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

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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" ☐ IPRED vs "X"

☐ PRED vs OBS ☐ IPRED vs OBS

☐ RES vs PRED

☐ WRES vs "X" ☐ IWRES vs "X"

☐ WRES vs PRED ☐ IWRES vs IPRED

☐ |WRES| vs PRED ☐ |IWRES| vs IPRED

☐ Distribution of RES or WRES ☐ Distribution of η_i

☐ Distribution of θ_i

☐ Others: ……

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 ☐ Not reported

Estimated parameters ☐ θ_i ☐ η_i ☐ All $_i$

☐ Other, define:……..

Statistic on ☐ AUC_i ☐ $Clearance_i$

☐ 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 ☐ Clearance

☐ 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 : .....

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 : .....

III. EXTERNAL

For the PK study ☐ Not reported

Validation dataset ***(in comparison to building dataset)***

same inclusion criteria ☐ Yes ☐ No ☐ Not reported

if no, differences in : ☐ Pathology ☐ Age ☐ Ethnic group

☐ Other, define: ……

similar dose regimen ☐ Yes ☐ No ☐ Not reported

if no, differences in : ☐ Dose ☐ Administration rhythm

similar sampling scheme ☐ Yes ☐ No ☐ Not reported

if no: ☐ Richer ☐ 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

For the PD study (or PKPD study) ☐ Not reported

Validation dataset ***(in comparison to building dataset)***

same inclusion criteria ☐ Yes ☐ No ☐ Not reported

if no, differences in : ☐ Pathology ☐ Age ☐ Ethnic group

☐ Other, define: ……

similar dose regimen ☐ Yes ☐ No ☐ Not reported

if no, differences in : ☐ Dose ☐ Administration rhythm

similar sampling scheme ☐ Yes ☐ No ☐ Not reported

if no: ☐ Richer ☐ 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 ☐

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 ☐ Not reported

Estimated parameters ☐ θ_i ☐ η_i ☐ All $_i$

☐ Other, define:……..

Statistic on ☐ AUC_i ☐ $Clearance_i$

☐ 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 ☐ Clearance

☐ 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 : .....

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