Prediction-based decisions in early stages: two applications

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Agenda

- Prediction-based decisions
- First application: efficacy prediction
- Second application: safety prediction
- Conclusions

Prediction-based decisions

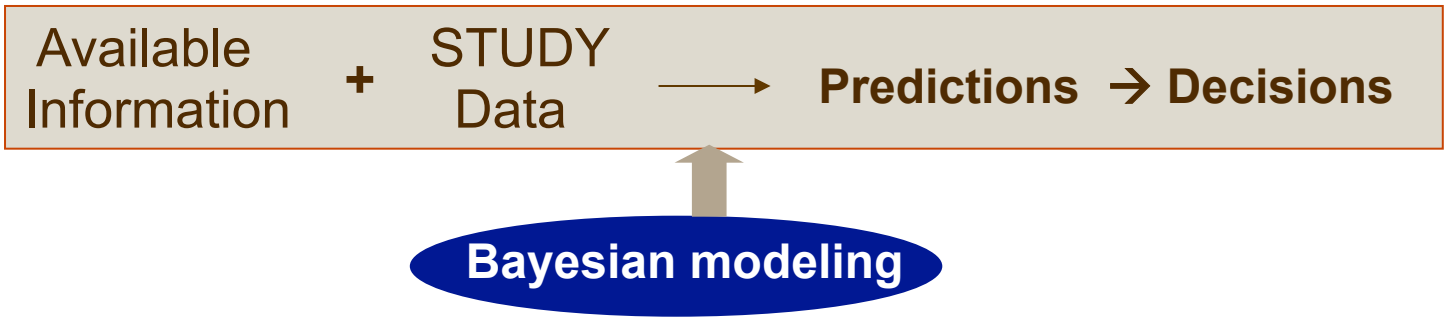
- *"The Bayesian updating process has profound implication for trial design. Perhaps its most useful consequence is the ability to quantify what is going to happen in a trial from any point on (including from the start of the trial), given the currently available results.*

  Future results cannot be predicted with certainty, of course, but the Bayesian approach allows for assessing the future with the appropriate amount of uncertainty".

Berry, D. 2006. A guide to drug discovery: Bayesian clinical trials. Nature Reviews Drug Discovery 5 (27-36)

Prediction-based decisions

- In other words :



- By combining the available information and the STUDY information, Bayesian modeling naturally provides predictions, with the appropriate uncertainty.
- Bayesian modeling allows to leverage all the available information at the decision time.

Prediction-based Decision is key in early stages.

First application : XX compound

Prediction of efficacy

Background of XX compound

- Let's call "*E*" a biomarker of efficacy used for the disease targeted by XX (*E* suppression).
- First in humans study already performed to collect safety and pharmacokinetic data in healthy volunteers.
- First in patients study ongoing

Study title

- Phase 1/2a

- A multicenter, randomized, double-blind, placebo-controlled, single dose study to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of intravenous and subcutaneous XX in male and female patients.

Objectives

- The primary objectives of this study are:

- To characterize the pharmacokinetic(PK)/pharmacodynamic (PD) relationship between systemic XX exposure and *E* suppression, following single dose XX administration via intravenous (iv) infusion and subcutaneous(sc) injection to patients.

- To evaluate the safety and tolerability of a single dose of XX in patients over a therapeutic dose range (as defined by *E* suppression).

Design

- Adaptive design with one interim analysis

Cohort 1 (N=36)

Group 1 (N=24): A mg (n=9) or B mg (n=9) or placebo iv (n=6)
Group 2 (N=12): C mg (n=9) or placebo (n=3) sc

Cohort 2 (N=36)

Group 3 (N=24): Optimized IV dose 1(n=9) or
Optimized IV dose 2(n=9) or placebo iv(n=6)
Group 4 (N=12): Optimized sc dose (n=9) or placebo sc(n=3)
OR
Group 3 (N=24): Optimized sc dose 1(n=9) or
Optimized sc dose 2(n=9) or placebo sc(n=6)
Group 4 (N=12): Optimized iv dose (n=9) or placebo iv(n=3)

↓ Single dose

⇣ Last visit

Design

- Pharmacokinetic/pharmacodynamic data from the 2 initial iv doses (A-mg and B-mg) and the sc dose (C-mg) in the first cohort will be required to optimize the doses (termed "optimized doses") and routes of administration used in the second cohort.

- Administration of optimized doses of XX in the second cohort of the study will occur once the 4-week PK/PD and safety results from all subjects in Cohort 1 of this study have been reviewed.

- The optimized doses will not exceed Z-mg for sc administration, nor exceed the highest tolerated iv dose explored in FIH study.

Design

- A decision will be made to use either 2 iv doses and 1 sc dose or 2 sc doses and 1 iv dose in the second cohort. This decision will take account of the PK/PD model which underpins the current study and the overall study objectives.

- In addition to safety and tolerability considerations, the optimized doses for Cohort 2 will be derived utilizing *E* and XX plasma concentration-time data, **for optimal exploration of the *E* response surface**. The doses that will be proposed based on the PK/PD models will be the doses that yield an **adequate understanding of the relationship between dose and *E* suppression**, within the constraints of the (maximum tolerated) dose range investigated in FIH study.

Design

- What will drive the selection of the optimal doses at interim analysis?

→ **optimal exploration of the *E* response surface**

Finding the optimal doses that will permit the **most reliable prediction of *E,*** using a PK/PD model.

- These prediction will be used for determining the dose and regimen in future phase II/III studies.

Available information

- Competitor of the same compound family: YY
  - PK/PD model of *E* published
- Preclinical and in vitro-in vivo information of XX
  - Linear clearance of XX 2-fold less than YY
  - Maximum possible non-linear clearance of XX 10-fold lower than YY
  - XX 5-fold more potent than YY with respect to its effect on *E*
- Results of a First in volunteers study
  - Pharmacokinetic data

PK/PD model of *E* for XX compound can be derived.

Available information

PK/PD model of *E* for XX compound:

=>Structure of the model

=>Prior distributions for all the model parameters

- **Plausible ranges ?**
- **The most plausible value ?**
- **Uniform? Normal? Log-normal ? Other ?**

WinBUGS model


```
model {

for (j in 1:N)
{
    for (i in 1:n.grid)
    {
   E[j,i]~dlnorm(logEmean[j,i],tauE[j])


   logEmean[j,i]<-log(baseline[j]*(1-(0.99*pow(CEFF[j,i],gamma[j])
                /(pow(ec50[j],gamma[j])+pow(CEFF[j,i], gamma
   [j])))) }
ec50[j]~dlnorm(logmuec50,tauec50)
gamma[j]~dlnorm(logmugamma,taugamma)
baseline[j]~dlnorm(logmubaseline,taubaseline
}
```

Loop on subjects

Loop on time points

Individual parameter distributed around a population mean with IIV

WinBUGS model


```
#Prior distributions

muec50~dlnorm(-2.1892,1)
logmuec50<-log(muec50)
tauec50~dgamma(1.538,2)
mugamma~dlnorm(0.53,1)
logmugamma<-log(mugamma)
taugamma~dgamma(2.29,1)
mubaseline~dlnorm(0.993,1)
logmubaseline<-log(mubaseline)
taubaseline~dgamma(1,0.01)
tauCRP~dgamma(tauCRP.a,tauCRP.b)}
```

Interim analysis

- For each dose, we simulate 1000 virtual patients

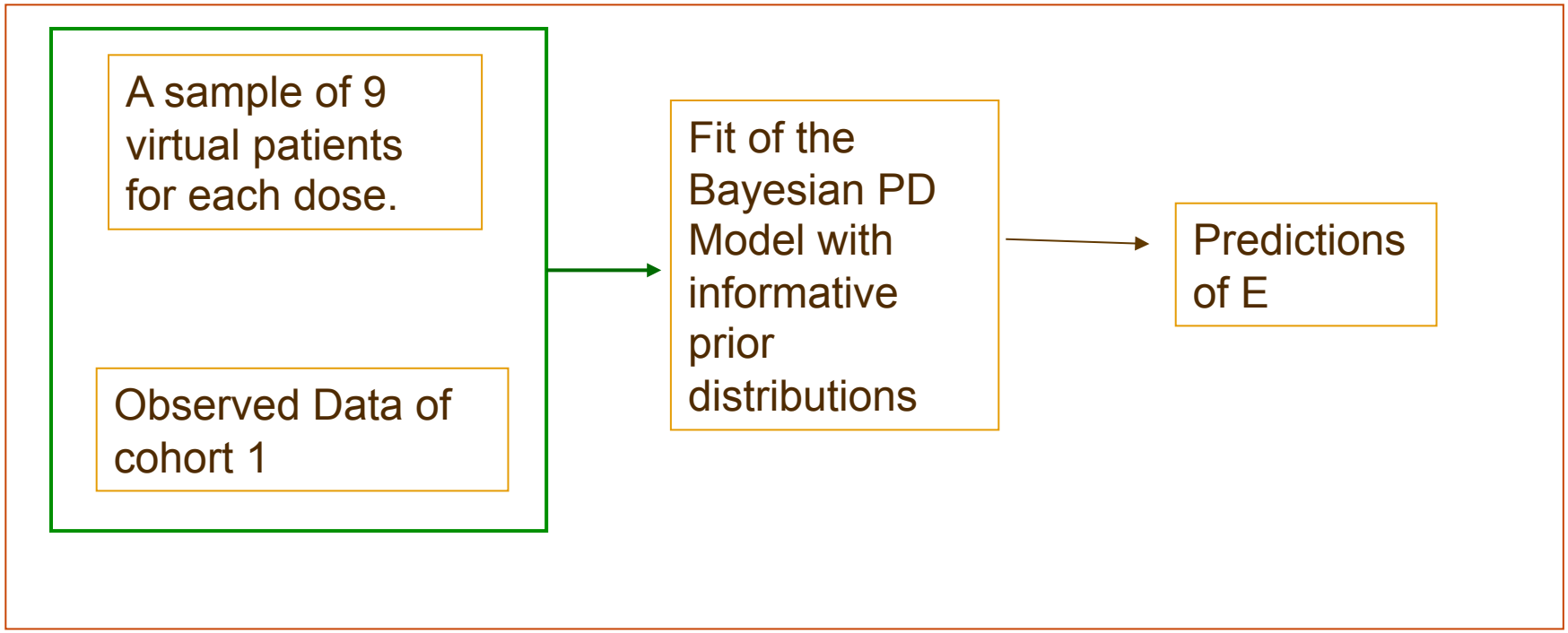
- For each dose, we generate 1000 **predicted** PK and PD profiles (at protocol time points)
  - Parameter uncertainty
  - Residual variability
  - Inter-subject variability

→ **Large database of virtual patients**

Interim analysis

- At interim, for ONE given combination of doses :

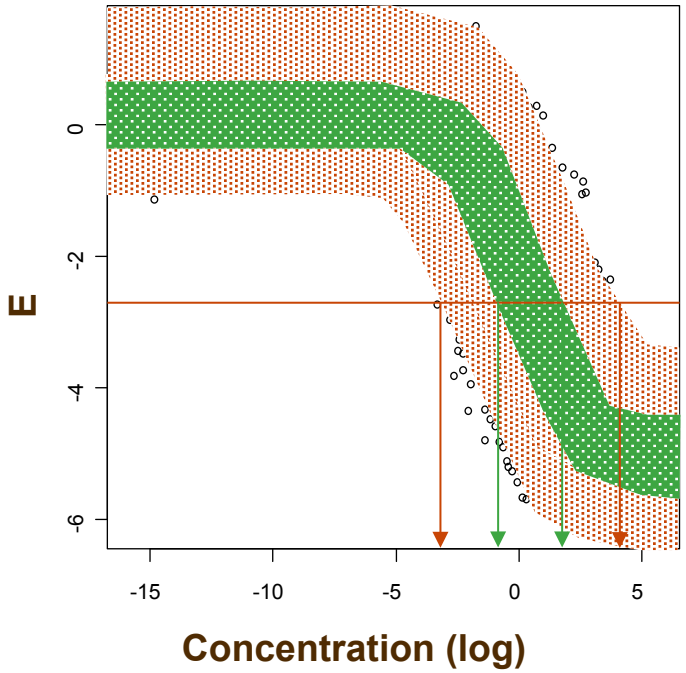
  For i in [1,…,500] do :



- Repeat for all the envisaged combinations of doses (2iv 1sc or 2sc 1 iv)

Selection criterion

- To select the optimal doses, the criterion is the surface of the predictions interval for the concentration-response curve.



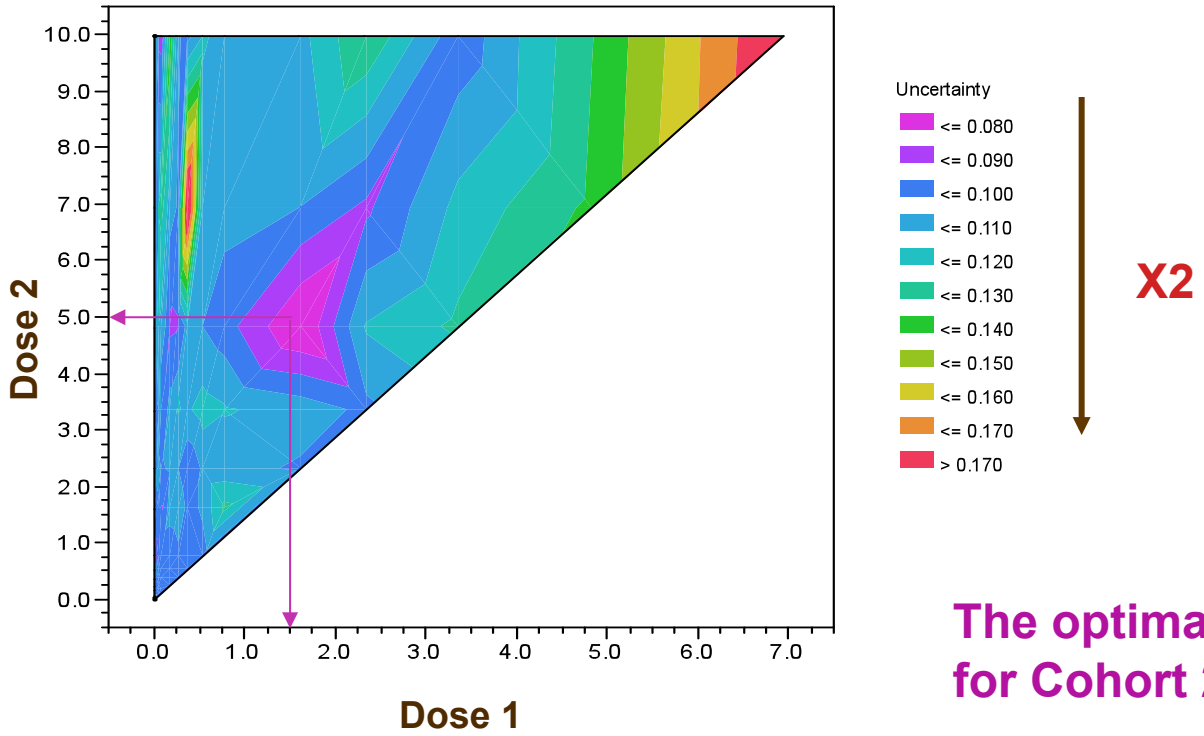
Predictions with set of doses without optimization

Predictions with optimal set of doses

- Simulations performed upfront to check the criterion

Simulations results

- Optimization process identifies the best 2 doses to improve quality (x2) of PD predictions.



The optimal set of doses for Cohort 2 is:

1.5 and 5 mg

Concluding remarks

- Selection of optimal doses at interim:

  - Better predictions of *E* response

  =>Better understanding of the mechanism

  =>Better design of further studies

Second application: “007” compound

Prediction of safety

Background of 007 compound

- Disease targeted by 007 compound: severe and rare disease (low recruitment rate)
- First in man study ongoing

- Competitor:
  - 008 compound, showed promising activity in Phase I in patients
  - But also showed an elevated incidence of thrombo-embolic events: 10% of the patients under study suffered from myocardial infarction, pulmonary embolism or stroke.

Study title

- A Two-Part, randomized, double-blind, placebo-controlled, single dose-escalating study to evaluate the safety, tolerability, pharmacokinetics, immunogenicity and to explore the pharmacodynamics 007 administered in healthy subjects and in patients

Study design

Cohort:	1	2	3	4	5	6	7	8	9	10
Dose (mg/kg)	0.001	0.05	0.025	0.4	1	5	7	15	30	45

- Each cohort will include 3 subjects that receive 007 at the dose indicated and 1 subject that will receive placebo.
- Dose level may be adapted following review of data from previous cohort

Study design

- Potential safety issue if too large exposure

- Adaptive design:

  The dose planned for the next cohort may be adapted based on safety and tolerability data and on the **predictive probability** that the AUC of the next planned dose level exceeds a **target value**

- Prediction-based decision: compute the predictive probability of a subject/patient being too largely exposed before taking the decision to give the next planned dose.

Study design

The target value has been defined as the NOAEL in a 3-month toxicolocy study :

- The 95th percentile of the distribution of the individual steady state exposures observed at the NOAEL of 50 mg/kg in a primate study.

Study design

- **The predicted probability** is obtained by fitting a Bayesian Pharmacokinetic model on all the available data from previous cohorts.
- The structure of the PK model and the prior distributions of its parameters are determined from preclinical studies and from 008 publications:
  - Two-compartment model
  - Ranges of a priori plausible values for Clearance, Volume of distribution,…
- AUC can be computed directly from the predicted clearance at next dose level.
- We compute the predicted probability that AUC exceeds the target limit at the next dose level.

WinBUGS model


```
model{
for(j in 1:M){
for(i in 1:ntp[j]){
    Y[j,i]~dnorm(mu[j,i],Prec[j,i]) I(,QL[j,i])
    mu[j,i] <- ((rate[j]*(k21[j]-L1[j])*(1-exp(L1[j]*(2/24))))/(V1[j]*L1[j]*(L1[j]-L2[j]))*exp(-
                        L1[j]*x[i]) + ((rate[j]*(L2[j]-k21[j])*(1-exp(L2[j]*(2/24))))/(V1[j]*L2[j]*
    (L1[j]-                         L2[j]))*exp(-L2[j]*x[i])))
    Var[j,i] <- (varmult*pow(mu[j,i],2)) + varadd
   Prec[j,i]<-1/Var[j,i]}

CL[j]~dlnorm(logmuCL,tauCL)
V1[j]~dlnorm(logmuV1,tauV1)
V2[j]~dlnorm(logmuV2,tauV2)
Q[j]<-exp(logmuQ)
k10[j]<-CL[j]/V1[j]
k12[j]<-Q[j]/V1[j]
k21[j]<-Q[j]/V2[j]
a[j]<- k10[j]+k12[j]+k21[j]
L1[j]<- (a[j]+sqrt((a[j]*a[j])-(4*k10[j]*k21[j])))/2
L2[j]<- (a[j]-sqrt((a[j]*a[j])-(4*k10[j]*k21[j])))/2 }
```

WinBUGS model


```
# Priors

logmuCL ~ dnorm (CLmean,CLprec)
tauCL~dgamma (CLa,CLb)
logmuV1 ~ dnorm (V1mean,V1prec)
tauV1~dgamma (V1a,V1b)
logmuV2 ~ dnorm (V2mean,V2prec)
tauV2~dgamma (V2a,V2b)
logmuQ ~ dnorm (Qmean,Qprec)
taumult ~ dgamma (varmulta,varmultb)
varmult<-1/taumult
tauadd ~ dgamma (varadda,varaddb)
varadd<-1/tauadd }
```

Empirical model

- For the first cohorts (very small doses), are we able to estimate a compartmental PK model?

  → Alternative method: empirical approach

- Trapezoidal method to compute AUC_{0-t} and extrapolation to get AUC:

  AUC=alpha*dose

- We compute the predicted probability that AUC exceeds the target limit at the next dose level.

Empirical model


```
model{

for(i in 1:M)
    {
      AUC[i] ~ dlnorm(logmuAUC[i],tau)
      muAUC[i] <- alpha*dose[i]
      logmuAUC[i]<-log(muAUC[i])
     }

#Priors
alpha ~ dunif(alphaa,alphab)
tau~dgamma(a.tau.empi,b.tau.empi)
}
```

Loop on the dose

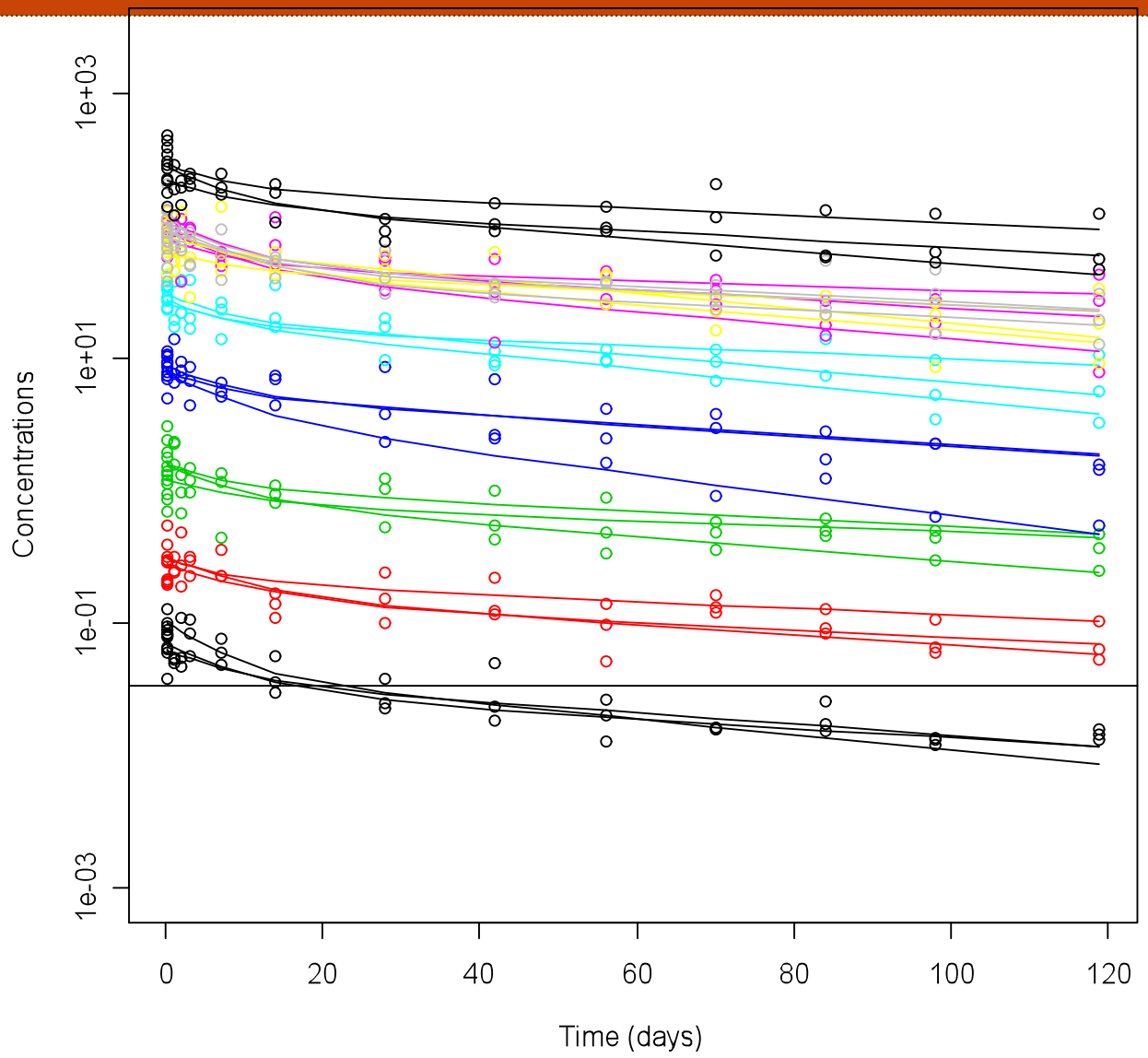
Simulations: which approach ?

- At which point are we able to switch from the empirical approach to the PK model-based approach ?

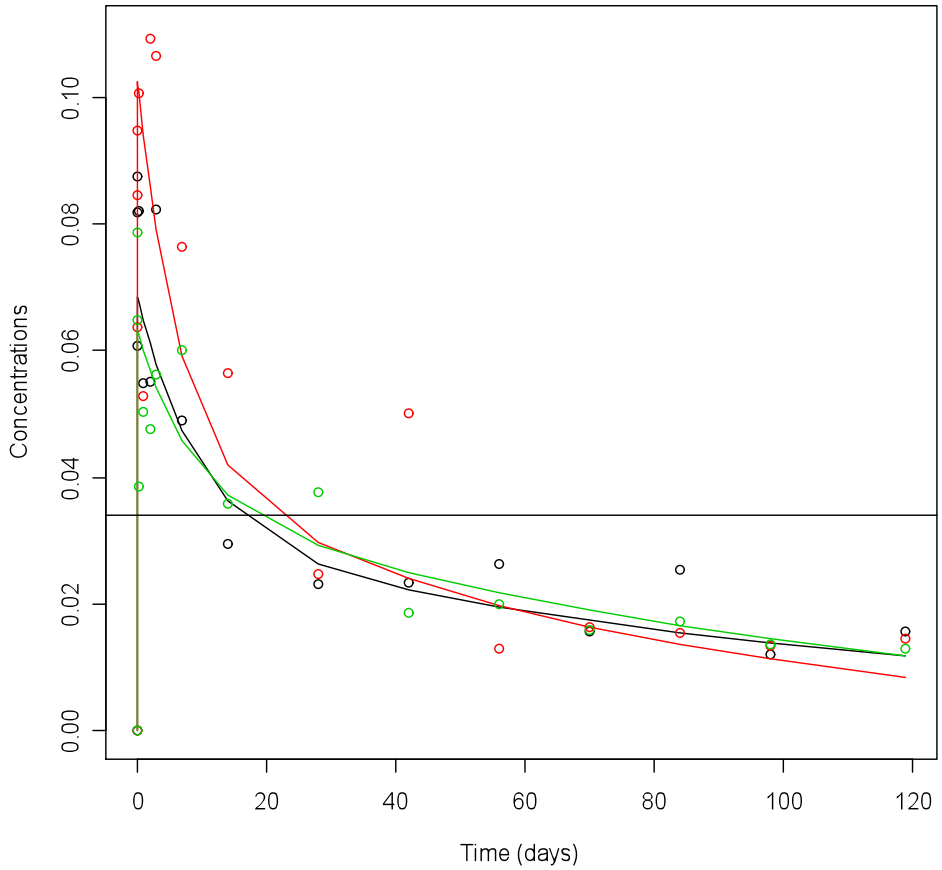
Simulations: Limit Of Quantitation

- Impact of LOQ on the capacity to estimate the model ?
  - Is the model estimable in all situations?
- Impact on the probability estimates with different strategies to handle the censored values ?
  - Automatic estimation in WinBUGS (Censoring)
  - Different imputation rules or use Lab Value
  - Keep as missing

Simulations: Limit Of Quantitation



Simulations: Limit Of Quantitation



Simulations: Variability

- Intra-subject variability
  - Additive and multiplicative error on the concentrations
- Inter-subject variability
  - In other studies: 30% and 25% CV
  - Different levels of inter-subject variability should be simulated and the influence on the estimates should be assessed.

Simulations : Missing values

- Study the influence of missing values for other reasons than BLQ (sample not done, not analyzed, not assessable, …)
- Different handling methods:
  - Automatic estimation in WinBUGS ()
  - Imputation rules
  - Keep as missing
- Simulate with different percentage of missing values at random

Simulations : scenarios

- Model structure and parameters values as expected (from the available information)
- Consider potential departures from the model: what if a bad scenario happens (exposure larger than expected)
  - Simulations with 3 levels of clearance : likely, bad, very bad

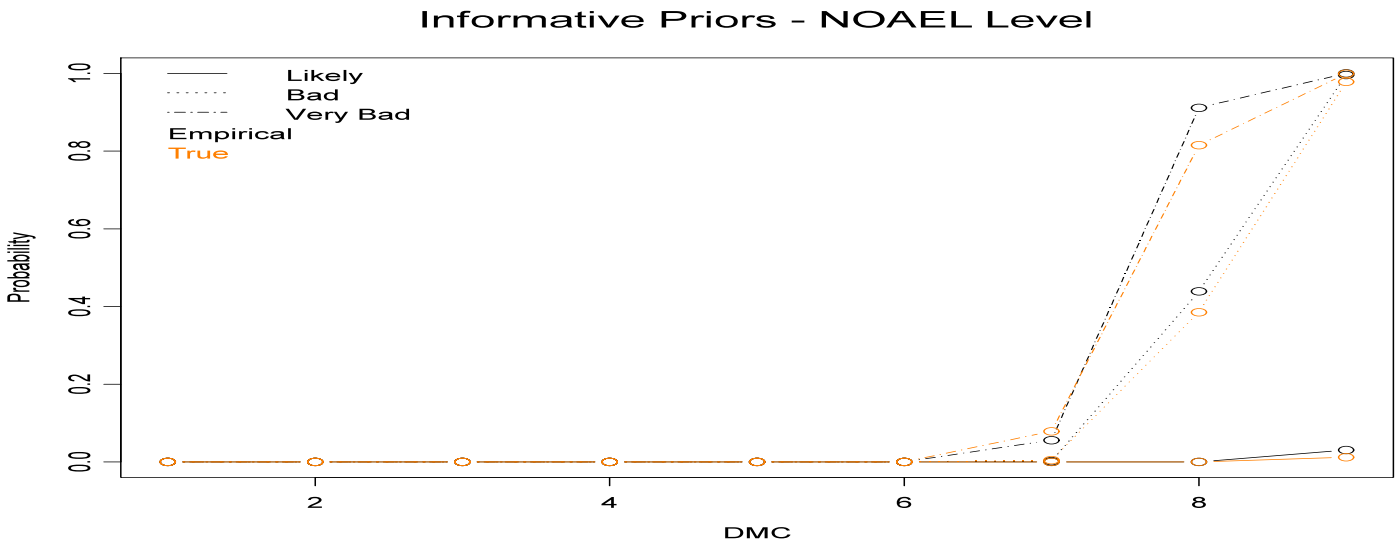
→ **preliminary work and team discussion are required !**

Simulations :Criteria

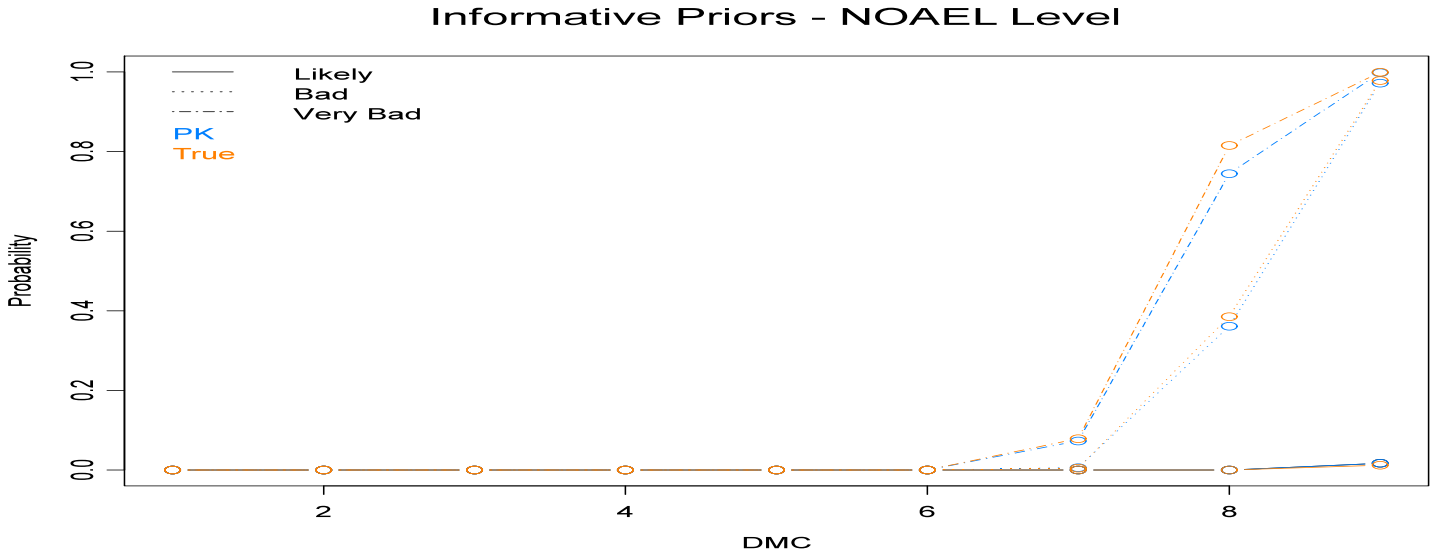
- We compare the true probability to exceed the limit at next dose with :
  - The estimated probability computed with the PK model
  - The estimated probability computed with the empirical model

- in various scenarios.

Simulations: results



Simulations: results



Simulations: results

- Probabilities to exceed the target level at next dose are well estimated with both approaches.

- We can use the model-based approach from first cohort
  - 3 patients
  - 7 days of PK (8 observations)
  - BLQ value

Conclusions

"The Bayesian approach provides tools for designing trials that

- *treat participants more effectively and*
- *that identify better drugs and*
- *appropriate doses more efficiently and faster".*

Berry, D. 2006. A guide to drug discovery: Bayesian clinical trials. Nature Reviews Drug Discovery 5 (27-36)

Conclusions

Predictions-based decisions implementation requires:

- Clear objective definition
- Integration with M&S team
- Closed connection to preclinical and clinical teams
- Simulations upfront

THANK YOU !