



Are population pharmacokinetic and/or pharmacodynamic models adequately evaluated? A survey of the literature from 2002 to 2004.

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► To cite this version:

Karl Brendel, Céline Dartois, Emmanuelle Comets, Annabelle Lemenuel-Diot, Christian Laveille, et al.. Are population pharmacokinetic and/or pharmacodynamic models adequately evaluated? A survey of the literature from 2002 to 2004.: Are population PK/PD models adequately evaluated?. *Clinical Pharmacokinetics*, Springer Verlag, 2007, 46 (3), pp.221-34. <inserm-00159124>

HAL Id: inserm-00159124

<http://www.hal.inserm.fr/inserm-00159124>

Submitted on 14 Sep 2009

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Data Abstraction Form for population PK/PD publications

MODEL EVALUATION

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ARTICLE IDENTIFICATION

DATE OF PUBLICATION (YEAR).....

TITLE.....

.....

.....

FIRST AUTHOR.....

I. BASIC INTERNAL

Goodness of fit

For the PK, PD study or the PKPD study

Were graphs plotted for basic evaluation?

Yes No

Which graphs are shown in the paper?

None

(OBS: Observations, PRED: Population Prediction, IPRED: Individual Prediction, WRES: Weighted residuals of population, IWRES: Weighted residuals of individual, COV: Covariates, RES: Difference between PRED and OBS, η_i : interindividual random effects, θ_i : individual parameters, "X": can be time or dose, Distribution: boxplot, histogram, or QQ plot)

OBS vs X with PRED

PRED vs "X"

PRED vs OBS

RES vs PRED

WRES vs "X"

WRES vs PRED

|WRES| vs PRED

Distribution of RES or WRES

Distribution of θ_i

Others:

IPRED vs "X"

IPRED vs OBS

IWRES vs "X"

IWRES vs IPRED

|IWRES| vs IPRED

Distribution of η_i

Uncertainty on parameters**For the PK study**

- SE or CV or CI on fixed effects
- SE or CV or CI on variance of random effects

SE or CV or CI are obtained by:

- Fisher information matrix
- Profile likelihood
- Bootstrap

Which type of bootstrap has been performed?

- On individuals (wild bootstrap)
- Other, define:

Number of bootstrap samples:

- SD of posterior distribution of the parameters (Bayesian methods)
- Graphs of posterior distribution of the parameters (Bayesian methods)
- Correlation between estimates were reported
- Others:

For the PD study (or PKPD study)

- SE or CV or CI on fixed effects
- SE or CV or CI on variance of random effects

SE or CV or CI are obtained by:

- Fisher information matrix
- Profile likelihood
- Bootstrap

Which type of bootstrap has been performed?

- On individuals (wild bootstrap)
- Other, define:

Number of bootstrap samples:

- SD of posterior distribution of the parameters (Bayesian methods)
- Graphs of posterior distribution of the parameters (Bayesian methods)
- Correlation between estimates were reported
- Others:

Evaluation of covariate model

For the PK study

Were graphs plotted for evaluation of covariates model? Yes No

Which graphs are shown in the paper? None

(WRES: Weighted residuals of population, IWRES: Weighted residuals of individual, COV: Covariates, RES: Difference between PRED and OBS, η_i : interindividual random effects, θ_i : individual parameters, θ : population parameters)

WRES vs COV η_i vs COV

RES vs COV θ_i vs COV

Other, define:

Randomisation test

Number of simulations:

Others, define:

For the PD study (or PKPD study)

Were graphs plotted for evaluation of covariates model? Yes No

Which graphs are shown in the paper? None

(WRES: Weighted residuals of population, IWRES: Weighted residuals of individual, COV: Covariates, RES: Difference between PRED and OBS, η_i : interindividual random effects, θ_i : individual parameters)

WRES vs COV η_i vs COV

RES vs COV θ_i vs COV

Other, define:

Randomisation test

Number of simulations:

Others, define:

Model sensitivity

For the PK study

- Sensitivity analysis to data outliers
 - Define method:
- Sensitivity analysis to individual outliers
 - Define method:
- Sensitivity analysis with respect to some parameters
 - Define method:

For the PD study (or PKPD study)

- Sensitivity analysis to data outliers
 - Define method:
- Sensitivity analysis to individual outliers
 - Define method:
- Sensitivity analysis with respect to some parameters
 - Define method:

II. ADVANCED INTERNAL

Data splitting

For the PK study

Yes No

Data (Validation dataset)

Selection

Not reported

Within patient

Between patient

Sequential

Randomisation

Stratification on covariates

Covariate distribution compared between validation and building datasets

Number of subjects (PK):

Not reported

Number of observations (PK):

Not reported

Final Data

Was the data reanalyzed by pooling building and validation datasets ?

Yes No

For the PD study (or PKPD study)

Yes No

Data (Validation dataset)

Selection

Not reported

Within patient

Between patient

Sequential

Randomisation

Stratification on covariates

Covariate distribution compared between validation and building datasets

Number of subjects (PK):

Not reported

Number of observations (PK):

Not reported

Final dataset

Was the data reanalyzed by pooling building and validation datasets ?

Yes No

Bootstrap

For the PK study

Yes No

Which type of bootstrap has been performed?

Not reported

On individuals (wild bootstrap)

Stratification on covariates

Others, define:

Number of bootstrap samples:

For the PD study (or PKPD study)

Yes No

Which type of bootstrap has been performed?

Not reported

On individuals (wild bootstrap)

Stratification on covariates

Others, define:

Number of bootstrap samples:

Cross-validation

For the PK study

Yes No

How cross-validation was performed?

Not reported

Stratification on covariates

Others, define:

Number of groups:

For the PD study (or PKPD study)

Yes No

How cross-validation was performed?

Not reported

Stratification on covariates

Others, define:

Number of groups:

Monte Carlo simulation of datasets

For the PK study

Yes No

Number of datasets

Not reported

Was design identical to original dataset?

Yes No

If no, Number of subjects:

Other differences, define:

How simulations were performed?

Not reported

With uncertainty on population parameters?

Yes No

If yes :

SE only

Full covariance matrix

Using bootstrap techniques

Distribution for the population parameter:

Multivariate normal or lognormal

Full posterior

Other, define:

Which Software has been used ?

NONMEM

SAS

R/S

TS2

Not reported

Other, define:

Were simulated datasets fitted?

Yes No

For the PD study (or PKPD study)

Yes No

Number of datasets

Not reported

Was design identical to original dataset?

Yes No

If no, Number of subjects:

Other differences, define:

How simulations were performed? Not reported

With uncertainty on population parameters? Yes No

If yes :

- SE only
- Full covariance matrix
- Using bootstrap techniques

Distribution for the population parameter:

- Multivariate normal or lognormal
- Full posterior
- Other, define:

Which Software has been used ?

NONMEM SAS R/S TS2 Not reported

Other, define:

Were simulated datasets fitted? Yes No

Other methods

For the PK study

Denomination:

Purpose:

Method steps:

.....

For the PD study

Denomination:

Purpose:

Method steps:

.....

Metrics

For the PK study

Prediction of validation dataset obtained: Not reported

with the model based on the building dataset without refitting

without covariate with covariates

with the model based on the building dataset and refitting

without covariate with covariates

without a model (Non Compartmental Analysis, individual parameters)

Other, define:

Metrics on observations (concentrations)

Types of metrics Not reported

Prediction errors PE (*residuals RES*)

Square prediction errors MSE or Root mean square prediction errors RMSE

Absolute prediction errors APE

Standardised prediction errors SPE (*weighted residuals WRES*)

SPE where E(C) and SD(C) obtained with Monte carlo simulations

Other metric :

Tests performed on metrics Yes No

Define :

Graphs Yes No

Define :

On individual statistic or parameter			<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> θ_i	<input type="checkbox"/> η_i	<input type="checkbox"/> All i
	<input type="checkbox"/> Other, define:.....		
Statistic on	<input type="checkbox"/> AUC $_i$	<input type="checkbox"/> Clearance $_i$	
	<input type="checkbox"/> Other, define:.....		
Types of metrics			
<input type="checkbox"/> Prediction errors PE			
<input type="checkbox"/> Square prediction errors MSE or Root mean square prediction errors RMSE			
<input type="checkbox"/> Absolute prediction errors APE			
<input type="checkbox"/> Standardised prediction errors SPE			
<input type="checkbox"/> Other metric :			
Tests performed on metrics	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<input type="checkbox"/> Define :			
Graphs	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<input type="checkbox"/> Define :			
On population statistic or parameter			<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> θ	<input type="checkbox"/> Variability	
	<input type="checkbox"/> Other, define:.....		
Statistic on	<input type="checkbox"/> AUC	<input type="checkbox"/> Clearance	
	<input type="checkbox"/> mean	<input type="checkbox"/> quartile	
	<input type="checkbox"/> Other, define:.....		
Types of metrics			
<input type="checkbox"/> Prediction errors PE			
<input type="checkbox"/> Square prediction errors MSE or Root mean square prediction errors RMSE			
<input type="checkbox"/> Absolute prediction errors APE			
<input type="checkbox"/> Standardised prediction errors SPE			
<input type="checkbox"/> Other metric :			
Tests performed on metrics	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<input type="checkbox"/> Define :			
Graphs	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<input type="checkbox"/> Define :			

For the PD study (or PKPD study)

Prediction of validation dataset obtained: Not reported

with the model based on the building dataset without refitting

without covariate with covariates

with the model based on the building dataset and refitting

without covariate with covariates

without a model (Non Compartmental Analysis, individual parameters)

Other, define:

Metrics on observations (effects)

Types of metrics Not reported

Prediction errors PE (*residuals RES*)

Square prediction errors MSE or Root mean square prediction errors RMSE

Absolute prediction errors APE

Standardised prediction errors SPE (*weighted residuals WRES*)

SPE where E(C) and SD(C) obtained with Monte carlo simulations

Other metric :

Tests performed on metrics Yes No

Define :

Graphs Yes No

Define :

On individual statistic or parameter		<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> θ_i <input type="checkbox"/> η_i <input type="checkbox"/> All i	
	<input type="checkbox"/> Other, define:.....	
Statistic on	<input type="checkbox"/> AUC(effet) $_i$ <input type="checkbox"/> EC50/ED50 $_i$	
	<input type="checkbox"/> Other, define:.....	
Types of metrics		
<input type="checkbox"/> Prediction errors PE		
<input type="checkbox"/> Square prediction errors MSE or Root mean square prediction errors RMSE		
<input type="checkbox"/> Absolute prediction errors APE		
<input type="checkbox"/> Standardised prediction errors SPE		
<input type="checkbox"/> Other metric :		
Tests performed on metrics	<input type="checkbox"/> Yes	<input type="checkbox"/> No
<input type="checkbox"/> Define :		
Graphs	<input type="checkbox"/> Yes	<input type="checkbox"/> No
<input type="checkbox"/> Define :		
On population statistic or parameter		<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> θ <input type="checkbox"/> Variability	
	<input type="checkbox"/> Other, define:.....	
Statistic on	<input type="checkbox"/> AUC(effet) <input type="checkbox"/> EC50/ED50	
	<input type="checkbox"/> mean <input type="checkbox"/> quartile	
	<input type="checkbox"/> Other, define:.....	
Types of metrics		
<input type="checkbox"/> Prediction errors PE		
<input type="checkbox"/> Square prediction errors MSE or Root mean square prediction errors RMSE		
<input type="checkbox"/> Absolute prediction errors APE		
<input type="checkbox"/> Standardised prediction errors SPE		
<input type="checkbox"/> Other metric :		
Tests performed on metrics	<input type="checkbox"/> Yes	<input type="checkbox"/> No
<input type="checkbox"/> Define :		
Graphs	<input type="checkbox"/> Yes	<input type="checkbox"/> No
<input type="checkbox"/> Define :		

III. EXTERNAL

<u>For the PK study</u>		<input type="checkbox"/> Not reported
Validation dataset (in comparison to building dataset)		
same inclusion criteria	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Not reported
if no, differences in :	<input type="checkbox"/> Pathology <input type="checkbox"/> Age	<input type="checkbox"/> Ethnic group
	<input type="checkbox"/> Other, define:	
similar dose regimen	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Not reported
if no, differences in :	<input type="checkbox"/> Dose <input type="checkbox"/> Administration rhythm	
similar sampling scheme	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Not reported
if no:	<input type="checkbox"/> Richer <input type="checkbox"/> More sparse	
Number of subjects (PK):		<input type="checkbox"/> Not reported
Number of observations (PK):		<input type="checkbox"/> Not reported
<input type="checkbox"/> Covariates compared between the validation and building datasets		
Final datasets		
Were the data reanalyzed by pooling building and validation datasets ?		
<input type="checkbox"/> yes <input type="checkbox"/> no		
<u>For the PD study (or PKPD study)</u>		<input type="checkbox"/> Not reported
Validation dataset (in comparison to building dataset)		
same inclusion criteria	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Not reported
if no, differences in :	<input type="checkbox"/> Pathology <input type="checkbox"/> Age	<input type="checkbox"/> Ethnic group
	<input type="checkbox"/> Other, define:	
similar dose regimen	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Not reported
if no, differences in :	<input type="checkbox"/> Dose <input type="checkbox"/> Administration rhythm	
similar sampling scheme	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Not reported
if no:	<input type="checkbox"/> Richer <input type="checkbox"/> More sparse	

Number of subjects (PK): Not reported

Number of observations (PK): Not reported

Covariates compared between the validation and building datasets

Final datasets

Were the data reanalyzed by pooling building and validation datasets ?

yes no

Monte Carlo simulation of datasets

For the PK study Yes No

Number of datasets Not reported

Was design identical to original dataset? Yes No

If no, Number of subjects:

Other differences, define:

How simulations were performed? Not reported

With uncertainty on population parameters? Yes No

If yes :

SE only

Full covariance matrix

Using bootstrap techniques

Distribution for the population parameter:

Multivariate normal or lognormal

Full posterior

Other, define:

Which Software has been used ?

NONMEM SAS R/S TS2 Not reported

Other, define:

Were simulated datasets fitted? Yes No

Metrics

For the PK study

- Prediction of validation dataset obtained:** Not reported
- with the model based on the building dataset without refitting
 - without covariate with covariates
 - with the model based on the building dataset and refitting
 - without covariate with covariates
 - without a model (Non Compartmental Analysis, individual parameters)
 - Other, define:

Metrics on observations (concentrations)

- Types of metrics Not reported
- Prediction errors PE (*residuals RES*)
 - Square prediction errors MSE or Root mean square prediction errors RMSE
 - Absolute prediction errors APE
 - Standardised prediction errors SPE (*weighted residuals WRES*)
 - SPE where E(C) and SD(C) obtained with Monte carlo simulations
 - Other metric :
- Tests performed on metrics Yes No
- Define :
- Graphs Yes No
- Define :

On individual statistic or parameter			<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> θ_i	<input type="checkbox"/> η_i	<input type="checkbox"/> All i
	<input type="checkbox"/> Other, define:.....		
Statistic on	<input type="checkbox"/> AUC $_i$	<input type="checkbox"/> Clearance $_i$	
	<input type="checkbox"/> Other, define:.....		
Types of metrics			
<input type="checkbox"/> Prediction errors PE			
<input type="checkbox"/> Square prediction errors MSE or Root mean square prediction errors RMSE			
<input type="checkbox"/> Absolute prediction errors APE			
<input type="checkbox"/> Standardised prediction errors SPE			
<input type="checkbox"/> Other metric :			
Tests performed on metrics	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<input type="checkbox"/> Define :			
Graphs	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<input type="checkbox"/> Define :			
On population statistic or parameter			<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> θ	<input type="checkbox"/> Variability	
	<input type="checkbox"/> Other, define:.....		
Statistic on	<input type="checkbox"/> AUC	<input type="checkbox"/> Clearance	
	<input type="checkbox"/> mean	<input type="checkbox"/> quartile	
	<input type="checkbox"/> Other, define:.....		
Types of metrics			
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<input type="checkbox"/> Absolute prediction errors APE			
<input type="checkbox"/> Standardised prediction errors SPE			
<input type="checkbox"/> Other metric :			
Tests performed on metrics	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<input type="checkbox"/> Define :			
Graphs	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<input type="checkbox"/> Define :			

For the PD study (or PKPD study)

Prediction of validation dataset obtained: Not reported

with the model based on the building dataset without refitting

without covariate with covariates

with the model based on the building dataset and refitting

without covariate with covariates

without a model (Non Compartmental Analysis, individual parameters)

Other, define:

Metrics on observations (effects)

Types of metrics Not reported

Prediction errors PE (*residuals RES*)

Square prediction errors MSE or Root mean square prediction errors RMSE

Absolute prediction errors APE

Standardised prediction errors SPE (*weighted residuals WRES*)

SPE where E(C) and SD(C) obtained with Monte carlo simulations

Other metric :

Tests performed on metrics Yes No

Define :

Graphs Yes No

Define :

On individual statistic or parameter Not reported

Estimated parameters θ_i η_i All i
 Other, define:.....

Statistic on AUC(effet) $_i$ EC50/ED50 $_i$
 Other, define:.....

Types of metrics
 Prediction errors PE
 Square prediction errors MSE or Root mean square prediction errors RMSE
 Absolute prediction errors APE
 Standardised prediction errors SPE
 Other metric :

Tests performed on metrics Yes No
 Define :

Graphs Yes No
 Define :

On population statistic or parameter Not reported

Estimated parameters θ Variability
 Other, define:.....

Statistic on AUC(effet) EC50/ED50
 mean quartile
 Other, define:.....

Types of metrics
 Prediction errors PE
 Square prediction errors MSE or Root mean square prediction errors RMSE
 Absolute prediction errors APE
 Standardised prediction errors SPE
 Other metric :

Tests performed on metrics Yes No
 Define :

Graphs Yes No
 Define :

SUBJECTIVE SYNTHESIS

Was there an attempt to evaluate the model?

No Poor Good Excellent

Was the choice of the metrics appropriate?

No Poor Good Excellent

Was the model evaluated?

No Poor Good Excellent