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

Karl Brendel, Céline Dartois, Emmanuelle Comets, Annabelle Lemenuel-Diot, Christian Laveille, Brigitte Tranchand, Pascal Girard, Céline M. Laffont, France Mentré

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# **Data Abstraction Form for population PK/PD publications**

## **MODEL EVALUATION**

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**ARTICLE IDENTIFICATION**

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**DATE OF PUBLICATION (YEAR)**..... |□□□□|

**TITLE**.....

.....

.....

**FIRST AUTHOR**.....

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## 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,  $\eta_i$ : interindividual random effects,

$\theta_i$ : 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  $\theta_i$

Others: .....

IPRED vs "X"

IPRED vs OBS

IWRES vs "X"

IWRES vs IPRED

|IWRES| vs IPRED

Distribution of  $\eta_i$

**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,  $\eta_i$ : interindividual random effects,  $\theta_i$ : individual parameters,  $\theta$ : population parameters)

WRES vs COV        $\eta_i$  vs COV

RES vs COV        $\theta_i$  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,  $\eta_i$ : interindividual random effects,  $\theta_i$ : individual parameters )

WRES vs COV        $\eta_i$  vs COV

RES vs COV        $\theta_i$  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 : .....

<b>On individual statistic or parameter</b>			<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> $\theta_i$	<input type="checkbox"/> $\eta_i$	<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 : .....			
<b>On population statistic or parameter</b>			<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> $\theta$	<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 : .....

<b>On individual statistic or parameter</b>		<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> $\theta_i$ <input type="checkbox"/> $\eta_i$ <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 : .....		
<b>On population statistic or parameter</b>		<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> $\theta$ <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 : .....		



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### III. EXTERNAL

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<b><u>For the PK study</u></b>		<input type="checkbox"/> Not reported
<b>Validation dataset (in comparison to building dataset)</b>		
same inclusion criteria	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Not reported
<b>if no, differences in :</b>	<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
<b>if no, differences in :</b>	<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
<b>if no:</b>	<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		
<b>Final datasets</b>		
Were the data reanalyzed by pooling building and validation datasets ?		
<input type="checkbox"/> yes <input type="checkbox"/> no		
<b><u>For the PD study (or PKPD study)</u></b>		<input type="checkbox"/> Not reported
<b>Validation dataset (in comparison to building dataset)</b>		
same inclusion criteria	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Not reported
<b>if no, differences in :</b>	<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
<b>if no, differences in :</b>	<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
<b>if no:</b>	<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

<b>For the PD study (or PKPD study)</b>		Yes <input type="checkbox"/>	No <input type="checkbox"/>
Number of datasets .....		<input type="checkbox"/> Not reported	
Was design identical to original dataset?		Yes <input type="checkbox"/>	No <input type="checkbox"/>
<b>If no,</b> Number of subjects: .....			
Other differences, define: .....			
How simulations were performed?		<input type="checkbox"/> Not reported	
With uncertainty on population parameters?		Yes <input type="checkbox"/>	No <input type="checkbox"/>
If yes :			
<input type="checkbox"/> SE only			
<input type="checkbox"/> Full covariance matrix			
<input type="checkbox"/> Using bootstrap techniques			
Distribution for the population parameter:			
<input type="checkbox"/> Multivariate normal or lognormal			
<input type="checkbox"/> Full posterior			
<input type="checkbox"/> Other, define: .....			
Which Software has been used ?			
<input type="checkbox"/> NONMEM	<input type="checkbox"/> SAS	<input type="checkbox"/> R/S	<input type="checkbox"/> TS2
<input type="checkbox"/> Other, define: .....		<input type="checkbox"/> Not reported	
Were simulated datasets fitted?		Yes <input type="checkbox"/>	No <input type="checkbox"/>

<b>Other methods</b>
<b><u>For the PK study</u></b>
Denomination: .....
Purpose: .....
Method steps: .....
.....
<b><u>For the PD study</u></b>
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 : .....

<b>On individual statistic or parameter</b>			<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> $\theta_i$	<input type="checkbox"/> $\eta_i$	<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 : .....			
<b>On population statistic or parameter</b>			<input type="checkbox"/> Not reported
Estimated parameters	<input type="checkbox"/> $\theta$	<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**  Not reported

Estimated parameters   $\theta_i$    $\eta_i$   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   $\theta$   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