene expression [1]. To achieve this objective, changes in toxicogenomic responses (gene expression profile) in the testes, whole or fractionated, will be investigated in rats exposed to FLU at different dose levels by oral gavage for 28 consecutive days.

Methods: 42 rats were randomized between 5 different arms: vehicle (control group), 0.2, 1, 6, and 30 mg/kg body weight/day. All rats were exposed to only one dose level. The dose levels were set after taking into account previously published toxicity data generated for FLU on rats exposed for 28 days [2]. For all 43,000 genes tested by DNA chips, the same sequence of hierarchical decision tree was applied to identify potential dose-gene-expression relationship. First, a simple linear model was applied to detect which log of gene-expression were significantly changed from simple baseline. False discovery rate was controlled during this first step. Second, for all significant changes, we applied various non-linear models, assuming homoscedasticity of residual variability: stimulation or inhibition models with exponential, Hill (power parameter fixed at 2) or logistic shape [3]. When change from baseline was found significant, choice between linear and one of the non-linear models was performed using the *Schwarz criterion* (*BIC*). The next step was to estimate the BMD. It is usually based on the assumption of homoscedasticity and normality of residuals. Consequently normality of residual distributions was tested using Kolmogorov-Smirnof or Shapiro Wilk test. When normality was not rejected the BMD was the dose level leading to a change in predicted baseline plus k SD, with k >=1 [1]. When residual normality was rejected, a bootstrap with 1,000 replications was used to estimate the corresponding quantile of the distribution.

Results: A significant linear change from baseline was detected for one sixth of the genes: For 52%, a stimulation model was chosen and for 48% an inhibitory model. Linear and Emax models were the main preferred significant models, while exponential and logistic models were marginal. For most models (>96%), assumption of normality of residuals was not rejected and benchmark dose was estimated as the dose leading to a difference from baseline.

Conclusions: An algorithm has been proposed to model linear and non-linear dose-effect relationship toxicity expressed by DNA chips. The algorithm allows to easily characterizing the benchmark doses for a large set of genes.

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Paolo Denti Modelling pre-dose concentrations in steady-state data. The importance of accounting for between-occasion variability and poor adherence.

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Objectives: In large Phase III/IV studies, data are often obtained from outpatients, who are under direct observation only on the day of their PK sampling. This leaves a large amount of uncertainty about the time of prior doses, since the information provided by patients may be imprecise or unreliable. Moreover, the PK of many drugs is subject to diurnal variation, meal-dependent absorption, and BOV. Thus, there is considerable variability in drug concentrations observed in the pre-dose samples. This variability needs to be properly accounted for in the model, even if the underlying causes cannot be measured because they are not related to the observed PK profile.

Methods: Using parameter values based on a published model of nevirapine [1], concentrations from a once-daily dosing regimen were simulated for 250 patients, with a rich sampling schedule (8 samples during 12 hours after dose), including a measurement 30 minutes before dose. Commonly encountered scenarios causing "unexplained" variability in the pre-dose concentrations were explored in the dataset: poor or no adherence to treatment, discrepancy between the actual and the reported dosing times, and large BOV in the PK. Different approaches to model such data were tested: inclusion or exclusion of the pre-dose samples, use of the assumption C0=C24 , introduction of BOV in bioavailability (BOVBIO), or baseline estimation using methods similar to those explained by Dansirikul et al. [2]. Results at population and individual level were compared.

Results: In our simulations, when C0 is assumed to equal C24, discarding pre-dose samples, or including them without accounting for the additional variability, led to overestimation of the BSV of ka, CL/F and V/F (about +30%, +55%, and +25% bias respectively). The naive inclusion of pre-dose samples resulted in overestimation of the additive RUV component (+145% bias). Introduction of BOVBIO partly solved these problems and reduced bias to within 20% for all population parameters, except the additive RUV, which was still overestimated (+90%). The estimate of BOVBIO was spuriously inflated, because it accounted for reduced adherence. The baseline estimation methods also performed well, but compared to BOVBIO, their BSV estimates were less precise. At individual level all the approaches greatly improved the fit for subjects whose pre-dose concentration was significantly different from the expected C24 value. In particular, more accurate estimates of individual clearance were obtained.

Conclusions: Variability in pre-dose concentrations should be appropriately modelled to avoid overestimation of RUV, and BSV of the PK parameters. Using a baseline estimation method or introducing BOV in bioavailability can satisfactorily overcome this problem and greatly improve the model fit for poorly adherent or "anomalous" subjects. Further investigation will be necessary to compare the proposed methods and fathom the effect of factors such as the size of measurement error and the sampling schedule.

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Gemma Dickinson Evaluation of a Method to Better Predict Human Absorption from Non-Clinical Data; Comparison of an in silico approach with population modelling of in vivo data

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Background: The accurate prediction of oral absorption and its associated variability is necessary to guide dose selection for phase I studies of novel drugs. Common practice is to calculate the bioavailability in preclinical species and take the average as an indicator of human bioavailability. This approach does not provide an estimate of population variability in absorption and is problematic for poorly soluble compounds where differences in formulations may have a large impact on bioavailability. In the current work, the success of an in silico approach predicting human data will be compared with current practice and the observed data.

Methods: In silico models for the prediction of bioavailability take into account various physiological factors, in combination with physicochemical and in vitro drug information. A valuable feature of such models is the assessment of population variability in absorption. One such model, the ADAM model (a compartmental model of drug absorption implemented within Simcyp®) was used for the current work. ADAM outputs were compared with estimates of bioavailability based on pre-clinical species and also with observed clinical data.

Results: As an example, pre-clinical experiments for a compound undergoing development demonstrated consistently high bioavailability. Therefore, the human prediction of bioavailability was 'high' (average of animal bioavailability ≈ 60%). However, a different formulation was used for the clinic and data from the first in human study demonstrated a 10-20 fold over-prediction of the oral exposure. The compound was poorly soluble and ADAM simulations indicated a more conservative estimate of bioavailability of ≈ 2 to 4% (assuming no first pass metabolism), which could have accounted for the over-prediction. Several further examples will be provided as well as an assessment of the predictability of the ADAM model for the absorption rate constant, compared to that estimated by NONMEM from human data.

Conclusions: Using the average of bioavailability in pre-clinical species to estimate human absorption prior to the clinic is not optimal since it ignores physiological differences between animal and human and does not accommodate the prediction of variability. Furthermore, such an approach should not be used when variability between animal species is high and/or where there are differences in formulations between the pre-clinical experiments and the clinic. In such cases, the use of in silico models, can provide more refined estimates of drug absorption and offers the added value of the prediction of variability in absorption parameters.

Aris Dokoumetzidis Fractional kinetics in multi-compartmental systems

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Objectives: Fractional calculus, the branch of calculus dealing with derivatives of non-integer order (e.g., the half-derivative) allows the formulation of fractional differential equations (FDEs), which have recently been applied to pharmacokinetics (PK) [1]. In this work we extend this theory to multi-compartmental models; we introduce a method to solve numerically such models and we also present applications in PK.

Methods: The solution of the fractional "one-compartment" model with linear elimination is a Mittag-Leffler function (MLF), which is the fractional analogue of the exponential function [1]. The MLF has good properties and behaves as a power law for long time scales while as an exponential for early times, hence it can describe kinetic data that follows power law terminal kinetics without exploding at t = 0. However, considering fractional multi-compartmental models is not as simple as changing the order of the ordinary derivatives on the left-hand side of the ODEs to fractional orders. We present a rationale of fractionalization of ODEs and a method of solving any linear system of FDEs based on a numerical inverse Laplace transform algorithm.

Results: Fractionalization of ODEs with different orders of fractional derivatives, when performed naively, may produce inconsistent systems, which violate mass balance. Our approach to fractionalization produces consistent systems and allows considering processes of different fractional orders to coexist in the same system. As an application, a two compartment model is considered, where elimination and transfer from compartment 1 to 2 are of the usual order 1, while transfer from compartment 2 to 1 is of fractional order $\alpha < 1$, accounting for anomalous kinetics and deep tissue trapping. The system is solved using numerical inverse Laplace transform which produces the correct profile when $\alpha = 1$ (classic 2-compartment model), hence verifying that the algorithm works. The system is fitted to PK data and parameters are estimated.

Conclusions: FDEs are a useful tool in pharmacokinetics, effectively modeling datasets that have power-law kinetics and accounting for anomalous diffusion and deep tissue trapping. Our approach allows the formulation of systems of FDEs, mixing different fractional orders, in a consistent manner and also provides for a numerical solution to these systems.

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Anne Dubois Model-based bioequivalence analysis of pharmacokinetic crossover trial compared to standard non-compartmental analysis

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Objectives: To assess pharmacokinetic (PK) bioequivalence in crossover trials, tests are usually performed on the area under the curve (AUC) and the maximal concentration (C_{max}) computed by a non-compartmental approach (NCA) as recommended by the guidelines [1,2]. Recently, bioequivalence tests based on nonlinear mixed effects models (NLMEM) have been developed [3,4,5]. Our objective is to mimic the standard bioequivalence analysis on AUC and C_{max} using NLMEM and Wald test.

Methods: In NLMEM, to perform the bioequivalence Wald test, the treatment effect of the concerned parameter and the corresponding standard error (SE) are used. Unfortunately, the PK model cannot be usually parametrized using C_{max} which is a secondary parameter of the model. Therefore, SE must be approximated and we propose to use the delta method [6] or simulations from the fixed effect estimates and their Fisher information matrix. We evaluate the bioequivalence Wald test performed on the treatment effect of AUC and C_{max} by simulation using 1000 replicates. Crossover trials are simulated under the null hypothesis using different numbers of subjects (N) and of samples (n), with treatment effect on clearance and volume of distribution. We estimate the NLMEM parameters by the SAEM algorithm implemented in MONOLIX 2.4 [7,8]. Treatment effect of AUC and its SE are directly derived from clearance ones. Delta method and simulations are used to estimate the SE of the treatment effect on C_{max}. Bioequivalence Wald tests are performed using the SE estimated by MONOLIX and the empirical SE computed as the standard deviation of 1000 replicates of the treatment effect estimate. The results of NCA and Wald tests are compared.

Results: Bioequivalence tests based on NCA show satisfactory properties, except when n is small or the residual error is high. For NLMEM using estimated SE, there is an inflation of the type I error for bioequivalence Wald test when N or n are small. This inflation is corrected by the used of empirical SE. The results for C_{max} are satisfactory and similar for delta method and simulations.

Conclusions: We show that the standard bioequivalence analysis can be transposed to NLMEM context, allowing sparser sampling design than NCA. However in NLMEM, asymptotic tests are used and correction for small sample size should be considered.

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Charles Ernest Predictor Identification in Time-to-Event Analyses

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Objectives: Analysis of time-to-event data can provide valuable insight in designing appropriate dosing regimens to maximize the benefit/risk ratios. When these events occur relatively rapid in comparison to long term therapy, or time of onset is a primary outcome, identification of the appropriate predictors of early exposure are paramount to accurately determining dosing. The aim of the analysis was to examine influence of sample size, between subject variability on oral absorption and range of time-to-event parameter estimates on predictor identification.

Methods: Data were simulated based on a 1-compartment pharmacokinetic model with between subject variability on Ka and Weibull distribution used to describe the time to an event. The sample sizes consisted of 175, 100 and 75 subjects receiving doses of 0-, 0.3-, 3-, 6- and 10-mg in equal proportion. Concentration was used as the predictor for the simulations based on an Emax model to describe drug effect with EC50 as the half maximal response concentration. An alternative model with dose as the predictor and ED50 as the half maximal response dose was used to compare the power of model discrimination and overall performance between the two predictors. Analysis was performed using NONMEM VI and PSN computed the summary statistics between the two different predictors.

Results: Power to correctly identify the true predictor (concentration) improved with increasing levels of between subject variability. However, the power was generally less than 80% with an N of 100 and 50. Estimates for the shape parameter and Emax did not deviate from the true values as much when concentration was used as the predictor as compared to dose. Estimation of the EC50 or ED50 value tended to be considerably over-estimated when simulated EC50 was low relative to the dosing regimen. However, as the simulated EC50 increased, estimation of EC50 was relatively less biased; whereas, estimated ED50 would project a considerably higher dose needed to achieve similar response. Examination of the relative probability density function demonstrated both predictors provided a reasonable concordance to the true model with respect to the median time of event. However, the maximum probability was impacted by changes in the scale, shape and Emax parameter estimates with changes in subject sample size.

Conclusions: Use of the Weibull distribution to describe time-to-event data using dose as the predictor when the true underling effect is driven by concentration can provide a reasonable estimation of the true model when sample sizes are relatively limited; however, doses based on the ED50 will be over-estimated. Examination of concentration as predictor should occur as sample sizes increase providing more power for model discrimination. Further work needs to examine the impact of between subject variability on clearance and volume of distribution in the pharmacokinetic model.

Farkad Ezzet Bronchial Allergen Challenge in Asthma: A Model for Inhaled Corticosteroids (ICS) and Montelukast using Literature Summary Data

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Objectives: To characterize effectiveness of anti-asthmatic treatments in studies using bronchial allergen challenge (AC)

Methods: Mean %FEV1 change from baseline following AC and treatment was modeled using data reported in 47 scientific publications. Studies were randomized placebo controlled cross-over investigating efficacy in mild asthmatic patients. Following AC, patients exhibit early asthmatic response (EAR) and late asthmatic response (LAR), within 30 minutes and 4-8 hours after inhalation of allergen, respectively [1]. EAR and LAR were modeled using a sum of 2 gamma density functions, if time =< or > t:

%FEV1(time) = - (time =**a**).Gamma(L1, K1, time) -

(time >t).S2 .(1-**b**).Gamma(L2, K2, time) (1)

The parameter S describes the magnitude of drop in %FEV1 due to AC. For a = b =0, equation (1) represents %FEV1 under placebo. Positive values of a and/or b represent %attenuation due to active treatment. Inter-trial random effects (proportional to S1 and S2) and an additive residual error were assumed normally distributed. The model was fitted using nlme, in Splus.

Results: Data set included 15 studies investigating ICS (6 compounds) and 7 investigating Montelukast. Equation (1) was found suitable in capturing %FEV1. S1 and S2, together with attenuation parameters a and b captured most of the differences in %FEV1 between treatments (while L and K were common to all treatments). For example, %attenuation in EAR and LAR for Montelukast (10 mg) was 58% and 65% respectively. For Fluticasone 250 mcg (an ICS) it was 16% and 58%. Budesonide was 11% and 62%. The value of t signifying end of EAR and beginning of LAR was between 2 and 3 hours. A similar value of objective function was achieved for t in this range. SD of residual error was small, 3%. Coefficient of variation of inter-study variability in S1 and S2 were 22% and 35%. Visual predictive checks and posterior predictive checks together with standard diagnostics indicated adequacy of the model fit. Model estimates were found invariant when subsets of the data used.

Conclusion: A sum of 2 gamma functions was found to be a flexible model to describing %FEV1 following AC. The attenuation parameters a and b captured most of the differences between treatments, allowing a simple and direct comparison. The literature model aids the interpretation of ongoing AC studies within Pfizer, as well as design of future AC studies, and can be updated with internal data from positive controls.

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Farkad Ezzet Modeling Adverse Event rates of Opioids for the Treatment of Osteoarthritis Pain using Literature Data

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Objectives: To characterize adverse event (AE) and dropout profiles of Opioids for the treatment of Osteoarthritis (OA) Pain using literature data.

Methods: A database was constructed using data from scientific literature of randomized controlled clinical trials investigating safety and efficacy of opioids. Attention was focused on dropout rates due to AE's and proportions reporting events of constipation and nausea. Using proportions together with sample size, the response is a binomial variable, and was thus modeled using a mixed effect general linear model with glme, Splus. The function operates on log(p/(1-p)), a linear function of model covariates, where p is the probability of an event. Inter-study random effect enters the model as an additive term. The main covariates of interest were opioid strength (none, moderate or strong) and treatment dose. Other effects investigated, included treatment formulation and study duration. Model diagnostics were explored to evaluate goodness of fit.

Results: The database included about 40 studies on 12 treatments involving over 12000 OA patients. There were a sufficient number of studies using moderate opioids (e.g. Tramadol and Codeine) and strong opioids (e.g. Oxycodone). With the outcome variable as a proportion, when converted to binomial, is equivalent to having access to patient level response from individual trials. The resulting large sample size would thus significantly increase power and precision of model estimates. Three models were established, which determined that strong opioids increase the chances of constipation, nausea and dropout rates. Using placebo as a reference group, strong opioids have odds ratios of 7.7, 5.6 and 5.3, respectively. For moderate opioids, the odds ratios were 3.3, 2.7 and 3.3 and for Non-opioids they were 1.5, 1.1 and 1.2. Inference on influence of dose is usually limited due to dose ranges investigated. However, the dropout model indicated a dose effect for moderate and strong opioids. Diagnostic plots indicated adequacy of the model fit.

Conclusion: The models established that rates of AE's and dropouts increase significantly with the strength of opioids. While benefits of Meta analysis using public literature are well established [1,2] , models for proportions have the added advantage of increased statistical power, a consequence of using subject level information.

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Farkad Ezzet Analysis of Adverse Events using Literature Data: a Simulation Study

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Objectives: To investigate the power of literature data in the analysis of Adverse Event (AE)

Methods: In meta analysis, a clinical outcome expressed as a proportion, such as %AE or %responders, may be treated as a continuous variable and modeled using standard mixed effects algorithms. Lack of fit will likely occur if proportions are close to the boundaries 0% or 100%. A Logit transformation (on proportions) in some instances helps but dose not resolve the problem completely. Instead, proportions are converted to a binary outcome and are modeled as such, using, say, glme in Splus or glmer in R. We explored the properties of the approach using simulated data that closely resemble outcome under clinical settings. The objectives were to determine 1) ability to estimate treatment effects accurately, 2) consequence of mixing studies of different sample size (N) and 3) usefulness of standard modeling diagnostics tools. Recently, this approach was implemented using literature data to investigate influence of treatment on AE's in cancer trials, and in another project on rates of AE's and dropout in osteoarthritis trials in patients treated with opioids [1]. The findings from patient data were compared with the simulations, but are not be reported here.

Results: Under different scenarios, model estimates using glme were in close agreement with the true values, including estimates of random effects and residual variances. Since the response is binomial, the contribution to the likelihood is inherently proportional to sample size, resulting in a proportional effect on model estimates, independent of random effects. Standard goodness of fit diagnostics based on fitted proportions can be misleading, especially when N is small. Instead, diagnostics should be based on residuals, e.g. Pearson residuals or adjusted deviance residuals. The findings of the meta analyses from the cancer trials and from the osteoarthritis trials where consistent with those of the simulation work.

Conclusion: Unlike meta analysis of mean data[2,3], no ad hoc weighting by sample size is necessary when outcome is a proportion. More importantly, expressing proportions as a binomial variable essentially re-constructs the observed outcome at the patient level. In meta analysis, the pooled trials thus retain original sample size and significantly increase statistical power. This is particularly useful when investigating rare events from a large number of small studies, as in early phase cancer trials.

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Support Knowledge Management and Decision-Making in Clinical Drug Development., AAPS National Biotechnology Conference, May 2008, Toronto, Canada

Leonid Gibiansky TMDD Model for Drugs that Bind Soluble and Membrane-Bound Targets: Can Quasi-Steady-State Approximation Estimate Unobservable Membrane-Bound Target Occupancy?

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Objectives: To develop an approach for description of drugs with target-mediated drug disposition (TMDD) that bind to soluble (S) and membrane-bound (M) targets; to demonstrate on the simulated example that models based on the quasi-steady-state (QSS) approximation can identify parameters of both targets based on the free drug and the total S-target concentrations.

Methods: The TMDD equations [1] were extended to describe drug interactions with multiple targets. The QSS approximation [2-4] of these equations was derived. A population data set (3250 unbound drug and 3305 total S-target concentrations from 224 subjects) was used to investigate identifiability of QSS model parameters. The drug and target concentrations were simulated for a monoclonal antibody that can bind to S and M targets. It was assumed that either unbound or total (unbound and bound to the S-target) drug concentration and the total S-target concentrations are observable while the M-target is not observable. The QSS approximation of the two-target TMDD model was used to fit the simulated data. Dependence of results on the relative contribution of the targets to drug elimination and on assay properties (limit of quantification) was also investigated.

Results: For the range of parameters typical for monoclonal antibodies with binding to S and M targets, S-target binding was described by the QSS approximation while Michaelis-Menten elimination term adequately described contribution of the M-target. Contributions of the two targets could not be separated when only the drug concentration data were available. However, when the S-target concentration data were also available, the model correctly estimated parameters of the drug and both targets, including the M-target production rate and the percent decrease from the baseline level of unbound M-target concentration. The parameters were estimated precisely, with the highest bias (10-15%) and the lowest precision (RSE=10-18%) observed for the M-target parameters. Results were the same whether the total or unbound drug concentrations were available, and whether the assay quantification limits were 0.1 nM or zero. When synthesis rate of the M-target was much smaller than that of the S-target, M-target parameters could not be identified in the absence of the M-target measurements.

Conclusions: The TMDD model and its approximations were derived for drugs that bind to more than one target. Single-subject simulations for a monoclonal antibody that binds to soluble and membrane-bound targets demonstrated that QSS approximation provided an excellent description of the data simulated from the full two-target TMDD model. Population-level simulations demonstrated identifiability of the two-target QSS model parameters, specifically, the ability of the model to obtain precise and unbiased parameter estimates for the drug, and both soluble and membrane-bound targets. Moreover, the model correctly estimated unobservable M-target production rate and percent decrease

from baseline of the unbound M-target concentration. However, identification of the M-target parameters was reliable only when the synthesis rate of this target was comparable or higher than the synthesis rate of the S-target.

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Leonid Gibiansky Target-Mediated Drug Disposition: New Derivation of the Michaelis-Menten Model, and Why It Is Often Sufficient for Description of Drugs with TMDD

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Purpose: To derive the Irreversible Binding (IB) and Michaelis-Menten (MM) approximations of the Target-Mediated Drug Disposition (TMDD) equations; to investigate parameter ranges where these approximations can be used for description of TMDD data and for estimation of target production rate and free target suppression.

Methods: The IB approximation was derived assuming that (i) the drug-target binding is irreversible and (ii) the free target concentration is in quasi-steady-state. Further, the MM approximation was derived assuming that the free target concentration is much smaller than the drug concentration. A population PK dataset (3355 observations from 224 subjects) was simulated using the full TMDD model. The MM approximation was used to describe the simulated data. Predicted drug concentrations were compared with the true values. Bias and precision of the parameter estimates were investigated.

Results: The IB equations for a drug that is described by a two-compartment model and administered as intravenous bolus (D_2), intravenous infusion (In(t)) and subcutaneous (D_1) doses are presented below:

$dA_d/dt=-k_aA_d$,
$A_d(0)=D_1$,
$dC_{dif}/dt =[In(t)+k_aA_d]/V - (k_{el}+k_{pt})C-k_{syn}C/(K_{IB}+C)+k_{tp}\ A_T/V$,
$C_{dif}(0)=D_2/V-R_0$,
$dA_T/dt=k_{pt}\,C\ V-k_{tp}\,A_T$,
$A_T(0)=0$,
$C = 0.5\ \{C_{dif}-K_{IB}+[\ (C_{dif}+K_{IB})^2+4\ R_0\ K_{IB}]^{1/2}\}$,
$K_{IB}=k_{deg}/k_{on}$

Here C_{dif}=C - R; C and R are the concentrations of the free (unbound) drug and the target in the central compartment, k_{el} is the linear elimination rate, k_{on}, k_{deg}, k_{int}, k_{syn} are the binding, degradation, internalization, and the target production rate; V is the central compartment volume; $R_0=k_{syn}/k_{deg}$ is the baseline target concentration.

The IB approximation is valid for high-affinity (large k_{on}) drugs in cases where the drug-target dissociation rate k_{off} is either small or much smaller than k_{int}. This is typical for the therapeutic monoclonal antibodies with membrane-bound targets. If R_0 is much smaller than C then C_{dif}=C and the irreversible binding equations are equivalent to the model with the Michaelis-Menten elimination ($V_{max}=k_{syn}$, $K_M=K_{IB}$,$R_0=0$). The discrepancy between the true and MM solutions does not exceed R_0. In

the simulation study for a system with R_0 significantly smaller than C, the MM model precisely estimated all relevant TMDD parameters and provided unbiased population and individual predictions of the unbound drug concentrations C and the target production rate k_{syn}.

Conclusions: The new IB and MM approximations of the TMDD equations were derived. The simulated examples demonstrated validity of these approximations and their ability to estimate the TMDD parameters. The results extend the parameter range where the Michaelis-Menten model describes the TMDD data.

Roberto Gomeni Integrated approach to overcome a food effect in clinical studies: an example of how in vitro, in vivo and simulation tools can help in determining an appropriate strategy

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Objectives: The between-subject variability in the absorption parameters may be reduced in humans when a drug is given with a standard breakfast, especially when its solubility is pH-dependent [1,2,3]. However co-administration of a drug with food is often considered a burden for its further development. The objective of the present work is to suggest an integrated, data-driven formulative approach to overcome the liability to progress a drug to further clinical studies with the burden of this food effect.

Methods: All available pre-clinical and clinical data of a weak base new chemical entity (NCE) were reviewed to decide the best dosing strategy to meet the study objectives of high exposure and controlled variability. Chemico-physical information on solubility and its pH dependency, permeability and food-binding were considered. In addition, single dose data were obtained in fed and fasted state. Simulations of absorption profiles were conducted with the use of Gastroplus [4,5] and other pharmacokinetic simulation tools, assuming the administration of the compound with beverages stabilizing the pH of the gastric media at different values.

Results: Review of clinical data showed that co-administration with food reduced between-subject variability on both Cmax and AUC (0-24) with no significant impact on mean exposure; this was more apparent at high single doses. Food appeared to improve the PK profile playing the role of an absorption regulating factor: reducing absorption in fast absorbing subjects and improving absorption in the slow absorbing subjects with an overall reduced variability. The pH-dependent solubility of the NCE, the wide physiological range of pH found in the stomach in fasted and fed conditions, the observed food binding of the molecule, all may have contributed to the large PK variability seen when the molecule was dosed in the fasted state. As stomach pH ranges physiologically between 2 and 5, the solubility of the molecule was found to decrease by ten thousand-fold and even when administering at low doses, there was a significant risk of incomplete solubilisation. Different simulations accounting for all these factors showed that dosing the drug with beverages with appropriate acidity in the fasted state may reduce between-subject variability. The same PK profile and variability was then expected when dosing in the fed state compared to the fasted state with drinks such as coke or ribena with relatively low pH values, suggesting a formulation opportunity to overcome this food effect.

Conclusions: The integration of *in-vitro* and *in-vivo* data in a simulation tool like Gastroplus, provided a model-driven opportunity to integrate data and knowledge regarding an NCE. The benefit of this approach is to identify the optimal experimental strategy to progress compounds characterized by lower

variability in fed condition. Understanding the source of variability guides most effective formulation design to address and mitigate the impact of physico-chemical properties on drug absorption.

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Thaddeus Grasela Forensic Pharmacometrics: Part 1 - Data Assembly

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Introduction: As modeling and simulation results become integral to a program's outcome, the consequences of lapses in data assembly and analytic result quality can jeopardize the role of pharmacometrics in contributing to the transition to model-based drug development. There are few standards available to define measures of acceptability and suggest strategies for assessing the "fit for purpose" of analysis datasets or model building efforts. These quality assurance activities might include, for example, a review of programming logic and coding, as well as the assumptions used to re-create dosing histories.

Objectives:
Describe a case study of a forensic assessment of analysis-ready datasets performed as part of a due diligence effort.
Describe methods used in the forensic assessment that identified problems and errors in the previously constructed datasets and propose proactive quality assurance activities.

Methods: A series of quality assurance checks comparing the analysis-ready datasets to the source data files were developed by both data programmers and scientists addressing their individual areas of expertise. Three teams, operating in parallel and consisting of a scientist and a data programmer, were constituted to focus on different aspects of the PK and PK/PD datasets and modeling. A review of the previously prepared technical reports was used to identify the assumptions and strategies that went into the original data assembly and model-building efforts.

Results: The forensic analysis of the datasets revealed a mismatch in demographic data with corresponding dosing and PK data in a large percentage of patients and systematic errors in the creation of dosing histories, including improper use of NONMEM®-derived data items (ADDL) and incorrect dose amounts in subsets of patients across studies. The descriptions of patient disposition and data deletions were insufficient in supplying reasons or rationale for the programming logic errors discovered.

Conclusions: A gap currently exists in defining the criteria for judging the quality of data assembly efforts along with the comprehensiveness of data programming, technical report, and other supportive work product documentation. Strategies for this assessment can be used as a basis for independent validation of pharmacometric work products prior to use in critical decision-making activities, as well as in the development of standards for quality assurance activities.

Thaddeus Grasela Forensic Pharmacometrics: Part 2 - Deliverables for Regulatory Submission

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Introduction: As modeling and simulation results become increasingly integral to critical development-related decision-making and program outcomes, the consequences of poor documentation of pharmacometric analyses can jeopardize the role of pharmacometrics in contributing to the transition to model-based drug development. While the EMEA and FDA Population PK Guidance documents recommend pharmacometric report content, forensic assessment of analysis inputs and outputs may enable the development of standards to define measures of acceptability and support the continued evolution of these methods.

Objective: Define and apply a process for the prospective forensic assessment of regulatory deliverables to gain understanding of common problems.

Methods: A review of recent externally-generated pharmacometric analysis inputs (analysis-ready datasets, analysis plans) and outputs (models, final technical reports), intended for submission to regulatory authorities, was performed using a systematic process for forensic assessment. For each deliverable, descriptive statistics summarizing categories of common problems were generated.

Results: The process included the following steps: (1) initial review and identification of issues for further investigation, (2) request for additional supporting information, (3) verification of consistency of supporting information, and (4) suggested strategy for correction. For analysis-ready datasets, the supporting information may include source data collection methods, additional exploratory graphical displays, or a flowchart of the programming logic applied in the data manipulation process. For analysis plans, a series of questions addressing how likely scenarios would be handled might be generated. For models described in technical reports, consistency between output tables of results, NM-TRAN code, NONMEM® report files, and text describing results can easily be confirmed. Based on this process, the following types of common issues were identified: systematic errors in the creation of dosing histories, incomplete strategies for assumption violations, and numerous inconsistencies in the reporting of modeling results.

Conclusions: The process developed for this assessment can be used as a basis for independent validation of pharmacometric deliverables intended for regulatory submission, as well as in the development of standards for quality assurance activities for pharmacometric analyses.

Ivelina Gueorguieva Is pharmacokinetic variability in microdosing trials comparable to variability following therapeutic doses?

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Objectives: Following a single ascending dose trial, knowledge on within and between subject variability around Cmax and AUC0-inf is often required to adhere to a certain margin of safety and when necessary to design drug-drug interaction trials. Accepting that microdosing can be used to understand mean pharmacokinetic behaviour (Lappin et al., 2006), there is currently no investigation on whether variability following microdosing is comparable to that after therapeutic doses. The objective of this analysis is to quantify observed pharmacokinetic variability in microdosing trials (CREAM). This is compared to variability from both similar small sample size trials in the same subjects as well as larger trials following therapeutic doses.

Methods: Data from the CREAM trial (Lappin et al., 2006) was used, where warfarin, diazepam and midazolam were administered as microdoses and pharmacologic doses to healthy volunteers in a cross over trial. Additionally, literature and in-house data following therapeutic dose administration to a larger size healthy volunteer population were available. Population PK compartment models were fitted using nonlinear mixed effects models as well as naïve pooling of data in NONMEM, version V. Between and within subject variability were quantified and confidence intervals around the mean population estimates as well as prediction intervals were projected.

Results: A two-compartment model with iv infusion best described diazepam concentration-time data following microdose and therapeutic doses. The predicted mean CL and Vss from the microdose and therapeutic doses were comparable. The estimated, albeit from differing sample sizes, between-subject variability were also consistent at approximately 26% for exposure. Prediction intervals from micro, therapeutic doses and large dataset (with therapeutic dose) were very close and were plotted together with dose normalized data. Similar analyses were performed for warfarin and midazolam.

Conclusions: It was previously shown that for 5 drugs, two of which not examined here, mean pharmacokinetic behaviour (Lappin et al., 2006) was comparable following therapeutic and micro doses. Additionally a demonstration of consistent variability for a large number of compounds will lead to acceptance of microdosing as a Phase 0 trial to help (1) decide whether a compound is likely to have the desired pharmacokinetic behaviour and (2) plan the ascending dose ranging study. This is undoubtedly desirable with Phase 0 trials requiring a much reduced safety testing package by regulatory agencies and with that quicker access to human testing.

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Acknowledgement We acknowledge CREAM and EUMAPP consortia for providing the data.

Michael Heathman Interactive Simulation and Visualization of Drug/Disease Models

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Objectives: Drug/disease modeling enables quantitative decision making in the drug development process, through codification of scientific information about disease states, comparators, and new molecular entities. Model-based simulations are a powerful tool to leverage this information, facilitating open discussion with clinicians and other key members of the drug-development team. Unfortunately, the ability to answer clinically relevant questions is impeded by the complexity of the simulation process, and the long turnaround time required to conduct large-scale simulations.
To address this problem we have undertaken the development of an interactive system for simulation and visualization of drug/disease models.

Methods: The system was designed to include the following capabilities:
1. A standardized model-specification language, compatible with mixed effect models developed in common software packages.
2. An interface which allows user input of model parameters, drug properties, and patient characteristics.
3. A real-time simulation engine, designed to generate virtual patients and/or study data in a parallel fashion on a cluster of networked computers.
4. An interface for visualization of simulation results, calculation of summary statistics, and output of virtual patients for further analysis in other statistical software.

Results: An interactive environment for simulation and visualization from drug/disease models has been implemented at Lilly. Model specification is performed using a library of standardized R functions, while a graphical interface allows specification of simulation parameters and job submission to the simulation engine. A custom interface for visualization of these results has been developed using TIBCO Spotfire®, allowing quick and easy analysis of simulation output.

Conclusions: This system achieves two key objectives: (1) generation of simulation results on timescales that support real-time collaborative analysis, and (2) expansion of simulation capability to a broader non-technical audience for increased exploration of drug/disease models. The resulting knowledge supports decision-making related to compound selection, dose selection, and study design optimization.

Ron Keizer Incorporation of concentration data below the limit of quantification in population pharmacokinetic analyses

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Introduction: In population pharmacokinetic (PopPK) analyses, the modeler is often confronted with concentrations below the lower limit of quantification (LLOQ), generally censored as "BLQ". The LLOQ is determined by a specified level of bias and precision (usually 20%) while concentration below the LLOQ may still by quantifiable albeit with increased bias and precision. Concentrations below the limit of detection (LOD) can not be quantified. In general the LLOQ is in the order of 3-5 times the LOD. Several methods have been proposed to handle these data, such as discarding them, replacing them with LLOQ/2, or the use of likelihood-based methods.(1-3) However, we hypothesize that using the actual concentration data extrapolated below the LLOQ has superior performance over the established methods, and decreases bias and imprecision of parameter estimates.

Objectives: Investigate the validity of using extrapolated BLQ concentration data in PopPK analyses, and compare performance to established BLQ methods.

Methods: First, to quantify the contribution of analytical error on overall residual error an analytical error model was constructed and fitted to results from analytical method validations from our own laboratory and from analyses published in literature. This model allowed description of the precision of the analytical methods over the entire concentration range (scaled using the LLOQ). Another model was defined which described a 'worst-case' analytical method that just complied with FDA standards. The analytical error model was combined with a proportional error model (20% error) to account for model misspecification.

Using these residual error models, simulation and re-estimation analyses were performed using R, NONMEM and Perl, for various levels of BLQ censoring (10%, 20% and 40%), and several i.v. and oral PK models. The performance (in terms of RMSE, and run success) was evaluated for the following BLQ approaches: 'Discard', in which BLQ data was discarded, 'LLOQ/2': all BLQ data in the absorption phase were substituted with LLOQ/2, and in the elimination phase the first BLQ observation was substituted with LLOQ/2 while subsequent points were discarded, 'M3': simultaneously modelling of the continuous data above the LLOQ and binary data below the LLOQ (1,2), 'All data': using all concentration data, including BLQ concentrations, as continuous data (but discarding data below the limit of detection). Subsequently, the influence of several additional factors was investigated: the use of NONMEM7 instead of NONMEM6, the use of the new SAEM estimation method in NONMEM7, and the use of another approach '$M3_{LOD}$' in which the M3 method was only used for points below the LOD.

Results: For all evaluated PK models and levels of censoring, RMSE values were lowest using the 'All data' method. Performance of the M3 method was generally better than the 'LLOQ/2' or 'Discard' method, while differences between all methods were small at the lowest level of censoring. Using the

‘M3' method, low percentages of runs were reported as successful (<50%) and even lower percentages of covariance steps were performed (<30%), although a considerable percentage of runs did produce parameter estimates (~90%).

The ‘worst-case' analytical error model showed bias and precision comparable to the situation of the ‘average' analytical error: RMSE values were lowest for the ‘All data' method, except at the highest level of BLQ censoring where the ‘M3' provided better results. NONMEM7 using either the Laplacian or the SAEM method provided similar performance to NONMEM6, although the percentages of successful runs was about 20% higher. The ‘$M3_{LOD}$‘ approach resulted in slightly larger RMSE values and more unsuccessful runs compared to the ‘All data' method.

Conclusion: The incorporation of BLQ concentration data showed superior performance in terms of bias and precision over established BLQ methods. This indicates that the use of BLQ data as a continuous data source is a valid approach in PopPK modelling. Investigations in the use of this approach for real PK datasets is in progress.

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William Knebel A Strategy for Efficient Implementation of NONMEM 7 and the Intel Fortran Compiler in a Distributed Computing Environment

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Objectives: NONMEM 7 (NM7) [1], was developed and optimized for compilation with the commercial Intel fortran compiler (IFC)[2]. IFC licensing for a grid implementation is issued at the user-level and requires the use of the FlexLM license manager. In order to increase license utilization efficiency, a strategy building upon the existing MIfuns [3, 4] R package, was developed for the deployment of NM7 with IFC in a distributed computing environment.

Methods: The R package, MIfuns (R version 2.7.2 or above) runs on single workstation computers (Windows XP or Mac OSX) and across computer grids (Mac OSx, NetBSD, linux) utilizing the Sun Grid Engine (SGE) [4] distributed computing software. SGE has built in functionality allowing for the use of license-managed software. NM7 via NMqual-7.0.2, SGE v6.1u4, FlexLM license manager, and a five-seat IFC cluster license were deployed in their standard configurations across a grid computing environment with 4 nodes (8 CPU cores/node) running Mac OSX Leopard Server. SGE was configured with a consumable resource equal to the number of IFC cluster seats and a special compile only queue (in addition to the standard set of queues). MIfuns was adapted to make use of the existing compile and execute flags available with an NMQual [5] mediated NONMEM installation.

Results: NM7 runs submitted to the grid via MIfuns were compiled then executed utilizing SGE. If IFC license seats were not available, the NM7 job would wait in a queue until a license was available for compiling. Once compiled the NM7 runs were executed and distributed across the grid (one job per CPU) via SGE. This approach was implemented on top of an existing grid system for running NONMEM 6 (NM6) with the g77 fortran compiler.

Conclusions: The application of MIfuns and SGE allowed for the distribution of NM7 runs in a grid environment, while efficiently managing IFC licenses. This approach also allowed for the simultaneous deployment of NM6 and NM7 in a grid environment.

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Brigitte Lacroix Simultaneous modeling of the three ACR improvement thresholds – 20, 50 and 70% - in rheumatoid arthritis patients treated with certolizumab pegol

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Background: Various approaches have been proposed to model the ACR (American College of Rheumatology) 20% and 50% improvement criteria in rheumatoid arthritis (RA) [1,2,3,4]. However, dichotomizing the composite ACR assessment into such binary variables is throwing away much information.

Objectives: To develop a new approach integrating the information from the 3 commonly used improvement thresholds of 20, 50 and 70% in order to be more informative in evaluating the drug effects.

Methods: Data from 1747 patients on certolizumab pegol (CZP) and 633 patients on placebo treatment were used for non-linear mixed effects modeling. Placebo or CZP at doses ranging from 50 to 800 mg was administered subcutaneously every 2 or 4 weeks for 8 to 48 weeks. At each visit, the subjects' response statuses with respect to the 3 ACR thresholds was assessed and converted in 4 categorical increasing response scores, 1) ACR20 non-responder, 2) ACR20 but not ACR50 responder, 3) ACR50 but not ACR70 responder and 4) ACR70 responder.
The model was constructed as a compartmental model with 4 compartments predicting the probabilities of the 4 ACR responses over time. Compared to the Markov model[3,4], this approach allows to describe all possible transitions between the 4 scores with fewer parameters, and to account for the score at the preceding visit within a model that is continuous in time (i.e. may predict intermediate states at intermediate times).
Dropout was modeled separately using a logistic regression model and the influence of the previous ACR response level on dropout probability was investigated.

Results: The model predicted the number of transitions and proportion of patients of each ACR response level well. The probability of attaining a higher ACR response increased non-linearly with time, with a fast onset of response, slightly delayed for increasing stringent criteria (90% of maximal effect at W12, W16 and W18 for ACR20, 50 and 70, respectively). The probability of attaining a higher ACR response increased with CZP exposure, affecting both transfer constant to higher and lower scores. The dropout probability increased with time and decreased with increasing ACR response at the preceding assessment.

Conclusions: This new modeling approach, integrating the outcomes from the 3 ACR improvement thresholds, enables greater information to be obtained from conventional ACR assessments. It allows simulation of coherent ACR20, ACR50 and ACR70 outcomes at a given visit for a given subject.

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Otilia Lillin-de Vries Population PK-PD modeling of thorough QT/QTc data allows for mechanistic understanding of observed QTc effects

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Objectives: Thorough QT/QTc trials (TQT) are designed for a yes/no outcome (ICH-E14 statistical analysis). Beyond yes/no more quantitative information can be retrieved by performing a population PK-PD analysis on data available from TQTs, information that is useful for internal decision making when the TQT is positive.

Methods: A PK-PD model (NONMEM VI) was fitted to QTc data from 44 adult HV receiving D mg of drug X (therapeutic dose), 38 HV receiving 5D mg of drug X (supra-therapeutic dose) and 44 HV receiving placebo (the active comparator data were not used). The PK-PD model was built in two steps: a baseline model incorporating demographic effects on QTc (sex, age, circadian rhythm) was built using baseline data and subsequently drug effect and placebo effect were quantified using all QTc data. Linear and non-linear concentration-effect models were tested as well as direct and indirect effect models. The observed time delay between Cmax and dQTc_max was accounted for with a hypothetical effect site model.

Results: 112 HV contributed to 1188 PK samples after doses of 0.7D - 5D mg X. 126 HV contributed to 2320 QTc samples after D mg X, 5D mg X and placebo. The final PK-PD model included covariates sex, age and circadian rhythm on the baseline QTc. An indirect linear drug effect model described the data best, since a time delay of about 2 h was observed between peak levels of X and peak dQTc. The most important model parameters were: baseline QTc for a typical woman was 409 ms and the slope of drug effect was 0.00177 ms/(ng/mL). The predicted dQTc at Tmax - mean (upper 95%CI) - was 3.2 (3.8) ms after D mg of X and 9.4 (11.2) ms after 5D mg X.

Discussion: In spite of the negative hERg tests performed on drug X, and a metabolite, the PK-PD model confirmed a QTc effect. The predicted concentrations of X in the hypothetical compartment of the PK-PD model matched observed concentrations of a metabolite of X. The PK-PD model indicates that the QTc prolongation could potentially be caused by the metabolite.

Conclusion: A population PK-PD model was successfully fitted to the data of a TQT trial. The TQT was positive and the PK-PD model could confirm a QTc prolongation effect slightly above the threshold of regulatory concern.

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Igor Locatelli The Development of a Link Model Consisting of in vitro Drug Release and Tablets Gastric Emptying Time: Application to Diclofenac Enteric Coated Tablets

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Objectives: The bioavailability of well permeable drugs administered as single-unit modified release tablet is markedly dependent on the gastric emptying time of such tablet, especially when taken in fasted stomach state. The influence of pH on drug release can be evaluated in vitro. On the other hand, the vector of tablets gastric emptying times is a random variable and can be generated from Weibull distribution function [1,2]. The purpose was to develop a link model consisting of the kinetics of drug release and the kinetics of gastric emptying of tablets under fasting conditions. With such model an in vivo drug release can be predicted.

Methods: In vitro release experiments were performed on enteric coated Voltaren tablets containing 50 mg of diclofenac sodium (Novartis Farma, Italy) using paddle method (USP Apparatus 2). The tablets were placed into simulated gastric fluid (SGF, pH = 1), which was replaced by simulated intestinal fluid (SIF, pH = 6.8) after 2, 10, 30, 50, 70, 90, 110, 130, 150, or 200 minutes in order to mimic several gastric residence times. The amount of diclofenac released was measured in 10 minutes intervals. Each in vitro experiment was performed in triplicates, resulting in total 30 diclofenac release profiles. Due to enteric coating and low diclofenac solubility in acid medium, the diclofenac release in SGF was extremely limited, whereas in SIF the release was rapid and complete. Modelling of diclofenac release data was performed in NONMEM IV.

Results: The diclofenac release data were described by the Weibull model with lag-time and inter-tablet variability on all model parameters. Additionally, a linear relationship between the tablets gastric residence time and the variability in lag-time parameter of the Weibull model was found to adequately describe a link between in vitro diclofenac release and gastric residence time. On the basis of Weibull distribution function with values of 70.2 min for shape parameter and 1.4 for scale parameter, 100 individual tablets gastric emptying times were generated in R environment. The shape and scale parameter values were previously estimated on the basis of the data collected from several studies evaluating the gastric emptying of tablets in healthy subjects under fasting conditions [1]. The generated tablets gastric emptying times were applied to the developed link model using NONMEM simulation step. The results consisted of 100 individual predicted in vivo release profiles. Additionally, the mean predicted in vivo diclofenac release profile was compared to the in vivo diclofenac absorption profile obtained by deconvolution of mean diclofenac plasma concentration profile.

Conclusions: The link between diclofenac release from enteric coated tablets and tablets gastric emptying time was estimated allowing prediction of in vivo diclofenac release profiles. Additionally, a

good correlation between the mean predicted in vivo release profile and mean absorption profile was established.

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Eugeniy Metelkin Application of pharmacokinetic-pharmacodynamic model to optimize dosing regime of antimicrobial drug Grammidin containing gramicidin S

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Objectives: To predict the dependence of antimicrobial effect of the gramicidin S applied as oral melting tablets on dosage, time of resorption and minimal inhibitory concentration (MIC) of the drug characterizing its ability to kill different bacteria.

Methods: Mechanism based PK/PD modeling of antimicrobial effect of gramicidin S.

Results: The model has been employed to optimize dosing regime of the commercially available drug Grammidin. Efficacy of the drug has been studied for the diverse gram-positive and gram-negative bacteria with different MIC. The number of bacteria located in the oral cavity and killed by one-pass administration of the drug (resolution of one tablet) has been calculated under condition of various dosing regimes.

Conclusions: Based on the simulation results it has been found [1] that (1) two fold prolongation of prescribed resorption time (from 30 min to 60 min) of the Grammidin tablet comprising standard dosage of 3 mg of gramicidin S results in 1.5-fold increase in efficacy, (2) 1.5-fold decrease in gramicidin S dosage (from 3 mg to 2 mg per administration) under condition of holding prescribed resorption time (30 min) does not lead to any considerable decrease in the efficacy of the drug.

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Carmen Navarro Bioequivalence trials simulation to select the best analyte for drugs with two metabolic pathways

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Objective: To evaluate the chemical substance (parent drug or metabolite) more suitable for BE analysis.

Method: A semi-physiological model was used including two metabolic pathways in pre-systemic intestinal and hepatic metabolism, in addition to the previous model [1, 2]. Simulations about four BCS drugs undergoing saturable and non saturable metabolism were performed. The studies were simulated using NONMEM VI.

Results: Results are presented as percentage of BE success. In non-saturable conditions, there are small differences between parent drug and metabolites in AUC and Cmax ratios.When the metabolism becomes saturable, the principal and secondary metabolites AUC and Cmax ratios are larger than parent drug ratios. However, when only the principal metabolic route is non-linear, although parent drug is more sensitive than both metabolites, as the dissolution constant rate decreases, the principal metabolite AUC increases and it reaches values higher than the reference one.

Conclusion: Evaluating drugs with two pre-systemic metabolic routes, the metabolites do not show higher sensitivity than the parent drug to detect changes in the pharmaceutical performance, even when pharmacokinetics of the parent drug is non-linear.

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Ackaert Oliver A true Markov model for sleep disturbance

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Objectives: The circadian sleep pattern in rats and humans is different, with more frequent transitions between different sleep states and from sleep to fully awake in rats [1-2]. As was demonstrated previously in humans, transitions between different sleep states can be described using a Markov approach [3]. To evaluate the effect of three drug candidates, which are expected to show different propensities for disturbing sleep, a true Markov model was developed to describe these treatment effects on the complex sleep pattern in rats.

Methods: To describe the transitions between different sleep states and assess treatment effects on these transitions it is crucial to consider the dependency between observations. For that purpose Markov models are better suited than proportional odds models [4]. In this study, sleep is considered to be a two-state process: asleep or awake. The two-state, continuous time Markov process was defined by the intensity of both states. In contrast to other Markov approaches [3], the transition probabilities from one state to another over a time interval were uniquely defined and were explicitly derived as functions of these intensities. It was assumed that drug effects can change these transition intensities. The predictive performance of the model was analyzed by comparing the rate of true *versus* false positive and estimating model accuracy.

Sprague-Dawley rats (n=8) were implanted with radiotelemetry transmitters under isoflurane anaesthesia for recording of electroencephalogram (EEG) and electromyogram (EMG). Data were continuously sampled for 12 hours and analyzed in 5 min epochs. Animals were orally dosed at light on-set with either vehicle or drug in a Latin Square design [5]. PK was derived from satellite animals.

Results: As demonstrated by simulations, the Markov model predicted the data better than a proportional odds model. The predictive performance of the Markov model was also better with low probability of misclassification. The true Markov model allowed estimation of the relative propensity of the 3 drugs to disturb sleep.

Conclusions: Markov models allow analysing longitudinal observations with recurring states. However, for Markov models showing goodness of fit is not sufficient to qualify model performance. Therefore, a received operating characteristics (ROC) technique was used to assess predictive performance and misclassification of the model. This ROC technique can also be used to discriminate between competing models.

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Henry Pertinez Bayesian POP-PK analysis of exposure data from a Phase IIb clinical trial

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Objectives: As part of an ongoing PhD project on modelling the pharmacokinetics of "Drug X", a plasma exposure dataset derived from a phase IIb clinical trial investigating the safety and efficacy of "Drug X" is being analysed. Simulation of the phase IIb study plasma profiles using parameters derived from a 3-compartment empirical model fitted to earlier phase I clinical trial data, revealed that while the steady state exposure during the dosing period was adequately described, an extended terminal phase only visible in the longer phase IIb timecourse was not. This phase is likely to reflect long term, "deep" distribution of "Drug X", which is of particular interest to describe accurately as it has the potential to influence "Drug X"s pharmacological effects. Furthermore, an accurate description of this terminal phase will be necessary if long term predictions of exposure are required, and also for development of a forcing function to allow open loop PBPK modelling of plasma and tissue data from the phase IIb clinical trial.

Methods: A Bayesian analysis using the WinBUGS software package was carried out to allow the information derived from the phase I studies to be carried forward to allow modelling of the sparsely sampled and noisy phase IIb data and so allow for a more appropriate description of the terminal phase. The richly sampled phase I data consisted of single dose IV infusion data (28 day profile, n=15), single dose PO tablet (28 day profile, n=24) and BID dosing PO tablet data (n=10 at 4 dose levels, BID dosing for 25 days with overall profile of 53 days). The pop-PK of these datasets was analysed in a single combined run in WinBUGS using a 3-compartment disposition model with saturable absorption to account for the nonlinear bioavailability seen in the 4 dose levels of the BID PO data. The parameters derived from this analysis were then used as informative priors for the mixed effects modelling of the phase IIb study dataset (n=80 at 3 dose levels, PO tablet BID dosing for 2 years with overall sampling profile of 3.5 years). A 4-compartment disposition model with saturable absorption was used in this analysis to allow the long-term timepoints of the phase IIb data timecourse to be described by an additional exponential phase, with informative priors used on the nested parameters of the model common to the prior 3-compartment analysis. After preliminary investigation, due to the lack of information in the phase IIb profiles on the earlier phases of the PK profile of "Drug X", the WinBUGS "CUT" function was used so that the phase IIb data would only be used to allow estimation of the parameters related to the 4th exponential phase of the model.

Results: The initial results of the Bayesian analysis are satisfactory (as assessed by visual predictive check), providing a description of the phase IIb dataset that captures the long terminal phase seen on this timescale, while remaining consistent with the modelling of the shorter timescale studies. This improved description of the data, will be more appropriate as a forcing function for future PBPK modelling efforts. Issues remain however regarding poor convergence of the WinBUGS MCMC

sampling chains in the analysis and work is ongoing to investigate various options to improve this convergence.

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Tarjinder Sahota Model-based safety thresholds for discrete adverse events

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Objectives: Safety thresholds in preclinical toxicology are used to understand the risk/benefit profile of the drug and inform starting doses in first in man experiments. Traditionally, these are obtained with the No-Adverse-Event-Level (NOAEL) approach. It is an empirical method that calculates the minimum systemic exposure levels in animals with recorded adverse events. The discrete nature of many recorded AEs, and the possibility of unrecorded AEs, however, makes the assessment of these improvements technically challenging and also provides a challenge for the model-based methodology. The objectives of this exercise are: a) to compare bias/accuracy of a model based approach to the NOAEL approach using "true" thresholds and b) demonstrate the feasibility of obtaining model-based safety estimates in standard toxicological experiments, for a variety of hypothetical AEs with different mechanisms.

Methods: An in-silico approach was used. Simulations were performed in NONMEM 6.2. The test species was rats and data was generated according to standard preclinical toxicological designs. A Markov model was used to simulate transition times and states representing the onset and severity of AEs. Four different biomarkers were used as covariates influencing transition probabilities:
Model 1) A one-compartment pharmacokinetic (PK) model with Michaelis-Menten elimination. Concentration of drug directly drives AE. Model 2) Irreversible binding to an enzyme which inhibits production of an endogenous compound with protective effects. Model 3) Formation of active metabolite with direct effects. Model 4) Indirect increase of production of a compound which drives AEs.
Safe-dosing thresholds were estimated via simulations and conservative safe estimates were obtained with simulations incorporating parameter uncertainty. Bias was assessed by deviation from a pre-defined safe exposure threshold and accuracy was also obtained and compared with the traditional NOAEL approach.

Results: The NOAEL approach exhibited the poorest accuracy and precision in comparison to the proposed methodology. The failure rate in determining a threshold was also higher.

Conclusions: Integrated use of data enables accurate modelling and predictive value. Even misspecified models outperform the NOAEL method. A model-based approach also allows for the incorporation of different definitions of acceptable risk for different AEs.

Tarjinder Sahota The Chicken and the Egg in Interoccasion Variability

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Objectives: The inclusion of interoccasion variability (IOV) on model parameters has been justified previously [1]. However, it is unclear at which step to include it during the model building process when covariates are being evaluated.

One school of thought emphasises the inclusion of fixed effects before introducing random effects. This view favours exploration of covariates before inclusion of IOV. This ignores the possibility of model misspecification with fixed effects. The opposing view is that random effects should come first and covariate explored only after IOV has been identified. We aim to use pharmacokinetic (PK) modelling of an oncology drug as an example to assess the difference between the two approaches in terms of model performance.

Methods: An integrated dataset on PK, demographic and treatment covariates was used from a variety of phase I and II studies. The basic model was obtained by including between-subject variability only. Stepwise covariate selection (SCM) was performed in PSN v.2.3.2 using forward addition ($p<0.05$) and backward deletion ($p<0.01$). IOV was explored on all parameters with occasion as varying between a) steady-state/non-steady-state, b) 5 day intervals and c) daily sampling. Model building was performed in NONMEM 6.2 using FOCEI estimation. Two different approaches were implemented. First a model was built by applying the SCM to the basic model and then incorporating IOV (Model A). Secondly, a model was built by applying IOV to the basic model and then performing the SCM (Model B). Model performance was assessed by goodness-of-fit plots, VPCs, NPCs, and PPCs of AUC and Cmax statistics.

Results: The use of IOV for each sampling day on bioavailability gave the largest drop in objective function for model A and B. However model A showed the large bias in population predictions. Model A identified co-administration of lapatanib and drugs affecting PH balance in the stomach as significant covariates, Model B did not. Posterior predictive checks showed that model A did not predict average exposure in individuals receiving co-medications. Model B correctly predicted these statistics.

Conclusions: Incorporation of IOV after exploration of significant covariate relationships may produce greater bias in final model predictions. Non-significant covariates may also be selected due to a biased fixed effects structure. Conventional wisdom should favour IOV being included before optional covariate relationships.

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Tobias Sing An R package for industrializing concentration-QT analysis

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Objectives: Since 2005, the FDA recommends a dedicated study (Thorough QT; tQT) to be conducted for every NME to determine the effect of the drug on the QT interval in healthy volunteers. The current regulatory opinion on the design and analysis of tQT studies is formulated in the ICH E14 guideline [1]. The purposes of this package are: (1) to provide a set of R functions that can be used flexibly to visualize, analyze, and model (concentration-) ECG data from a clinical study (tQT or other); (2) to provide a "one-click" approach to perform a standardized, pre-specified analysis; (3) to automate the creation of analysis datasets from clinical databases; (4) to automate the insertion of analysis results into a Word template report for concentration-QT analyses.

Methods: The package was implemented in R and only relies on nlme (linear/nonlinear mixed-effects modeling) as an additional package.

Results: The package contains functions to perform all the steps of a typical (concentration-) QT analysis, including: correcting QT for variation in the RR interval; performing baseline- and placebo correction; exploratory graphics; point-wise t-test according to E14 guideline with graphical presentation; pre-implemented exposure-QT models (extensible by user); tabular and graphical model summaries and diagnostics; nonparametric bootstrap to assess uncertainty of population prediction for any linear or nonlinear mixed-effects model; visual predictive check.

Conclusions: The QT package for R facilitates, speeds up, and industrializes the analysis of ECG data from clinical studies. A standardized, pre-specified analysis can be performed with a single command. Alternatively, the user can also tailor analyses to their specific needs by using the functions of the package individually. All functions can also be modified and extended within R.

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Kuenhi Tsai Estimation Comparison of Pharmacokinetic Models Using MONOLIX, PKBUGS, and NONMEM

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Objectives: FO, FOCE, and Laplacia methods in NONMEM6 [1] have been shown to have difficulty converging in certain scenarios. Two newer packages, PKBUGS 1.1 [2]and MONOLIX 2.4 and 3.1 [3], feature recent computational advances and have begun to be embraced by practitioners. Although earlier studies have shown similarities in the performance of the three software packages [4][5][6], bias and reliability have not been sufficiently tested. This analysis uses several criteria to compare the three packages using results from multiple replications of two different PK model scenarios.

Methods: The 1st scenario used a one-compartment model with first-order absorption and elimination and incorporated sparse sampling where each subject was sampled at two points drawn from a set of 12 values from 0 to 70 units. The 2nd scenario used a PK model defined by two differential equations with combined first-order and saturated elimination, with inter-subject variability incorporated for two of the population parameters. 100 datasets were generated for each scenario using R for the 1st scenario and NONMEM for the 2nd scenario. Each dataset was analyzed with all three packages. From the 100 estimates produced for each model, accuracy and precision of the parameter estimates were assessed using means, mean estimation error, root mean squared error (RMSE), and the percentage of 95% confidence intervals (CIs) which cover the ture parameter value.

Results: In the sparse sampling scenario, MONOLIX outperformed NONMEM and PKBUGS since it converged each time and produced better RMSE and CI coverage. NONMEM failed to converge in 1 of the datasets because of sensitivity to the initial values. PKBUGS took the longest time to run and unreliably estimated one of the inter-subject variability parameters, but otherwise it performed comparably to NONMEM. On the 2nd scenario, NONMEM produced estimates with the smallest bias and RMSE than MONOLIX or PKBUGS. Sereral runs of PKBUGS failed to converge, yielding biased estiamted with high RMSE, but the coverage was still better than in MONOLIX. All assessments in MONOLIX 2.4 were poor. Using version 3.1 and increasing the number of "burn-in" iterations from the default number improved the estimation, but it still performed worse than the other two packages. MONOLIX also underestimated the standard error resulting in low CI coverage.

Conclusions: MONOLIX performs well with a sparse sampling scheme when all parameters are associated with inter-subject variability. Simulation results show that caution should be taken when data are fitted in a model with inter-subject variability limited to some, but not all, parameters in MONOLIX and, to a lesser extend, PKBUGS. If initial values are not the converging issue, PKBUGS may not be as desirable a choice for complex PK applications as NONMEM unless convergence is monitored carefully.

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Coen van Hasselt Implementation of an affordable computing cluster for pharmacometric analysis

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Objectives: The aim of this project was to construct a dedicated computing cluster for our population analysis group. The following specifications were defined for this cluster:

1. Central installation of software enabling control of integrity and installation;
2. access to the cluster from internal and external networks;
3. easily extendable with additional nodes;
4. use of affordable consumer hardware and preferably open-source software.

Methods: The computing cluster consists of 1 master node and 9 computing nodes. Each node was configured with an Intel quad core CPU allowing execution of 4 processes simultaneously at maximum efficiency. We used Ubuntu Linux Server edition as the operating system. To dynamically distribute computing tasks over the cluster, the software package Sun Grid Engine was used. This package allows efficient distribution of computational tasks across the cluster. Furthermore, a range of applications for pharmacometric data analysis were installed. These included several versions of NONMEM and Fortran compilers, PsN[1], R[2] and Matlab. The in-house developed and freely available modelling environment Pirana[3] was installed to allow easy access to the pharmacometric software, to offer integrated access to study data, and for processing of results.

User access to the cluster was offered via an SSH connection, both from the internal network and over the internet. Display of graphical interfaces of software that is executed remotely on the cluster, can be easily accomplished using X-forwarding over SSH. As user-side operating system, either Windows, Mac OSX or Linux can be used. The central installation of software on the cluster system enables version control of software, ensuring use of identical versions by all users. Finally, validated scripts, data, models and results can be stored on the cluster with read-only access, improving the regulatory compliance for computerized systems.

Results: The developed computing cluster offers a dedicated and reliable solution for the computational resources needed within our modelling group. Sufficient computing power is available, and this can easily be extended with additional nodes if necessary. Moreover, this system was built using consumer hardware, which makes the system very affordable. Total costs of this system were approximately € 4000,-. The centralized environment in which applications are installed, controlled and executed, increases the integrity of pharmacometric analyses. The installation of Piraña as user

interface to the various pharmacometric software, facilitated use of the cluster for both novice and expert users.

Conclusions: This project demonstrates the feasibility of the setup of an affordable and scalable cluster in the pharmacometric setting

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Paul Westwood A Pharmacokinetic Study of Ranitidine in a Paediatric Population

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Objectives: Ranitidine is a histamine-2-receptor-antagonist widely used in intensive care units as prophylaxis against stress ulcer syndrome, gastro oesophageal reflux, persistent vomiting and gastric aspiration, or to negate the harmful effects of steroids. The purpose of this study was to use sparse data to investigate the pharmacokinetic (PK) profile of both i.v. (infusion and intermittent bolus dosing) and oral ranitidine in a paediatric population and to determine the influence of patient demographics; age, gender, weight, concomitant drugs and disease states.

Methods: The population PK analysis was performed in NONMEM (v.6.1). Several models were tested including one- and two-compartment disposition and double peak absorption models. Influence of the patient demographics was assessed as both continuous and categorical covariates. Development of the final model was guided by the relevant plots, reduction in the errors, and the change in the objective function using a multi-stage forward and backward stepwise elimination modeling approach. Three methods were used to evaluate the final model for the ranitidine dataset; a variation on the Jack-Knifing technique, Bootstrapping and Principal Component Analysis.

Results: Data from 78 children attending The Royal Belfast Hospital for Sick Children between 1998 and 2006 (mean age 4.57±4.48 years and mean weight 16.27±12.24kg) provided 248 opportunistically drawn samples with a median of 2 samples per patient (range 1 to 13). Conditions were separated into five main categories including stomach surgery and management of heart defects. There were 247 concomitant drug therapies identified from the individual patient records. A one compartment model best described the data. The final parameter estimates for the population were 32.1L/hr (CV 60%) for total clearance and 285L (CV 85%) for volume, both allometrically scaled for a 70kg adult and final estimates for the typical absorption rate constant and bioavailability of 1.31hr-1 and 27.5%, respectively. Weight was the most significant covariate in the model and the presence of heart-related conditions was shown to significantly reduce ranitidine clearance by 54%.

Conclusions: This PK study of ranitidine in a paediatric population found that the presence of a heart condition significantly decreased the clearance, and dose adjustments and careful monitoring are recommended for paediatric patients with heart conditions who are receiving ranitidine.

Justin Wilkins A comparison of two model-based approaches to investigating covariate effects on the dose-exposure relationship in a Phase III context

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Objectives: Linear and nonlinear mixed-effects model-based approaches to investigating covariate effects on exposure were compared in order to determine whether the more straightforward linear approach was sufficient for addressing this question in a subject-rich but observation-poor context.

Methods: Sparse concentration-time data were simulated according to commonly-used Phase III pivotal study designs and pharmacokinetic sampling schemes. A one-compartment model with linear absorption and elimination, incorporating covariate effects (analogous to age and body weight) on CL/F and V/F, was used as the basis for simulation. The simulated covariate relationships exerted effects of between 5% and 50% on model parameters. Variability was included in model parameters – 40% in CL/F, 40% in V/F and 50% in KA. Each scenario was replicated 1000 times, after which each replicate was analyzed using two discrete approaches: nonlinear mixed-effects (NLME) analysis of all the simulated data in a given scenario using a compartmental model implemented in NONMEM VI, and linear mixed-effects (LME) analysis of observed peaks and pre-dose troughs, implemented in R 2.8.1. Relative efficiency of the approaches was evaluated in terms of the rate at which each approach in each scenario failed to select the included "true" covariate relationship at the 5% significance level, as well as in terms of bias and precision in the quantitative estimates of the magnitude of the covariate effect in each case.

Results: Although analysis is ongoing, preliminary results indicate that LME models provided an answer in a fraction of the computing time required for full NLME analyses, although the NLME approach generally provided more precise estimates of the magnitude of the effect. The complete analysis will be presented.

Conclusions: Although work in ongoing and definitive conclusions cannot yet be drawn, LME analyses are much faster than NLME analyses in this context, and seem to identify important covariate relationships appropriately, given the typical design scenarios studied. In the context of population pharmacokinetic analysis for the determination of covariate influences on the dose-exposure relationship in Phase III, the LME approach may be an acceptable alternative to a full compartmental analysis using NLME.

Hesham Al-Sallami A semi-mechanistic model for estimating lean body weight in children

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Objectives: Body size correlates with clearance and can be used to scale drug doses. Lean body weight (LBW) has been proposed to be a better size descriptor than other measures of weight. Mathematical models for estimating LBW have been developed in adults. There are currently no models available to predict in children. The aim of this project is to develop a semi-mechanistic model to quantify LBW in paediatric patients.

Methods: A general model for maturation was developed for LBW using NONMEM VI. An index dataset (496 females and 515 males) containing demographic data and body composition measurements was used to estimate model parameters. Missing data were imputed.
An empirical model for LBW was developed using STATA 11.
The predictive ability of the adult model (Janmahasatian et al, 2005) and the general maturation model were evaluated with respect to the empirical model using the mean squared error (MSE).
A test dataset (90 females and 86 males) was used to evaluate the general maturation model.

Results: A semi-mechanistic sigmoid Emax maturation model was developed:

LBWchildren = baseline LBW + AGE^GAMMA/(AGE^GAMMA + AGE50^GAMMA) x LBWadults

An empirical model with 9 terms (including interactions) was developed using mixed-effect linear regression.
Using the index dataset, the adult model had a variance of 15 kg^2 whereas the maturation model had a variance of 12 kg^2. The increment in MSE using the adult model in relation to the empirical model (which had a variance of 6 kg^2) was 146%; the increment in MSE using the maturation model in relation to the empirical model was 99%.
Using the test dataset, the adult model had a variance of 16.5 kg^2 whereas the maturation model had a variance of 12.2 kg^2. The increment in MSE using the adult model in relation to the empirical model (which had a variance of 8.5 kg^2) was 94%; the increment in MSE using the maturation model in relation to the empirical model was 44%.

Conclusions: The adult model provided an unbiased descriptor of LBW in children. The general model for maturation for LBW in children provided a more precise estimate of LBW in children than the adult model. The loss of predictive performance was significantly less for the general model for maturation compared to the adult model for both internal and external evaluation.

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Marilee Andrew Physiologically Based Pharmacokinetic (PBPK) Modeling of Midazolam Disposition in Pregnant and Postpartum Women

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Objectives: Pregnancy alters the pharmacokinetics of midazolam (MDZ) [1], a probe for CYP 3A activity. The aim of this study was to investigate physiological mechanisms responsible for altered MDZ disposition.

Methods: The model was developed in MATLAB (The Mathworks); maternal and fetal circuits were coupled through the placenta. Previously published volumes and flows [2] were scaled for gestational age, while partition coefficient and protein binding parameters were obtained from a previously published modeling study [3]. Small intestine (duodenum, jejunum and ileum) and hepatic metabolism were described by Michaelis-Menten kinetics [4]; metabolism could be varied independently in each tissue. Intestinal metabolism only occurred during first pass, while hepatic metabolism occurred both first pass and systemically.

Results: Predictions first were compared with observations following 7.5, 15, and 30 mg PO dosing in healthy, non-pregnant subjects [5]. Comparison of AUC, CLsys, Cmax and Tmax demonstrated good (within 2 fold) agreement when metabolic expression was altered from base by 1.7 fold. Base expression in the model was thus ‘tuned’ to this value. Predictions then were compared to observations following IV and PO dosing in women undergoing Caesarian section [6,7]. Three to 5 fold increases in hepatic metabolic expression were required to achieve good agreement between prediction and observation, but did not fully explain observations. Lastly, predictions were compared to observations following 2 mg PO dose to women in late pregnancy [1]. Simulations required 7 fold and 5 fold increases in the tuned hepatic expression rate in late pregnancy and 10 weeks postpartum, respectively, to obtain good agreement with observations, although the model still over-predicted the elimination phase of the time course. Good agreement was obtained between predicted and observed maternal-fetal plasma concentration ratio shortly after maternal dosing, but not several hours post-dosing. Sensitivity analysis was used to identify parameters influencing key portions of the predicted time courses.

Conclusions: The PBPK model can be used to predict MDZ time courses in pregnant and 10 weeks postpartum women; however, hepatic metabolic expression required substantial increases to describe observations compared to those required to describe observations in non-pregnant subjects. Research is needed to further explore metabolic mechanisms and the potential effects of altered intestinal and hepatic blood flow on pharmacokinetics during gestation.

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Karina Claaßen Physiology-based Simulations of Amikacin Pharmacokinetics in Preterm Neonates

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Objectives: This work aimed to extend the database of the physiology-based pharmacokinetic (PBPK) software PK-Sim® to enable simulations in preterm neonates down to 24 weeks of gestational age (GA). The implemented model accounts for both intrauterine development and the postnatal growth and maturation of anatomical and physiological parameters relevant for PBPK modeling.

Methods: Information about physiological parameters of neonates born between 24 and 40 weeks of gestation have been collected from the literature and implemented into the database of PK-Sim®. The aminoglycoside antibiotic amikacin was chosen as a model drug based on the availability of a previously established amikacin model for adults and therapeutic drug monitoring (TDM) data in preterms reported by Allegaert et al [1], [2]. Plasma concentration time curves after a single intravenous dose of amikacin were simulated in virtual populations and compared to the experimental data obtained in neonates with a maximum postnatal age of 6 days.

Results: Simulation results of amikacin pharmacokinetics demonstrate a reasonable representation of TDM data in preterm neonates. Most data points fall within the 5th to 95th percentile of the simulated populations. Only a slight possible bias to lower predicted concentrations is observed.

Conclusions: A physiology-based model to simulate pharmacokinetics in preterm neonates has been developed and implemented in PK-Sim®. A comparison of simulated amikacin plasma concentrations with in vivo TDM data demonstrates the predictive capabilities of the preterm PBPK model.

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Cecile Gerard Influence of cyclosporin dosing schedule on receptor occupancy in bone marrow transplantation: analysis with a PBPK-PD model

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Objectives: In bone marrow transplantation, cyclosporin is administered to prevent graft-versus-host disease (aGvHD), which occurs mainly in three organs (skin, intestines and liver). This immunosuppressant drug acts on T lymphocytes and has some nephrotoxicity. Because its disposition depends on several sources of nonlinearity [1], organ exposure may be higher after intermittent infusions (II) than after continuous infusions (CI).

Methods: A physiologically-based pharmacokinetic model was developed in order to estimate cyclosporin exposure in interstitial fluid (space of T lymphocytes) of the target organs of aGvHD and in intracellular space of kidneys (nephrotoxicity). These simulations were used to compare exposures and receptor occupancies (RO) of pediatric patients that received cyclosporin either by II or CI. The relevant biological parameters and their interindividual variability were based on a clinical study in 2 groups of pediatric patients that received cyclosporin either by II (n = 31) or CI (n = 30) at an initial dose of 3 mg/kg/day.

Results: Simulations showed that the exposure to cyclosporin in the interstitial fluid of aGvHD target organs was greater at day 1 after II than after CI (mean area under the curve (AUC) of 2.65 *vs* 2.39 h.mg/l). At steady state, there was no difference. By contrast, the exposure to cyclosporin in the intracellular space of kidney was greater at day 1 and at steady-state after CI than after II (mean AUC of 129 *vs* 112 h.mg/l). Regarding exposure of RO, AUC_{RO} in interstitial fluid of aGvHD target organs and in kidney cells at day 1 and at steady state were greater after CI than after II (mean AUC AUC_{RO} of 14.7 *vs* 12.9 h.mg/l). The therapeutic index, estimated as the ratio of AUC_{RO} in blood to AUC_{RO} in kidney cells, was 0.62 with CI *versus* 0.52 with II.

Conclusions: Regarding organ exposure, II may be more favorable than CI because of a greater exposure in target organs of GvHD and a lower exposure in kidney cells. However, concerning the receptor occupancies, the therapeutic index was slightly better after CI than after II. Further analyses are required to determine whether cyclosporin efficacy and toxicity depends on the average concentration or on the entire concentration profile in the interstitial or intracellular space of target organs. Ultimately, this information will contribute to determining the optimal mode of cyclosporin administration.

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Julia Hövener Evaluation of a Physiologically-Based Pharmacokinetic (PBPK) Model for the Application of Low Dose Etoposide in Children

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Objectives: Etoposide is a widely-used anticancer drug in both pediatric and adult oncology. The pharmacokinetics is well characterized with high inter-patient and intra-patient variability in individual exposure possibly due to drug interactions during polychemotherapy regimens or enzyme polymorphism. The aim of the current project was to evaluate a physiology-based pharmacokinetic (PBPK) model - implemented in PK-Sim® - to predict the systemic drug exposure of low dose etoposide in children treated in the NB 97 regimen for neuroblastoma.

Methods: The simulations of etoposide were performed with the software PK-Sim®. Based on a previously established PBPK model for adults, individual simulations for every pediatric patient (n = 40, medium age = 3,78 a) were performed. To describe the main metabolism and excretion processes by P450 enzymes and drug transporters, Michaelis-Menten kinetics using parameters from *in-vitro* experiments reported in the literature were applied. Enzyme activities of CYP3A4 and UGT1A1 were scaled with age to account for growth and maturation processes in the pediatric patients.The concentration-time profiles from these patients receiving intravenous etoposide longtime infusion of 96h in the NB 97 regimen were compared to observed 24h and 95h plasma concentrations.

Results: The mean plasma concentration-time data of protein-bound and free etoposide observed in children treated in the NB 97 regimen were well predicted, but the inter-individual variability was underestimated by the model. The age-dependent scaling procedure for the Michaelis-Menten parameters was adequate to describe the metabolization and elimination of etoposide in children in different age groups.

Conclusions: This PBPK-model can be used to predict the etoposide pharmacokinetics in a low dose regimen in children after appropriate scaling of model parameters for metabolism and excretion from the adult model. In general, PBPK simulations in children can be a useful tool for pediatric clinical trial design.

Wojciech Krzyzanski An Interpretation of Transit Compartment Pharmacodynamic Models As Lifespan Based Indirect Response Models.

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Objectives: Transit compartments (TC) models are used to describe pharmacodynamic responses that involve drug action on cells undergoing differentiation and maturation [1-3]. Such PD systems can also be described by lifespan based indirect response (LIDR) models [4]. Our objectives were to determine the lifespan distribution for which the LIDR model coincides with the TC model, to show that if the number of transit compartments n increases to infinity, then the TC model approaches the basic LIDR model with the point lifespan distribution centered at the mean lifespan T_R, and to propose a new class of LIDR models for agents acting on the cell lifespan distribution.

Methods: An integral representation of a solution to the TC model has been used to determine the lifespan distribution for cell population described by this model. This distribution served as a basis for definition of new LIDR models that are mathematically identical to the TC models. Time courses of responses for both types of models were simulated for the monoexponential PK function. The limit response was calculated as n approached infinity. The difference between the limit response and TC responses were evaluated by computer simulations using MATLAB 7.7.

Results: The TC model is a special case of the LIDR model with the lifespan distribution described by the gamma function. If drug affects only the production of cells, then the cell lifespan distribution is time invariant. If the drug inhibits or stimulates cell aging, the cell lifespan distribution becomes time dependent revealing a new mechanism for drug effect on the gamma p.d.f. The TC model with a large number of transit compartments converges to a LIDR model. The TC model curves were simulated for n =1 to 100. The difference between TC and LIDR curves was highest for the peak times and ranged between models 14.1%-47.8% for n =10, 9.4%-43.7%, for n =20, and 4.6%-35.5% for n = 100. The new LIDR models are described by a functional operator acting on invariant lifespan distributions and resulting in a time variant distributions due to the changes caused by a time dependent drug effect.

Conclusions: The TC models can be considered as LIDR models with the gamma lifespan distribution. If the number of compartments increases and the mean lifespan is constant, then the TC models approach a basic LIDR model with a point lifespan distribution. TC models with the number of TCs between 5 and 20 provide a good approximation of the basic LIDR model.

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Jörg Lippert Separating individual physiological variability from drug related properties using PBPK Modeling with PK-Sim® and MoBi® – Theophylline

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Objectives: Physiologically-based pharmacokinetic and pharmacodynamic (PBPK/PD) modeling and classical compartimental methods using NLME or Bayesian Markov Chain Monte Carlo simulation have been considered as complementary approaches to PKPD. But only Bayesian PBPK/PD as a completely knowledge-based approach allows a systematic identification of highly valuable drug-independent information about individual physiological processes. In using this approach every experiment will lead to an improvement of understanding of substance-specific behavior and its interaction with individual physiological processes.

Methods: The classical theophylline example [1] was used to develop and evaluate the integrated statistified PBPK/PD approach. All modeling was done in the systems biology software platform consisting of PK-Sim® and MoBi®. Prior knowledge about anatomical and physiological structure, population parameters and their variability was automatically loaded from PK-Sim®'s built-in database [2]. Global, compound specific parameters, e.g. lipophilicity, and individual physiological parameters like intestinal transit time were modeled. We implemented Metropolis Sampling [3] in our platform which allows sampling nonstandard posterior distributions for all parameters of interest.

Results: The use of physiologically proper prior information allows fitting of high-dimensional PBPK-models. The statistified PBPK gives a clear identification of aimed parameter values and automatically identifies the subset of relevant parameters. The resulting pharmacokinetic curves show a superior fit compared to [4].

Conclusion: PK-Sim® and MoBi® greatly facilitate combined PBPK/PD modeling and statistical analysis by statistical methods. In contrast to compartmental models where physiological properties and drug properties are represented by joint parameters and intra- and inter-individual variation is only indirectly represented by substance-specific parameters and variabilities, Bayesian PBPK/PD directly deconvolutes variability of physiological processes. This allows interpretability of results and generates knowledge about individual physiological processes that can be applied even in the context of further substances and will lead to advancements in interpretation and prediction of drug trials.

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Jörg Lippert Mechanistic analysis of fusion proteins: PBPK applied in an Albuferon case study

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Objectives: The pharmacokinetics of protein therapeutics is governed by unspecific and specific processes[1,2]:

1. Exchange across vascular endothelium by convection and diffusion.
2. Return of drug from interstitial space in organs to circulation by lymph flow.
3. Degradation mediated by neonatal Fc receptor (FcRn) in cellular endosome.
4. Target-mediated deposition and clearance

A physiologically-based pharmacokinetics (PBPK) model for Albuferon, an albumin–interferon-fusion protein, has been developed using generic sub-models. Albuferon was chosen since it allowed to explore the influence of both unspecific endothelial exchange and lymph flow as well as the specific effects of FcRn-mediated recycling and target mediated deposition and clearance.

Methods: The model was built in a modular way using parameterization established for IgG-antibodies (FcRn related processes) and interferons (target mediated processes). All PBPK models were implemented in PK-Sim® and MoBi®. Competitive binding of endo- and exogenous ligands to FcRn takes place in the endosome of endothelial cells in each organ. To describe protection by FcRn the model Albuferon was coupled with a model of endogenous albumin. Target-mediated deposition and clearance is described by reversible binding of drug to interferon receptor (IFNAR2) and irreversible complex internalization. The PBPK model for Albuferon was build based on the models for the IgG-antibodies and interferon-α/β. The rate of formation of endogenous albumin was set to match steady state concentration of albumin.

Results: The PK of Albuferon is dose-linear and a model not taking the IFNAR2 receptor binding into account matches experimental data best. Target mediated deposition and clearance appears to have a negligible effect on the PK of Albuferon. The PBPK model was extended by a first order release rate into the interstitial space of the skin to describe s.c. applications [3,4,5]. For monkey, a good description of the data is obtained, if a release rate is chosen to be insensitively small. The rapid release indicates dominance of lymph flow rates for the absorption rate of Albuferon. For humans, however, the first order release rate has to be set to a half-life of 125 h to match experimental data and terminal half life is largely determined by subcutaneous release. The reason for the difference between monkeys and humans is not known.

Conclusion: Albuferon pharmacokinetics could be predicted using PBPK sub-models established independently from Albuferon, using benchmarking compounds and prior knowledge only. A detailed analysis revealed that IFNAR mediated deposition plays a minor role for Albuferon while it is highly relevant for "naked" reference interferons. Following s.c. application, terminal half-life is determined by subcutaneous release in human but not in monkey.

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Jörg Lippert Identifying cancer drug MoAs and cell-line properties using signaling cascade models and Bayesian analysis: From throw-away experiments to persistent information

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Objectives: Clarifying the Mode-of-Action (MoA) of a drug often is a highly non-trivial task. This can mostly be done by performing specifically designed experiments. Depending on the complexity of the drug mthe required number of experiments to undoubtedly solve this question may be significant. Often performing significantly less standardized experiments would be sufficient for identification of the MoA if on the one hand prior experiments allowed a deconvolution of cell-line properties and drug induced effects and on the other hand a methodology was available which could make systematic use of this prior knowledge. Both is possible using Bayesian analysis of the data. We illustrate our approach by studying the MAPK signaling cascade [1] which is responsible for the regulation of gene expression and prevention of apoptosis and is often altered in cancer cells.

Methods: We use an established model [1], extended to be able to simulate two possible MoA's (inhibition of RAS or inhibition of EGFR) in our modeling software platform MoBi®. Inter-individual variation of expression levels for RAS, MEK, ERK and EGFR is estimated using CGAP data [2]. Noisy measurements of activated ERK percentage for each of 8-14 individuals are generated (incorporating variability) for the basic model, two mutants showing overexpression of RAS or the EGF-receptor and for one RAS and one EGFR-inhibitor. Identification of cell-line properties is performed using a Bayesian/MCMC approach [3] implemented in R [4] & MoBi®. During the first iteration an uninformative prior distribution of the four parameters RAS, MEK, ERK and EGFR is used. The identified posterior distributions are used as prior information at the second stage where the strength of the inhibition is additionally identified (uninformative prior). The results are compared to using uninformative priors on all six parameters.

Results: Identification of MoA during the second iteration was never possible using uninformative priors. Application of the posterior distributions of the first stage allowed identification of the MoA for three cell lines. In one case the model could not predict strength but could rule out the incorrect MoA.

Conclusion: This method provides the possibility to use previously conducted experiments independent of their experimental design for new questions. Thus we have a generic method to continuously and systematically enhance knowledge about cell lines and answer relevant questions with possibly less experiments.

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Jörg Lippert Clinical trial simulation with multiscale models: Integrating whole-body physiology, disease biology, and molecular reaction networks

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Objectives: Biology is multi-scale by nature. However, projects as well as software tools usually focus on isolated aspects of drug action such as pharmacokinetics at the whole-body scale or pharmacodynamic interaction on the molecular level. The objectives of this study are i) to introduce a software platform allowing for integrative modeling and simulation across biological scales, and ii) to illustrate the modeling concept realized in the platform by establishing a prototypical multiscale model for the progression of a pancreatic tumor in human patients and its treatment by pharmacotherapy.

Methods: The software platform consisting of PK-Sim® [1], MoBi® [2], and interfaces to R [3] and MATLAB® [4] offers both graphical user interfaces for model building and simulation as well as powerful command line functionalities for extended simulation and analysis tasks.

Results: Virtual patients are constructed and treated with an inactive prodrug that is activated by hepatic metabolization. Tumor growth in the model is driven by growth factor activation and MAPK signal transduction at the sub-cellular level [5]. Local free tumor concentrations of the active metabolite inhibit Raf kinase in the cascade and thereby cell cycle progression. In a virtual clinical study, the individual therapeutic outcome of drug therapy is simulated for a large virtual population with a reported heterogeneous genomic background [6,7]. The phenotype of the hepatic enzyme activating the prodrug has a strong impact on tumor progression under therapy. Oncogenic Ras mutations [8] influence tumor growth depending on the growth phase.

Conclusions: The application example presented demonstrates that efficient model building and integration of biological knowledge and prior data from all biological scales is feasible. The impact of events and processes at the molecular and organ level onto the physiology and pathophysiology of the whole organism can be readily studied by simulation. Experimental in vitro model systems can thereby be linked with observations in animal experiments and clinical trials. Thus, modern software tools solve the technical problem of model establishment and allow the application of multiscale modeling on demand, whenever business driven questions arise in the course of a project. Highly relevant clinical topics such as pharmacogenomics, drug-drug or drug-metabolite interactions can be studied based on a mechanistic, insight driven approach.

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Jörg Lippert Influence of CYP1A1 induction by cigarette smoke on pharmacokinetics of erlotinib: a computer-based evaluation of smoke-induced CYP1A1 activity in different tissues

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Objectives: Human cytochrome P-450 1A1 (CYP1A1) is located primarily in extrahepatic tissues and is known to be inducible by polycyclic aromatic hydrocarbons (PAHs) present in cigarette smoke and chargrilled meat [1-3]. Higher tissue levels of CYP1A1 can lead to a significant reduction in drug exposure in smokers or individuals with high consumption of barbecued meat and thus to a decrease in therapeutic efficacy. In order to evaluate the degree of CYP1A1 induction by tobacco smoke in different tissues, pharmacokinetics of erlotinib, a known substrate of CYP1A1, was analyzed using physiologically-based pharmacokinetic (PBPK) modeling.

Methods: A PBPK model for single dose intravenous (iv) and per oral (po) administration of erlotinib was developed integrating reported relative baseline expression levels for the relevant metabolizing enzymes CYP3A4 and CYP1A1 in liver, lung, and intestine [4, 5]. The model was implemented in the software tools PK-Sim® and MoBi® [6, 7] and adjusted to experimental plasma concentrations [8] taking into account study data to CYP3A4 inhibition with ketoconazole for estimation of residual CYP1A1 activity [9] and study data of smokers vs. non-smokers for evaluation of CYP1A1 induction [10].

Results: Two scenarios were evaluated. The first scenario assumed identical CYP1A1 induction in lung, liver, and intestine, leading to a predicted relative increase in enzymatic activity in all three tissues of 5.5 +/- 0.3 %. The second scenario allowed for local differences in CYP1A1 induction representing the expectation that CYP1A1 induction should be highest in lung since it is the tissue exposed to the highest concentrations of PAHs. In line with this expectation model scenario 2 predicted a relative increase of CYP1A1 activity in smokers of 12 +/- 6 % in lung, 5.4 +/- 0.3 % in liver, and 2.6 +/- 1.2 % in intestine, respectively. The model-based analysis of erlotinib pharmacokinetics in smokers and non-smokers predicted CYP1A1 induction levels in different tissues which are in accordance with experimental expression levels reported in literature [11-13].

Conclusions: PBPK modeling provides a valuable means of predicting drug pharmacokinetics in response to environmental chemicals such as PAHs in cigarette smoke or other compounds known to modify protein expression levels using information to relative changes in enzymatic activities.

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Jörg Lippert Simulation of the pharmacokinetics of flibanserin under itraconazole co-mediaction with an integrated physiologically-based pharmacokinetic model

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Objectives: The aim of this analysis was to evaluate the effect of high dose itraconazole (ITZ) 200 mg BID on the exposure of flibanserin and two CYP3A4 related metabolites by physiologically-based pharmacokinetic (PBPK) simulation. For model evaluation, data was available from a drug drug interaction study where flibanserin was given with and without 200 mg ITZ once daily.

Methods: The coupled PBPK model for flibanserin and metabolites was established by use of physicochemical data, demographics, mass balance and plasma concentrations after i.v. and p.o. dosing from an ADME trial. A previously established and validated itraconazole CYP3A4 inhibition model [1] was then integrated. The model was evaluated by simulating the flibanserin plasma concentrations of a previous interaction study, where 200 mg ITZ was given once daily. The model was then applied to predict flibanserin and metabolite plasma concentrations when given with the highest labelled ITZ dose, 200 mg BID.

Results: With the coupled flibanserin-ITZ PBPK model, the predicted geometric mean increase in AUC0-∞ was 2.93-fold for the previous drug interaction study and thus lies within the reported 90% confidence interval for the point estimator of the AUC0-∞ ratio with/without ITZ (2.56 [90% CI: 2.15-3.06]) while the predicted increase in Cmax was 2.20-fold and thereby slightly outside the reported 90% CI of the point estimator for the observed data (1.69 [90% CI: 1.42-2.02]). The simulation of co-administration with 200 mg BID ITZ led to a 3.32-fold and 2.38-fold increase in flibanserin AUC0-∞ and Cmax. The metabolite's AUC0-∞ and Cmax decreased to 27-28% of initial values.

Conclusion: The simulation showed that increasing the dose of ITZ resulted in only a minor additional increase in flibanserin AUC and Cmax. These results confirm the moderate impact of potent CYP3A4 inhibitors on flibanserin.

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Jörg Lippert Using relative gene expression measurements for PBPK modeling of pravastatin

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Objectives: Passive distribution of a drug in the body largely depends on the physicochemical properties of the compound, whereas both metabolization and active transport are dependent on the availability of enzymes or transporters and occur simultaneously in different tissues. A quantitative description of these processes, however, is difficult due to a limited experimental accessibility of tissue-specific protein activity in vivo. Here, we propose a novel method for the incorporation of expression data as a surrogate for protein activity into physiologically-based pharmacokinetic (PBPK) models. The general feasibility of this approach is demonstrated in a case study of pravastatin PK model building. The resulting model contains a reduced number of free parameters and presents a physiological description of the molecular mechanisms underlying metabolism and distribution.

Methods: To evaluate the incorporation of expression measurements in PBPK modeling, three publicly available sources were considered for building a PBPK model of pravastatin: EST counts from Unigene [1], expression data from ArrayExpress [2], and RT-PCR results from literature [3-5]. Expression data from these databases were used to build three independently parameterized models, which include the active processes relevant for pravastatin pharmacokinetics [6, 7]: uptake by OATP1B1 in the liver, transport by MRP2 in intestine, liver and kidney, and metabolization by sulfotransferases (SULTs) in intestine, liver and kidney. The PBPK model for pravastatin was built using the software tools PK-Sim® and MoBi® [8, 9]. The models for single dose iv and po administration were adjusted to experimental plasma concentrations and urinary secretion data [10-12].

Results: Incorporation of gene expression data from three independent sources (Unigene, ArrayExpress, and literature) into a PBPK model of pravastatin yielded plasma concentration curves that showed a good agreement with experimental PK data reported in humans. Depending on the relative distribution of either transporters or enzymes in different tissues, slight differences in the plasma concentration-time profiles were observed.

Conclusions: The new approach using relative expression measurements to reduce the number of free parameters in a PBPK model combines top-down pharmacokinetic modeling at the whole-body level with experimental measurements at the tissue scale. It supports mechanistic analyses of clinical studies and their design.

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Zinnia Parra Nonlinear Pharmacokinetic Model For Interleukin-12 Gene Therapy

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Objectives: Several animal and human clinical studies have shown the therapeutic potential of interleukin-12 (IL-12) for the treatment of cancer and chronic viral hepatitis, although an adaptive response that down-regulated the levels of IL-12 was observed in long-term treatments. Pharmacokinetic modelling is a useful tool to understand the mechanisms of the different biological processes involved in this therapeutic response. The aim of the study is to develop a pharmacokinetic model that describes the behaviour of IL-12 and IFNγ at different doses in mice.

Methods: Mice were infected with two doses (2x1e8 and 5x1e8 iu) of a viral vector that codified for the interleukin gene. Interleukin expression was induced daily by the administration of mifepristone (RU) and levels of IL-12 and IFNγ were measured for 10 days. Berkeley-Madonna and Nonmem 6 software programmes were used to develop a semi-mechanistic model able to describe the data obtained.

Results: A three compartmental model was initially developed to describe the kinetic of IL-12 and the negative feedback of the IFNγ at low dose, but it was not able to describe the results obtained at higher doses. Receptor mediated endocytosis is known to play an important role in cellular uptake and disposition. The nonlinear pharmacokinetic behaviour previously observed was explained by incorporating the concept of receptor mediated endocytosis to the pharmacokinetic model.

Conclusions: Berkeley-Madonna was used to explore and improved the pharmacokinetic model developed by incorporating the concept of receptor mediated endocytosis. This model will be further explored using knock-out mice for the IFNγ receptor.

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Sabine Pilari Lumping of Physiologically Based Pharmacokinetic Models and a Mechanistic Derivation of Classical Compartmental Models

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Objectives: In drug discovery and development, classical compartment models and physiologically based pharmacokinetic (PBPK) models are successfully used to analyze and predict the pharmacokinetics of drugs. So far, however, both approaches are used exclusively or in parallel, with little to no cross-fertilization. An approach that directly links classical compartment and PBPK models is highly desirable.

Methods: We reduce the dimensionality of a PBPK model to derive mechanistically lumped compartment models and establish a direct link to classical compartment models by interpreting the mechanistically lumped parameters in terms of the classical pharmacokinetic parameters. We exploit the fact that drug concentrations in different compartments of the PBPK model are often strongly kinetically dependent of each other. This dependence is quantified and exploited in order to establish the lumped model and relate the lumped compartment concentrations back to the original ones.

Results: We derived a new mechanistic lumping approach for reducing the complexity of PBPK models that has several advantages over existing methods: Perfusion and permeability rate limited models can be lumped---in any order and into any number of lumped compartments. The lumped model allows for predicting the original organ concentrations. The volume of distribution at steady state is preserved by the lumping method. To inform classical compartmental model development, we introduce the concept of a minimal lumped model that allows for predicting the venous plasma concentration with as few compartments as possible. The minimal lumped parameter values may serve as initial values for any subsequent parameter estimation process.

Conclusions: The proposed lumping approach established for the first time a direct derivation of simple compartment models from PBPK models and enables a mechanistic interpretation of classical compartment models. The reduction of PBPK models allows for translating prior knowledge on the pharmacokinetics of a compound given in form of a PBPK model into the development of classical compartmental models in all stages of the drug development process.

Kirstin Thelen A novel physiological model to simulate gastrointestinal fluid dynamics, transit of luminal contents, absorption, and pre-systemic metabolism of orally administered drugs in humans

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Objectives: To allow for a precise prediction of oral drug absorption, drug-drug interactions within the gut wall, and the effects of active transport and gut wall metabolism, a new compartmental absorption model was developed. This model reflects detailed knowledge of human gastrointestinal (GI) physiology such as anatomical dimensions, local pH profiles, fluid secretion as well as absorption rates and GI transit rates of solid and liquid components. Furthermore, the model comprises a detailed representation of the mucosa, which is particularly involved in oral drug absorption and intestinal first pass metabolism. The GI model will be integrated into the whole-body physiology based pharmacokinetic (PBPK) software tool PK-Sim®.

Methods: Physiological information regarding GI anatomy and physiology of humans was collected from the literature. The alimentary canal from the stomach to the rectum was divided into 12 compartments each representing a particular segment of the GI tract. In parallel to each luminal compartment the respective mucosal compartment was added and connected with the respective luminal compartment and the portal vein blood flow via ordinary differential equations according to their physiology. The intestinal permeability coefficient can be calculated based on physicochemical information of the drug to be modelled using a semi-empirical equation [1]. A data set of 111 compounds with reported human fractions of dose absorbed [2] was used to determine an optimal set of parameters for this equation. The new gut model was subsequently validated using experimental plasma concentration time profiles of 8 test compounds with diverse physicochemical properties obtained after oral administration.

Results: A good correlation between the predicted and known fractions of dose absorbed was obtained for the passively absorbed compounds under permeability-limited conditions. Plasma concentration time profiles of the 8 test compounds from different BCS classes were very well predicted by the model.

Conclusions: A novel physiological multicompartmental model for GI transit and absorption was presented. Oral drug absorption of permeability-limited drugs could be very well simulated with the new model. The detailed physiological model can help to better understand the complex processes of oral drug absorption and pre-systemic metabolism in the gut wall and will be useful during the drug research and developmental process.

References:

[1] Leahy, D.E. et al. (1989) In Novel Drug Delivery and Its Therapeutic Application; Prescott, F.F., Nimmo, W.S., Eds., John Wiley & Sons: New York, 33-44
[2] Willmann, S. et al. (2004) J. Med. Chem. 47, 4022-4031