# Non-linear mixed-effects models for tests of interaction or of lack of interaction in cross-over and parallel pharmacokinetic studies: application to the test of interaction between protease inhibitors and nucleoside analogs in HIV patients

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***oral presentation***

**Introduction:** Pharmacokinetic (PK) interaction, or lack of interaction, of a drug B on a drug A, is usually tested by comparing the log AUC and the log $C_{max}$ of A given alone (or with placebo) versus A given with B. The standard method, recommended in guidelines, is the comparison of log AUC and log $C_{max}$ of A, using a Student test or a Schuirmann's two-one sided test (TOST) to test interaction or absence of interaction, respectively. In order to take benefit of the knowledge accumulated on the PK of the studied drugs and to decrease the number of samples per patient, tests based on non-linear mixed effects models (NLMEM) are a good approach. Our objectives were to propose and evaluate tests based on NLMEM for evaluation of both PK interaction or absence of interaction, first in cross-over PK trials, which are designed to test such interactions, and second during usual population PK analyses, where interactions are usually tested a posteriori.

## Cross-over PK trials

*a) Methods*

We focused on tests based on log AUC, but the proposed methods can easily be extended to log $C_{max}$. Both for evaluation of interaction or lack of interaction, several tests can be proposed based on NLMEM, to compare the log AUC of drug A taken with or without drug B. First, concentration data of A can be analysed to derive individual Empirical Bayes (EB) estimates, separately in the two groups of data with and without comedication with B. Second, they can be analyzed globally, with or without the estimation of the effect of drug B. Four tests for testing interaction on the log AUC can therefore be derived: paired parametric and non parametric tests comparing the EB estimates, the likelihood ratio test (LRT) between a model with or without interaction effect and a Wald test on the interaction effect. We adapted these approaches to the test of lack of interaction, i.e. equivalence, except the LRT, which does not have any simple extension. More precisely, we extended the method of the TOST to the EB tests and to the Wald test, using the standard error (SE) of the interaction effect.

*b) Evaluation by simulation without modelling inter-occasion variability (IOV)*

We evaluated by simulation the type I error and the power of both the proposed interaction or lack of interaction tests in cross-over trials [1]. Trials mimicking the theophyllin data set were simulated under H0 and several H1 and analysed with the nlme function, assuming a one-compartment model with first order absorption and elimination parametrized in $k_a$, AUC and V/F. Different configurations of the number of patients (N = 12, 24 and 40) and of the number of samples per patient (n = 10, 5 and 3) were evaluated. The type I errors of the Wald interaction tests in 5000 trial replications were 22% in the original design (N = 12, n = 10), 14% in the intermediate design (N = 24, n = 5) and 7.7% for the sparse design (N=40, n=3). The LRT achieved very similar results. Power was satisfactory for both tests, after Monte-Carlo correction of the significance threshold. Similar results were obtained for lack of interaction or equivalence tests: the type I errors of the Wald test in the 5000 replications were 25%,

16% and 7.4% in the original, intermediate and sparse designs, respectively. In both types of tests, the Wald test presented the best power after correction of the significance threshold. EB tests achieved satisfactory type I error and power in the interaction case, but were not of a great value for testing equivalence.

*c) Evaluation by simulation when modelling IOV*
In the preceding simulation study, we did not model IOV since the simulated IOV was small: 5% for V/F and 10% for ka and AUC. As we found that global tests (LRT and Wald) suffered from an important inflation of the type I error, we evaluated the impact of modelling IOV on the properties of those tests. For interaction tests when IOV was estimated on each parameter, the type I errors of the Wald test on the 5000 replications were 7.5%, 6.4% and 3.5% in the original, intermediate and sparse designs, respectively, which were much closer to 5% than when IOV was not taken into account. The LRT achieved very similar results. Power was satisfactory for both tests and for the three considered designs. For tests of absence of interaction when IOV was estimated, the type I errors were found to be 6.4%, 5.7% and 4.2% for the original, intermediate and sparse designs, respectively. NLMEM is therefore confirmed as a good and useful approach to test interaction or lack of interaction in cross-over trials. Global tests like LRT or Wald seem to achieve adequate type I error only if IOV, even small, is taken into account.

*d) Application to the interaction of tenofovir (TFV) on the PK of atazanavir (ATZ)*
The Wald test was applied to compare the PK of ATZ, an HIV protease inhibitor, administered with and without TFV, a nucleoside analog, in a cross-over study which was a PK substudy of the ANRS 107 - Puzzle 2 trial conducted in 11 HIV-infected patients. Six blood samples (1, 2, 3, 5, 8 and 24h after dosing) were taken at two periods: first without and then with co-administration of TFV. Concentration data of both periods were analysed assuming a one-compartment model with zero order absorption and first order elimination parametrized in absorption duration ($T_{abs}$), AUC and V/F. For each PK parameter, inter-individual variability (IIV), IOV and a treatment effect were estimated. Significant effects of comedication with TFV were found on ATZ AUC ($p<10^{-4}$) and $T_{abs}$ ($p<10^{-3}$), which were decreased by decreased by 1.46 fold and increased by 1.45 fold, respectively, when patients received TFV.

**Test of interaction during usual population PK analyses**
*a) Methods*
Several authors showed an inflation of the type I error for the test of binary covariates in population analyses which might lead to false inclusion of effects. This inflation can be important for limited number of patients, for sparse sampling designs, for large residual error or when the structural model is complex. One method to correct that inflation is the use of randomization tests. This method can be applied to a posteriori test of PK interaction. We extended it to the test of lack of interaction using, as for cross-over trials, a TOST based on the estimate of the treatment effect and its SE.

*b) Application to the interaction of zidovudine (ZDV) on the PK of nelfinavir (NFV) and its metabolite*
We applied the randomization test to the effect of ZDV in the simultaneous population PK analysis of NFV and its major metabolite M8 [2]. Concentration data were obtained from 46 patients enrolled in the Cophar 1 - ANRS 102 study. Seven blood samples were taken per patient, five at a first visit (before and 0.5, 1, 3, 6 and 12 h after dosing) and

two at a second visit 3 months later (before and 3 h after dosing). A one-compartment model with first order absorption and elimination was used to describe NFV concentrations, with an additional compartment with a first order rate-constant $k_m$ describing metabolization into M8. The identifiable parameters were V/F, Cl/F and $k_a$ for NFV, and $V_m/Fk_m$ and $Cl_m/Fk_m$ for M8. Concentrations of NFV and M8 from both visits were modelled simultaneously in all patients with the nlme function. IIV was estimated on V/F, Cl/F and $Cl_m/Fk_m$, and IOV was estimated on Cl/F. Interaction effects with nucleoside analogs were tested using the Wald test. The only significant interaction effect was that of ZDV, received by 27 patients, on $Cl_m/Fk_m$ ($p=0.011$), which decreased by 1.8 fold in patients receiving ZDV. We then evaluated the real p-value of this effect by a randomization test. We performed R=1000 random permutations of comedication with ZDV, and analysed the corresponding data sets using the previous PK model. The type I error for the Wald test was found to be 6% for $Cl_m/Fk_m$, which led to a corrected p-value of 0.016 for the original data set. This result, obtained with nlme, did not confirm the necessity of correcting the type I error of interaction tests based on NLMEM even in a complex PK model with limited number of patients and large variability.

**Conclusion:** Tests based on NLMEM allow both to test PK interaction or lack of interaction while greatly decreasing the number of samples per patient. This point is of great interest when performing such trials in patients, for instance in HIV patients as illustrated here, or in special populations (children, older patients). The necessity of using or not a correction method for the type I error should be further evaluated and depends on the estimation method or algorithm. Our next step is the design of such PK interaction studies. Since the expected standard error of the interaction effect can be estimated with IOV using an extension of PFIM [3], the power of the interaction or lack of interaction test can be derived and thus the sample size for a given power.

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# A Study Comparing the Performance of the Proportional Odds Model to that of the Differential Drug Effect Model for Cumulative Logits

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***oral presentation***

**Introduction:** In 1994, Lewis Sheiner proposed the use of the proportional odds model, a special case of the cumulative logit model, for the analysis of ordered categorical data within the area of PK/PD mixed effects modelling [1]. The model (Eq. 1 for the $j^{th}$ observation in the $i^{th}$ individual of an m-categorical effect Y) assumes that for all monotonically increasing drug effects ($f_D$), the relative increase in probability increases with increasing categorical level regardless of the exposure (C). This constrain of the proportional odds model is expressed in Eq. 2.

$$P(Y_{ij} <= Y_m | eta_i) = e^{f(alpha, C, eta)} / (1+e^{f(alpha, C, eta)})$$

$$f(alpha, C, eta) = SUM_{n=1}^{m-1} alpha_n + f_D + eta_i \quad (1)$$

where $eta_i$=N(0,*omega*), and *alpha* are the fixed effects for the intercepts.

$$P(Y_m|C<0)/P(Y_m|C=0) / P(Y_{m-1}|C<0)/P(Y_{m-1}|C=0) > 1 \quad (2)$$

While this may be a valid assumption for many types of ordered categorical data, it may not apply to all. In an extension to the proportional odds model, here called differential drug effect model for cumulative logits, an additional, category-specific, factor, $f_{diff}$ multiplies the drug effect (Eq. 3). This relaxes the assumption made in the proportional odds model, but by its constraint to be in the 0-1 interval, retains the order of the cumulative logits.

$$f_{diff} = PRODUCT_{n=2}^{m-1} e^{beta\ n} / (1+e^{beta\ n}) \quad (3)$$

The objective with this study was to evaluate the relative performance of the proportional odds model and the differential drug effect model for cumulative logits.

**Data:** The differential drug effect model was applied to four datasets:

1. 4-Category simulated data. The simulated dataset consisted of 1000 patients evenly divided into 4 dose groups (0, 1, 2 and 4 units of drug), with each patient having 1 baseline observation and 3 after study drug intervention. Each trial was replicated 1000 times. This simulation was performed to investigate the Type I error rate of the differential drug effect model compared to the proportional odds model.

2. 3-Category T-cell data following a phase I clinical study of an antibody, where the response represents categorized continuous data of T-cell receptor density measured by FACS [2].

3. 6-Category data on sedation as a side-effect and natural consequence of stroke in a placebo-controlled trial of clomethiazole as a neuroprotective drug in stroke patients [3].

4. 5-Category data on diarrhea severity as a side-effect of anti-cancer treatment with irinotecan [4].

Datasets 2-4 have been previously published with a proportional odds model for the drug effect. The drug effects, $f_{D,}$ have been described with step (sedation [3]), linear (diarrhea [4], simulations) and sigmoid Emax (T-cell [2]) models.

**Method:** The proportional odds model and the differential drug effect model are nested and the statistical significance was assessed using the likelihood ratio test, based on the difference in objective function value (deltaOFV).

**Results:** The model for sedation data was significantly improved ($p<0.0005$, deltaOFV=74, df=5) using the differential drug effect model. This improvement of the fit was also evident on visual inspection. In addition, the PD model, $f_D$, changed from a step effect to a more mechanistically plausible graded effect.

Neither for the diarrhea data nor for the T-cell data were there a significant ($p>0.05$) improvement for including the differential drug effect model. For the simulated data, the Type I error rate was as expected, 4.9% and 0.86% at a nominal value of 5% and 1% (998 successful minimizations of 1000).

**Discussion:** In line with expectations [5], the differential drug effect model did not improve the fit to the simulated data or to the categorized continuous T-cell data. As opposed to the T-cell data, the sedation data do not represent a categorization of an underlying continuous variable, but a clinical interpretation of a state, likely to be multifactorial in its origin, using different stimuli (observation, communication and pain infliction) in the assessment. In such a situation, it is not surprising that a drug may have differential effects on the different levels of sedation. For the diarrhea data the categories appear to approximately represent a categorization of an underlying continuous scale.

**Conclusion:** The differential drug effect model appeared to have the desirable properties of not being indicated when not necessary, but to provide meaningful improvement in the description of ordered categorical clinical pharmacodynamic data when needed.

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# A Disease Model Describing the Regulation of the Glucose-Insulin System in Diabetic Patients after IVGTT and OGTT

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***oral presentation***

**Objectives:** Extension of a disease model describing the regulation of the glucose-insulin system after an intravenous glucose tolerance test (IVGTT) to the oral glucose tolerance test (OGTT).

**Background:** Since the 1960s, several attempts have been made to describe the glucose-insulin system with mathematical models [e.g. 1-3]. Such models have been used for the characterization of disease states (primarily with respect to diabetes mellitus) as well as for drug development. Most of the models published so far focus on either glucose or insulin while treating the other variable as known input. As feedback mechanisms play a crucial role in the glucose-insulin system, simultaneous modeling of both variables should be preferred [4]. A project aiming at developing an integrated mechanism-based model that can describe and simulate glucose and insulin concentration-time profiles following different types of glucose provocation experiments in healthy volunteers and in type II diabetic patients is currently under development at the University of Uppsala and Roche Basel. This work is part of the overall project.

**Methods:** The 9-compartment model describing the time courses of glucose and insulin following i.v. glucose administration developed by Silber et al. [5] was used as a starting point. This model was developed based on physiological knowledge of the glucose-insulin system. In brief, it consisted of two-compartment disposition submodels for glucose and labeled glucose with endogenous production and insulin-dependent and insulin-independent elimination. The insulin submodel was a one-compartment disposition model with endogenous production, distinguishing between a fast primary and a slow secondary release phase, and linear elimination. Feedback loops were incorporated for the regulation of the production of endogenous glucose and insulin, both depending on blood glucose concentrations, and for the regulation of glucose elimination depending on insulin concentrations. The delay of action of these regulations was mediated through effect compartments.

Concentration versus time data was modeled simultaneously by non-linear mixed effect modeling using NONMEM (version VI beta). Drug free data collected after OGTT and insulin modified IVGTT from 42 patients was used. For the OGTT, patients were required to drink a solution of 75 g dextrose in 300 ml of juice within 5 minutes. Six blood samples for the determination of plasma glucose and insulin were collected pre-dose and until 240 minutes after the glucose load. An IVGTT was performed in the same subjects on the following day. A total of 300 mg glucose per kg body weight of a glucose solution enriched with 13 ± 5 % of stable labeled glucose ([6,6-$^2H_2$] glucose) was infused intravenously within 30 seconds. An i.v. infusion of 0.05 U of insulin per kg body weight was given over a period of 5 minutes starting 20 minutes after the

glucose load. Thirty-four blood samples were collected pre-dose and until 240 minutes post-dose for the measurement of insulin, stable-labeled glucose and total glucose concentrations.

**Results and Discussion:** The absorption phase of glucose following the OGTT was adequately described by extending the IVGTT model with a flexible absorption model using transit compartments [6] and a first-order absorption. A similar delay model was used to account for the insulin secretion observed after the OGTT.

The main deviating parameters between IVGTT and OGTT were the first-phase insulin secretion and the insulin-dependent glucose elimination which were both higher after the OGTT. First-phase insulin secretion after i.v. glucose administration hardly occurred in patients at all, whereas following oral glucose administration, it was significant. This result was in line with previous findings in the literature, stating that glucose administration via the gastrointestinal tract has a potentiating effect on insulin secretion [7]. This potentiating effect of oral glucose administration is known to be related to the release of the insulin secretagogue GLP-1 (glucagon-like peptide-1) from the gastrointestinal tissues [8,9]. After the OGTT, the estimated insulin-dependent clearance of glucose was found to be 2-3 fold higher compared to the IVGTT. Higher insulin-dependent glucose disposal after an OGTT compared to an IVGTT has already been observed in previous works [10,11]. This may be due to gastrointestinal factors or first-pass effects enhancing insulin sensitivity in the liver or the muscle tissue that remain to be identified.

Diagnostic plots showed that the model described the data very well. All parameters were well estimated (CV < 25%), residual errors were approximately 5% CV for glucose and labeled glucose, and 29% for insulin. The model was also found to adequately simulate glucose and insulin concentration-time profiles in diabetic patients following intravenous and oral glucose tolerance tests.

**Conclusions:** The disease model developed previously on IVGTT data was successfully extended to OGTT data. The next step will be to further expand this model to describe other types of glucose excursions such as meal tests. This present model extends to previous modeling of the glucose insulin system as it provides the first integrated model for insulin and glucose following an OGTT, and it simultaneously addresses more than one type of provocation.

The ability of this model to distinguish between endogenous glucose production and administered glucose on the one hand, and between insulin-dependent and insulin-independent glucose elimination on the other hand, especially after an OGTT, could be very useful in drug development in the future. In particular, it might be a valuable tool for proof of concept, i.e. support for hypothesized mechanisms of action. In addition, this model could provide good estimates of inter- and intra-patient variability within a type II-diabetic population. Moreover, it might be used to quantify drug effects and to optimize the design of future clinical trials.

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## Resisting population PK, the story of P-gp inhibition and co-administered chemotherapy.

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***oral presentation***

Multidrug resistance is an ongoing barrier for the effective treatment of cancer patients. P-gp is a significant contributor with respect to multidrug resistance. Despite the fact that this protein was identified in the 1970's and many clinical P-gp inhibitors have been identified, the use of these agents in cancer patients has never been proven. Part of the limitation has been excessive toxicity when co-administered with chemotherapy and therapeutic doses which inturn may have resulted not only from a pharmacodynamic effect but also from a very profound pharmacokinetic interaction. Many P-gp inhibitors have failed in combination due to inadequate mechanistic understanding of the contribution of both P-gp inhibition and cytotoxic chemotherapy to the overall therapeutic effect. By using a more mechanistic PK model it is possible to balance more appropriately the PK interaction and potential toxicity to the PK. The development of a 3$^{rd}$ generation P-gp inhibitor Zosuquidar.3HCL illustrates the potential utility of these techniques. The development of Zosuquidar.3HCL from phase I to POC will be discussed as an example of prospective use of a population pk/pd approach.

## Preclinical Population PK/PD of TGF beta RI Kinase inhibitor for Cancer

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***oral presentation***

**Objectives**: The primary objective of PK/PD modeling in preparation for the First Human Dose study was to estimate a pharmacologically effective dose range in humans based on preclinical data

**Methods:** Data from tumor growth kinetics Xenograft model in mice and from in vivo target inhibition (IVTI) in rats and in mice were incorporated in our PK/PD analysis. The PK/PD model in mice integrated the time course of the pharmacokinetics of the compound, the inhibition of SMAD phosphorylation (biomarker) and the tumor growth data in terms of pharmacodynamics. An indirect response model was used to relate the predicted plasma concentrations with the observed pSMAD data The model assumed the existence of factors within the tumor cell responsible for the synthesis and degration of pSMAD. A Gompertz model was applied to describe the tumor growth curve. This model can be extended to further understand the relationship between the time course of the tumor growth and the time course of TGF beta RI kinase inhibitor A PK/PD model in rats based on SMAD phosphorylation was also built. This model incorporated the pharmacokinetics and the inhibition of the pSMAD from the IVTI studies This model supported an understanding of TGF beta RI kinase inhibitor concentrations and the relationship to the inhibition of the SMAD phosphorylation. Both models enabled prediction of the targeted inhibition of SMAD phosphorylation under different dosing regimens

**Results and Conclusions**: In both models, the variability of the biomarker was incorporated to assess the variability in the response, in order to simulate profiles in humans. Simulations were performed in order to assist the dose range selection for the First Human Dose (FHD) study. Potentially with these two approaches, the relationship between the time course of TGF beta RI kinase inhibitor concentrations and the clinical tumor response was defined The PK/PD modeling would provide guidance for the design of future studies, as these models will be updated as new data become available from the FHD study

## Prospective Bayesian pharmacokinetically guided dosing of cyclophosphamide, thiotepa and carboplatin in high-dose chemotherapy.

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***oral presentation***

**Objectives:** High-dose chemotherapy with cyclophosphamide (CP), thiotepa (TT) and carboplatin (CA) (CTC) can be complicated by the occurrence of severe toxicities such as mucositis, veno-occlusive disease of the liver (VOD), hemorrhagic cystitis, oto- and cardiotoxicity. Variability in occurrence of these toxicities may be due to substantial differences in pharmacokinetics of CP, TT and CA between individuals, resulting in markedly different exposures, as expressed by the area under the plasma concentration-time curve (AUC), to the individual drugs and their metabolites in patients treated at the same dose levels. Relationships between toxicity and pharmacokinetics have been demonstrated in CTC chemotherapy [1]. The aim of our prospective study was to evaluate whether variability in exposure to CP, TT and CA, and their relevant activated metabolites, can be decreased with pharmacokinetically guided dose administration. Moreover, the clinical effect of targeted drug dosing in comparison with conventional dosing was evaluated.

**Methods:** Patients received single or multiple courses of high CP (1000 or 1500 mg/m$^2$/day), TT (80 or 120 mg/m$^2$/day) and CA (dose calculated using the Calvert formula with 13.3 or 20 mg*min/ml as target AUC) for four consecutive days. Standard doses were administered on day one and two of the first course. Doses of all three compounds were adapted on day three based on pharmacokinetic analyses of CP and its active metabolite 4-hydroxycyclophosphamide (4OHCP), TT and its metabolite tepa (T) [2] and ultrafilterable CA performed on day one. A Bayesian algorithm was used to estimate individual pharmacokinetic parameters, using previously developed population pharmacokinetic models developed with NONMEM [3]. This dosing strategy was designed to obtain a pre-specified whole-course target AUC of 4OHCP (105 or 140 μM*h), a combined target AUC of TT and T (276 or 367 μM*h), and a target AUC of ultrafilterable CA (13.3 or 20 mg*min/ml). On day three or four pharmacokinetic samples were obtained to evaluate the dose adjustment. Dose adjustments were also carried out before and during second and third courses based on the findings of previous courses. Observed toxicity was compared with the toxicity in a similar historical patient population who received standard dose CTC (n=43).

**Results:** A total of 46 patients (108 courses) were included in the study. For CP, TT and CA, respectively, a total number of 39, 58 and 65 dose adaptations were performed within courses and 17, 40 and 43 before start of a second or third course. After pharmacokinetically guided dose adaptations, the precision within which the target exposure was reached improved compared with no adaptation, especially after adaptations during a course (for CP, TT and CA, precision after within-course adaptations: 19, 16 and 13%; precision after between-course adaptations 19, 32 and 19%, respectively). More than 85% of the dose adjustments for all agents led to an

exposure within ±25% of the target, compared to 60% when no dose adjustments were performed. Exposures >50% above the target were successfully prevented since all patients who would have had these exposures were within 35% of the target after within-course dose adjustment. The occurrence of mucositis, neuropathy, ototoxicity, cardiotoxicity and hemorrhagic cystitis in this population was similar to that observed in a reference population, however, no cases of VOD were seen in patients with CP dose adaptations, compared with 4 cases in the reference population.

**Conclusion:** The Bayesian pharmacokinetically guided dosing strategy for CP, TT and CA in the CTC regimen was feasible and led to a marked reduction in variability of exposure, especially when dose adaptations were performed within the short time-span of a 4-day course. Extremely high and low exposures were prevented successfully. More patients should be included to draw significant conclusions on the clinical impact of the dosing strategy.

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## History and new developments in estimation methods in nonlinear mixed-effects models

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***oral presentation***

NONMEM software, which included FO and then FOCE methods, was developed in the late 70's before statistician got really involved in linear mixed-effects models and before any other software was available in that area. NONMEM is the software the most used in population PK/PD and is defined as the reference in drug industry.

Since the 80's, various developments in statistical methods for linear and nonlinear models were performed, which can roughly be grouped in 4 periods. In the 80's, developments in linear mixed effects models were performed, as well as, for nonlinear models, the apparition of the EM algorithm, nonparametric (i.e. NPML, ...) or Bayesian methods (i.e. MCMC, ...). The 90's was certainly the period of increased used of NONMEM FOCE and of growing interest among statisticians. Several other methods were published based on linearisation and other functions were developed (i.e. SAS, Splus, ...). New Bayesian and nonparametric methods were also developed and incorporated in software (i.e. NPEM, PKBUGS, ...). Since 2000, several papers have discussed the non-consistency of estimators based on FOCE and several simulations have illustrated some of the drawbacks of this approach. Better approximation methods have been developed, and especially, methods for Maximum Likelihood Estimation based on stochastic algorithms appeared recently (i.e. SPML, PEM, MCPEM, SAEM, ...).

With the increased used of nonlinear mixed effects models and of their results both in drug development and for drug use, these new methods are promising because they should provide results with better statistical properties.

# A comparison of estimation methods in nonlinear mixed effects models using a blind analysis

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***oral presentation***

**Background:** In 1994, a blind evaluation of several estimation algorithms on one population PK simulated data set was presented American Statistical Association meeting[1]. Since this date NONMEM software and nlme function in Splus™ and R have allowed large diffusion of population PK-PD in industry and academic research. At the same period, several new methods based on maximum (approximate or not) likelihood (ML) for non-linear mixed effect models were developed[2], in particular the use of Gauss Hermitte quadrature[3]and stochastic approximation EM algorithm[4,5]. Given those developments it was interesting to perform a new comparison between gold standard and newly developed methods using several simulated data sets that would be serially, automatically and blindly analysed (i.e. ignoring the true value of the parameters).

**Objectives:** To compare various "newly" developed and classical algorithms for non-linear mixed effect models using ML parametric estimate according to bias, precision and standard error estimates.

**Methods:** Simulate 100 population PK data sets using a one compartment model with first order absorption and first order elimination, the parameters being volume of distribution, elimination rate constant (Ke) and absorption rate constant (Ka). To avoid flip-flop during simulation, Ka is expressed as Ke+θ, θ being the parameter to be estimated. Three random effects, a full covariance matrix and an exponential error model complete the model. Each data set contains approximately one hundred patients receiving one single dose and having 1 to 4 concentration points. Proportion of patients having 3 or 4 points is on average 74% dataset. These datasets were proposed to several statisticians or pharmacometricians who are well-known for their skills or have developed algorithms for non-linear mixed effect models. The exact true pharmaco-statistical model was also provided as well as rough estimates of fixed effect parameters. Each participant is supposed to fit each of the one hundred data sets, using an automated fitting procedure in order to avoid the potential effect of the analyst's skills and experience on the results. Results will be analyzed by computing relative bias and RMSE as well as by comparing standard errors with empirical SE defined as SD of the 100 estimated parameters. A crude comparison of CPU times will also be provided.

**Results:** Following statisticians or pharmacometricians have accepted to participate into this blind comparison (algorithm or software in parenthesis): Niclas Jonsson (NONMEM™ V & VI); José Pinheiro and Chyi-Hung Hsu (nlme Splus™ function); J. Hans Proost (Iterative Two-Stage Bayesian method); Bob Leary (PEM); Serge Guzy (MCPEM); Marc Lavielle (SAEM); Russ Wolfinger (SAS™ proc nlmixed). Extensive results will be presented at PAGE 2005 meeting.

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simulated data: results from the population modeling workgroup. *Stat.Med.* 16:1241-1262, 1997.
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## Analyzing Event History Data with nlme in S

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***oral presentation***

Pharmacokinetic (PK) and pharmacodynamic (PD) data are often collected in *event history* format, in which records representing different types of events (concentration measurements, dose administration, etc) are included in chronological order. This is the standard data format used with NONMEM, for example, because it lends itself to efficient event-driven, *recursive* representations of PK/PD models as used in that software. The event history format, however, is not particularly well suited for use with the S language, which is most efficient when operations can be *vectorized*. This incompatibility between the standard format of PK/PD data and the desire for efficient vectorized model representations in S has been one of the main obstacles preventing broader use of the nlme function within the PK/PD community. This talk describes a set of functions and methods developed in S to extend the capabilities available in the NLME library to efficiently handle event history data. These include functions for reading NONMEM-like event history text files and creating a special class of data.frames extending the groupedData class in NLME; plot methods suitable for displaying event history data; and recursive representations of common compartment models (written in C) which can be used with the nlme function for efficient and flexible population PK modeling of event history data. The resulting fitted objects can be used as any other nlme object which can be used with all available nlme methods (*e.g.*, diagnostic plots, simulations, etc.) Real and simulated event history PK data will be used to illustrate the different methods.

## An approach to formal decision making in exploratory development

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***oral presentation***

Decision making is an everyday activity in pharmaceutical research and development. Sometimes decision making is formalized according to predefined mathematical criteria such as performed in hypothesis tests for pivotal trials. The exact criteria for such trials are often drawn up in agreement with regulatory authorities or standards. However such formal decision procedures are applied less often in exploratory development. Moreover, applying the "pivotal" paradigm to the exploratory setting is often not appropriate in any case.

From a business perspective, good decision making in exploratory development is essential as it can act as a "gate-keeper" which prevents poor candidates from unnecessarily entering large expensive full development trials. This presentation will provide an example of the steps required to apply a formal decision making at Proof of Concept (PoC).

PoC is the exploratory development decision point at which a candidate is promoted to full development or not. Arriving at this decision requires the following:

- definition of a treatment difference that is relevant for the development decision
- definition of a probabilistic threshold which balances the risk of false positives and negatives against current developmental costs
- definition of the data needs to support the decision and definition of the analytical methods that will be used to turn this information into decision relevant information

The definition of a relevant treatment response, although an essential clinical task, is often mistaken for a statistical question of statistically relevant difference. It is surprising how often this mistake is made and how difficult it can be to pin down the difference that would be considered relevant for further development.

The definition of the probabilistic threshold is perhaps one of the most difficult tasks as it requires balancing current investment (i.e. expense of PoC programme) with the consequences of making a bad decision for the next stage of development. If the next stage of development is very expensive, then a high threshold has to be chosen to reduce the chance of false positives; however, if the threshold is set too high we may also kill potentially good compounds as false negatives. It should be remembered the expense of the next step is sometimes itself a design issue. Setting this threshold is a team activity, driven by the statistician, which requires much discussion and iteration to weigh up the various development scenarios and knowledge of the next steps beyond PoC.

Given an out line of these decision properties, it is now possible to focus on efficient generation of information to support the decision. Data generation, i.e. PoC program design, is intimately linked with the analytical methods that will be used to transform

the data into decision relevant information. Model based approaches which take into account the underlying pharmacology are an efficient means of generating quantitative information which not only guides the strategy in terms of study designs, but also provides the information necessary to underwrite the decisions themselves. Defining and employing these methods requires both pharmacological and statistical input.

Thus, the aim of a PoC strategy becomes one of designing studies to provide data, which is in turn transformed into decision relevant information and fed into the pre-defined decision making process. The overall strategy will be defined by the clinical team who need to take into account both the developmental constraints and the ultimate deliverables of the overall strategy.

This approach to the PoC strategy will be illustrated by some generic examples.

## Application of Pharmacokinetic/Pharmacodynamic Concepts to Modeling in Gene Therapy

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***oral presentation***

**Introduction:** Gene therapy seen as a tool for drug delivery implies accessibility to the site of action, release of the active components and their coupling with the proper structures within the nucleus, and finally response induction. Those processes are similar to the absorption/disposition and response-related (receptor binding, signal transduction, homeostasis, etc) processes that can be identified and quantified after more traditional therapy using pharmacokinetic/pharmacodynamic modeling. However, there are differences such as that during gene therapy "drug disposition" is not measured and usually the induced responses last for very long periods.

**Methods:** Models using the indirect response, precursor, and push-pull concepts as the main platform, and resembling different possible mechanisms of transduction were fitted to the response data. Response data consisted on Luciferase activity measured in vivo in mice liver over an one month period after simultaneous administration of three recombinant plasmids via tail vein. Three different groups were analyzed: 1- pLuc+control plasmid+ pIFN-alpha, 2- pLuc+pIFN-alpha+ pDcR, 3- pLuc+ placZ+ pIFN-alpha.

**Results:** More than one model provided a reasonable description of the data, which was charaterized in general by an intial burst followed by a pseudo steady-state in response. Computer simulations helped to identify design conditions maximizing differences in performance between model candidates.

**Conclusion:** Applying semimechanistic modelling to this type of data allowed to discriminate between possible mechanisms and to design future studies to adquire insight in the transduction processes.

# Do we need a perfect basic structural model before exploring the covariate model? Example with enoxaparin

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***oral presentation***

**Background:** Major bleeding complications with low-molecular-weight heparin (LMWH) treatment have been reported from pharmacovigilance, randomised and observational studies, especially in elderly patients. An accumulating effect in patients with renal impairment was referred to explain this phenomena, because of the exclusive kidney elimination route of LMWH. As a result, monitoring anti-factor Xa activity is recommended in special situations, even without clear knowledge of normal targeted range. A population pharmacokinetic study was conducted to estimate distribution parameters of anti-Xa activity in the elderly and factors yielding in a potential between-subject variability.

**Methods:** We conducted a prospective study in a cohort of consecutive patients older than 75 years and treated with 4000 IU subcutaneous injection of enoxaparin once daily for medical or surgical venous thrombo-embolism prophylaxis. Dosing history and sparse samplings for anti-factor Xa activity were collected throughout the duration of treatment. Additional data included, weight, gender, age, renal function, medical history and concomitant medication. Population parameters and inter-individual variability were estimated using NONMEM(r) V program (ADVAN2 and ADVAN4). Model validation will be performed by using a posterior predictive check.

**Results:** Anti-Xa activity was available in 189 patients receiving enoxaparin for the prevention of venous thrombo-embolism (160 medical and 29 orthopaedic patients). Mean age (± sd) was 82 ± 5 years, 21% of patients had body weight lower than 55 kg; 49% presented severe or moderate renal impairment according to creatinine clearance estimated by Cockcroft and Gault formula lower than 50 ml/min. An average of 2.4 measurements of anti-Xa levels per patient was available; anti-Xa levels varied from 0.05 to 1.0 IU/ml. A large panel of population pharmacokinetic models were tested using FOCE INTERACTION in NONMEM but all presented the same fitting problem on population prediction: according to the graphical approach, the measured anti-Xa activities were systematically predicted below 0.5 IU/ml even when the observed values were up to 1.0 IU/ml. Several paths were explored without any fit improvement:

i) changing the structural model (one, two, or three-compartment model) [1,2], the absorption model (first-order and zero-order) or introducing non-linear Michaelis-Menten elimination;
ii) changing the error model from multiplicative to additive or mixed error model;
iii) using transformation both sides with logarithm-transformed data and prediction;
iv) adding anti-factor Xa endogenous baseline activity [1-3];
v) omitting or replacing data below the LOQ [4].

**Conclusion:** Nearly all evaluated models were already described in the literature without any consensus [1-2, 5-6]. In fact, the choice of model seems to be dosage regimen-dependant (curative or prophylactic treatment), design-dependant (sparse or rich data), and drug-dependant (tinzaparin or enoxaparin). The best model found in this PK study, according to objective function, was a two-compartment model with a first-order absorption, without endogenous activity. However this model was unsatisfactory in predicting higher activities above 0.5 IU/ml which represented only 13% of the total number of measured activities, but could potentially be related with higher bleeding risks.

Other model improvements are actually explored as mixture models, between patient variability of residual variance and integration of covariates. The issues that have to be fixed are the following: which other model improvement can be added to correct the systematic prediction error? Do we need to have a perfect basic structural model before exploring the covariate model? Once correct model for anti-Xa activity in the elderly will be identified and qualified using posterior predictive check, it will be used for dose adjustment recommendation and/or optimisation.

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## Challenges in modelling the pharmacokinetics of isoniazid in South African tuberculosis patients

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***oral presentation***

**Objectives:** The modelling of isoniazid was part of a larger project investigating the interindividual and interoccasional variability in the pharmacokinetics of drugs for the treatment of tuberculosis in South African pulmonary tuberculosis patients. The pharmacokinetics of isoniazid in this group exhibited a number of unusual features, which made model-building interesting. This talk will focus on the specific issues involved in modelling the drug.

**Methods:** A prospective study was planned and executed in 91 pulmonary tuberculosis patients, using a design involving sparse data on multiple occasions. The resulting isoniazid concentration-time measurements were pooled with rich data from 175 pre-existing pulmonary tuberculosis patients from two previously executed studies. Population pharmacokinetic modelling using NONMEM was carried out to characterize the variability-related characteristics of the drug. During model development, models were selected by graphical analyses of residuals and predictions using NONMEMory, a software utility developed by the first author, as well as by comparing the relative standard errors of parameter estimates. Differences in the objective function value (OFV) were used to discriminate between hierarchical nested models.

**Results:** The pharmacokinetics of isoniazid in the studied population had a number of unusual characteristics. Firstly, the well-known polymorphism in the acetylation of the drug was clear, as two subpopulations separated by a 2.5-fold difference in clearance were identified. In addition, a subset of patients exhibited sharply reduced and delayed bioavailability in comparison to the rest of the population. Another subpopulation showed significantly different absorption characteristics in comparison with the rest of the group. Enterohepatic circulation has previously been shown in the literature and was evident in the present data. Finally, interoccasion variability, as the primary objective of the project, was investigated for the different parameters on 27 discrete dosing occasions. The final model described the data well, and dealt with the bimodal absorption by using dual absorption compartments assigned differing proportions of total bioavailability. Interoccasion variability on apparent clearance and absorption half-life was included, and acetylator phenotype was addressed through the use of a mixture model. It was not possible to include enterohepatic circulation, since it was not supported by the data.

**Conclusions:** The modelling process was directed towards addressing the primary purpose of the study, interindividual and interoccasion variability in isoniazid pharmacokinetics. While enterohepatic circulation and the observed malabsorptive

syndrome were undeniably interesting and clinically relevant, they were unsupported by the data, and therefore not included in the model. The final model answered the

questions posited by the study and described the data well, and was therefore appropriate.

## Population pharmacokinetic modeling of total and unbound docetaxel plasma concentrations in cancer patients with poor liver function

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***oral presentation***

**Objectives**: Docetaxel is a chemotherapy agent approved for treatment of breast cancers, non-small cell lung cancers and androgen-independent prostate cancers. Unfortunately docetaxel has a large interindividual variability in total CL and patients with poor liver function exhibit even more variability [1]. Because a reduction in predicted clearance of just 25% is associated with a 150% increased risk of febrile neutropenia, patients with poor liver function are often not treated with docetaxel. However, recent studies have suggested that liver function tests and CYP3A activity could be used as covariates in a population PK model to reduce the predicted CL variability in poor liver function patients [2, 3].

**Methods:** PK data was collected during cycle 1 of therapy for 71 cancer patients. 21 of these patients had poor liver function. Total and unbound concentration measurements, liver function measurements, CYP3A activity measurements (using the erythromycin breath test - EBT) and other standard covariate measurements (including AAG) were made. We initially developed separate models for unbound concentration measurements separately for the poor and normal liver function groups. However, due to the complexity of the model (4-compartment) and the relatively low number of poor liver function patients, we decided to combine the two groups so that the normal liver function patients' data could inform the model on parameters that were similar between the two groups. Thereafter, we developed a binding model and a correlated residual error structure, to simultaneously analyze total and unbound docetaxel concentrations. Finally, covariates were added to the model.

**Results:** The data in this experiment was collected for a considerably longer time than previous investigations and we found that a four-compartment model fit the data better than the three-compartment model published previously on docetaxel [4]. For the good liver function group, CL includes the EBT measurements as a covariate. For the poor liver function group, covariates include EBT AAG and sex. The model significantly reduces the unexplained variability in unbound clearance estimates for both liver function groups. The unbound CL variability of the poor liver function group is lower than for the good liver function group (40% CV vs. 15% CV).

**Conclusions:** Our final model reduces the variability of CL in the poor liver function group to 15% CV, and should be useful in developing dosing strategies for these patients once a PD model is developed.

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## An Application of Modelling and Simulation to Type 2 Diabetes: Development of a general drug-disease model based on a meta analysis of over 40 studies investigating 5 PPAR drugs

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***oral presentation***

The $PPAR_{\gamma}$ / $PPAR_{\alpha\gamma}$ class of drugs represent an excellent addition to the pharmacotherapeutic choices for the management of type 2 diabetes.

The primary goal of this project was to describe this pharmacotherapeutic area with a drug/disease model, such that an investigational new drug completing Phase 2 could be incorporated into the model, and various potential phase 3 designs could be prospectively simulated and evaluated.

To date, 42 studies investigating 5 drugs (Actos, Avandia, Rezulin, Ragaglitazar and GI262570), with over 130 treatment arms, have been considered in a complex longitudinal model that describes the changes in glycosylated haemoglobin ($HbA_{1c}$) and fasting plasma glucose (FPG) as a function of drug, dose, dosing regimen, treatment duration, concomitant therapy, and baseline patient characteristics. Unlike classical meta analysis, the use of a longitudinal model, combined with multiple study level random effects, permitted the aggregation of studies with various designs, and the resulting model effectively described all the key features of how the glycaemic responses changed with time, and the similarities and differences between studies.

Both standard model qualification and additional PPC's via simulation showed that the general drug-disease model for Type 2 diabetes was adequate for the purpose for which it was developed. With this knowledge, new potential study designs could be investigated. A range of important metrics were defined and then determined from the simulations. These included:

- Dose Response (predicted differences) versus placebo (and baseline).
- Predicted differences versus comparator Y (at any dose).
- Likelihood of achieving superiority/non-inferiority in a given active control phase 3 design.
- Impact of different inclusion criteria (e.g. patient population).
- Extrapolation of phase 2 results to longer treatment durations.
- Associated prediction intervals on all of the above figures.

Key results were also subject to a range of sensitivity analyses, and showed than the main conclusions where robust.

In conclusion, a prospectively planned development of a general drug disease model for Type 2 diabetes allowed the fast synthesis of the results from an investigational new

drug completing Phase 2 into the broader pharmacotherapeutic model, thus allowing an extensive range of potential phase 3 designs to be predicted and evaluated shortly after the data was available.

## A physiologically based population pharmacokinetic model describing the non-linear disposition and blood distribution of indisulam in Caucasian and Japanese patients

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***oral presentation***

**Objectives:** The pharmacokinetic profile of the investigational anti-cancer agent indisulam is nonlinear. This may partially be explained by its saturable distribution to erythrocytes and the saturable plasma protein binding. The aim of the current study was to develop a mechanistic population pharmacokinetic model for Caucasian and Japanese patients, which adequately describes the pharmacokinetic profile of indisulam in various physiological compartments and which provides a basis for rational PK-PD relationships. The model allows unraveling of various physiological processes and their contribution to the pharmacokinetics of indisulam. A simulation study was performed to examine the role of distribution to erythrocytes and protein binding in indisulam pharmacokinetics.

**Methods:** Pharmacokinetic sampling was carried out in Caucasian and Japanese patients after administration of indisulam in several phase I studies at a large range of dose levels. The population PK analysis was performed using NONMEM (version V, level 1.1). The first order (FO) method was applied throughout to fit logarithmically transformed data. Concentrations in plasma, plasma ultrafiltrate and in erythrocytes were used to develop a physiological population pharmacokinetic model in which both the distribution of indisulam (in plasma, erythrocytes, interstitial fluid and tissue) and its elimination were integrated. Established physiological knowledge regarding distribution volumes of the different compartments was incorporated in the model a priori. A previously developed Langmuir model for the in vitro saturable binding of indisulam to plasma proteins was verified in vivo. In order to describe the distribution of indisulam to erythrocytes, saturable Langmuir models with or without a non-specific binding component were considered. Linear and saturable models were tested to describe tissue binding and drug elimination. Correlations between individual PK parameter estimates and various demographic, hematological and blood chemistry variables were investigated to identify relevant covariate relationships. The model was evaluated by the performance of sensitivity tests, the jack-knife procedure and likelihood profiling. Simulations were performed to explore the impact of hematocrit and plasma albumin level on the disposition of indisulam.

**Results:** The backbone of physiological parameters proved to be an adequate starting point while it was amplified with drug-specific parameters. The maximal protein binding capacity in plasma corresponded with individual plasma albumin concentrations and the equilibrium dissociation constant was 0.25 (±0.012) mg/L. Binding to erythrocytes was best described by a two site binding model, comprising one class of saturable binding sites and one class of non-specific binding sites. The population value

of the maximal specific erythrocyte binding capacity was 59.0 (± 4.2) mg/L and was similar to typical erythrocyte carbonic anhydrase concentrations. Tissue distribution was represented by a linear and a saturable component and was different for Caucasian and Japanese patients. Free indisulam was cleared from the plasma compartment through a Michaelis Menten pathway (major route of elimination) and a linear first order process. The Michaelis Menten elimination constant (Km) for free indisulam was 1.07 (±0.17) ug/L. Interindividual differences in the maximal elimination rate were partially explained by differences in body surface area. Simulation studies demonstrated that the hematocrit does not have a clinically relevant impact on indisulam disposition. A decreased plasma albumin level, however, considerably influenced total plasma concentrations of indisulam, whereas free concentrations in plasma, concentrations in erythrocytes and the amount distributed to tissue remained relatively unaffected.

**Conclusion and discussion:** The presented physiological population pharmacokinetic model allowed adequate prediction of the time profiles of indisulam concentrations in Caucasian and Japanese patients in all monitored compartments for a large range of dose levels and several treatment regimens. This project has led to a better understanding of the physiological mechanisms behind the pharmacokinetics of indisulam. This improved insight has facilitated the elucidation of the important impact of the plasma albumin level on indisulam disposition. Simulations have illustrated that total plasma concentrations were highly dependent on the plasma albumin level. Total plasma concentrations may therefore not be a preferable target in pharmacokinetic studies of indisulam. Alternatively, indisulam concentrations in erythrocytes may be well suitable to define PK-PD relationships. This finding may support the development of new rational PK-PD relationships.

## Pharmacokinetic-Pharmacodynamic Modelling of QT-Prolongation following Deliberate Self-Poisonings with Citalopram

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***oral presentation***

**Objectives:** Pharmacokinetic-pharmacodynamic (PKPD) models describing the time-course of QT-prolongation after overdoses would be valuable to predict the required time of observation and the probability of life-threatening toxicities. The antidepressant drug citalopram causes QT-prolongation more frequently compared to other SSRIs when taken in overdose [1], and has been implicated as a cause of Torsades de Pointes (TdP) [2,3]. The effect of activated charcoal administration in reducing the QT interval is not known. The aim of this study was to develop a PKPD model to describe the time-course of QT-prolongation after citalopram overdose and to evaluate the effect of charcoal on the risk of TdP.

**Methods:** A fully Bayesian method was used where prior information on the PK parameters was elicited from 14 published studies on citalopram when taken in therapeutic doses while for PD parameters, biologically plausible prior distributions were applied. Plasma concentrations and ECG data from 53 patients after 63 citalopram overdose events (dose range: 20-1700 mg) were analysed in WinBUGS [4]. Activated charcoal was administered after 17 of the overdose events. The developed PKPD model was used for predicting the probability of having a QT interval greater than the 97.5$^{th}$ percentile of normal QT and heart rate combinations [5], here defined as an increased hazard for TdP, with and without charcoal.

**Results:** The PK data were described by a 1-compartment model with a baseline concentration in patients who were taking citalopram therapeutically, and an estimated uncertainty of the overdose amount. Activated charcoal was estimated to reduce the fraction absorbed by 22% and increase clearance by 72%. The absolute QT interval was related to the observed heart rate by a power function with an estimated individual heart rate correction factor. The heart rate corrected QT interval was linearly related to the predicted citalopram concentration in a hypothetical effect-compartment ($t_{eq}$=1.4 h). The heart rate corrected QT at baseline increased with female gender and with age. Charcoal significantly reduced the QT interval and was predicted to reduce the relative risk of TdP by approximately 60% for citalopram doses above 400 mg.

**Conclusion:** The developed PKPD-model may be useful for predicting the required time of observation after citalopram overdoses. Administration of activated charcoal significantly reduced the QT-interval and the relative risk for TdP.

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## Model-Based Drug Development: A FDA Critical Path Opportunity

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***oral presentation***

The unprecedented growth over the past decade in public and private investment in biomedical science has yielded a rich harvest of scientific discovery and technological advancement. However, there is growing concern (FDA white paper "Innovation or Stagnation: Crisis on the Critical Path to New Medical Products" http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf) that there has not been a corresponding increase in the number of novel therapeutic agents produced by the pharmaceutical and biotechnology industries for diseases that do not have good therapies. The causes of this "dry pipeline" are complex and most likely arise from our still incomplete understanding of many diseases, but as well as from our inability to speed the translation of basic science information into therapeutic benefits through clinical research and drug development.

One factor that certainly plays a role in slowing the rate of appearance of novel therapeutic agents is the drug development process itself. Despite broad progress in the scientific and technical areas that underlie this important enterprise, the development of novel candidate molecular entities into safe and effective new drugs remains a laborious, inefficient, time-consuming and expensive process that has not changed appreciably in decades. To the extent that systemic inadequacies in the drug development process result in excessive risks, costs, and prolongation of safety and efficacy evaluation, society as a whole is adversely affected.

The presentation will review the role that drug regulatory science can play in the needed change in the drug development process. Specifically, the focus of the presentation will review current approaches and concepts at the Food and Drug Administration involving the concept of "Model-based Drug Development".

Model-based drug development uses drug and disease models to aggregate and integrate knowledge, over time, for the drug effect(s), disease progression, dose response, relevant covariates and efficacy/safety/toxicity. This model-based approach becomes the basis of clinical trial simulation. The role of these concepts to improved decision-making in clinical drug development and regulatory review will be highlighted.

## Positioning Drug Candidates in a Competitive Landscape - an integrated, data-driven approach

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***oral presentation***

Drug development decision making is greatly facilitated by having a model of the likely clinical profile of the new investigational drug (NCE) readily available. The model of the clinical profile should quantify the probability distribution of clinical safety, tolerability and efficacy as a function of treatment strategy (dose) and patient population attributes. Preferably the model should include competitors or treatment alternatives so that a quantitative assessment can be made of the clinical benefits and drawbacks of the NCE relative to those competitors. Building such an integrated model requires the joint analysis of data from multiple sources, different levels of detail, and potentially different endpoints. This often includes study level data from individual patients available for the NCE as well as summary data on competitors found in the literature.

For instance, for a team trying to develop a Factor Xa Inhibitor (NUXa) indicated for the prophylaxis of deep vein thrombosis, the following questions may be relevant.

- How does the efficacy of NUXa 3 mg compare to that of enoxaparin 40 mg
- How does the safety of NUXa 3 mg compare to that of enoxaparin 40 mg
- If interested in lowering DVT by 5% over enoxaparin 40 mg, what is the likely dose of NUXa?
    - Is safety a concern with this dose?
- What's the optimal registration strategy for product differentiation?

The purpose of this talk is to show an example of how such integrated modeling together with DMX$^{TM}$ technology was used to support key development decisions for gemcabene, an investigational new drug that lowers low-density lipoprotein cholesterol (LDL-C), decreases triglycerides and raises high-density lipoprotein cholesterol (HDL-C) (1). HMG-CoA reductase inhibitors, or statins, are the most widely used drugs to reduce LDL-C and six statins, atorvastatin, rosuvastatin, simvastatin, lovastatin, pravastatin and fluvastatin, are currently on the market. The major distinguishing feature between the statins is the magnitude by which they lower LDL-C in the available dose range. Recently ezetimibe, a chlosterol absorption inhibitor, was introduced to the market to be given in combination with statins to further reduce LDL-C and achieve the aggressive new target levels that were set by the U.S. National Cholesterol Education Program (NCEP) (2). Like ezetimibe, gemcabene was intended to be given in combination with a statin. To evaluate the product profile of gemcabene, alone and in combination with a statin, we developed a model for the lipid effects (LDL-C and HDL-C), adverse effect such as persistent ALT elevation and myalgia, and tolerability issues such as headache for five of the currently marketed statins, ezetimibe, and gemcabene and the combination of ezetimibe or gemcabene with a statin. To evaluate the impact of treatment with a combination of a statin with gemcabene or ezetimibe on coronary artery disease, a model was established to predict the risk reduction relative to placebo or compared to other statin treatments on basis of the lipid

effects. Whereas all aspects of the product profile contributed to decision making, the LDL-C effect was an important deciding factor and is the main focus of this paper