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GUIDELINE ON REPORTING THE RESULTS OF POPULATION PHARMACOKINETIC ANALYSES

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GUIDELINE ON REPORTING THE RESULTS OF POPULATION PHARMACOKINETIC ANALYSES

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EXECUTIVE SUMMARY

This guideline provides guidance on how to present the results of a population pharmacokinetic analysis, in order to provide a level of details that will enable a secondary evaluation (i.e. assessment by regulatory authorities of the conducted analysis and conclusions drawn). Guidance on the content of the analysis plan for the population PK analysis is presented and recommendations for information to be included in key sections of the report are provided.

1. INTRODUCTION

Population pharmacokinetics is the study of variability in drug concentrations between individuals (healthy volunteers or patients). It comprises the assessment of variability within the population and to account for the variability in terms of patient characteristics such as age, renal function or disease state [1]. The non-linear mixed effects modelling approach [2] has become increasingly used for population pharmacokinetics and this guideline implies the use of such approach.

The efficacy and safety of a new chemical entity (NCE) is generally characterised in phase III studies in a well defined restricted patient population. The pharmacokinetic (PK) information is used to extrapolate the safety and efficacy findings to the wider patient population who may receive the NCE in question. Today, population PK analyses are a regular part of the documentation of an NCE and form one way in which an applicant can choose to provide PK information.

Population PK studies are also submitted to regulatory agencies as part of type II variations of approved products or line extensions (e.g. in dose-finding studies in paediatric populations, for new indications or new formulations), and can in these applications constitute a large or even the main part of the clinical documentation.

Currently, results from population analyses are most frequently used to characterise the PK in the target population, to provide PK data in special populations (elderly, children, renally impaired etc.) and to support dosing recommendations for these populations. To make the information resulting from a population analysis useful during the regulatory assessment, the report should include sufficient detail to enable a secondary evaluation by a regulatory assessor. The analysis and report of the analysis need to be of sufficient quality so that the final model can be judged to be a good description of the data and that the results and conclusions ensuing from the population analysis can be considered valid.

2. SCOPE

The aim of this guideline is to detail what the European regulatory assessors look for in a report of population PK analyses (population PK report) and the main components to be included in a population PK report. In contrast to the FDA guidance on population PK analyses[a] [3], this guideline does not provide guidance on how to conduct a population PK analysis, but rather provides guidance on points to consider when presenting the results from such an analysis, in order to provide a level of detail which will enable a secondary evaluation by a regulatory assessor. Every population PK model will depend on the data and decisions made by the model developer, and every model has therefore unique properties. It is therefore vital that every assumption and decision made during model development is made clear for the assessor. Although the information in this guideline focuses on population pharmacokinetics, the principles discussed here are equally applicable to population pharmacodynamic (PD) and PK/PD studies. The guideline has been written based on current knowledge. Population pharmacokinetics is an evolving science, and this must be taken into account in the interpretation of this guideline. It is expected that the reader in the future also will apply additional knowledge gained.

The vast majority of population PK reports received by the EU regulatory agencies have been carried out using nonlinear mixed effects modelling with the software NONMEM [4]. The nomenclature of this guideline is therefore most relevant for NONMEM, but if other programs are used, then it is assumed that the reader can generalize the points made in this guideline to the software used in their

[a] The FDA guidance should be read bearing in mind that it was written in 1999 and that population pharmacokinetics is an evolving science.

particular analysis. The general recommendations of the guideline might be appropriate for most analyses, however, in particular cases they can be adjusted.

This guideline is, to a large extent, based on a publication by Wade JR, Edholm M and Salmonson T.: A Guide for Reporting the Results of Population Pharmacokinetic Analyses: A Swedish Perspective [5].

3. LEGAL BASIS

This guideline applies to all Marketing Authorisation Applications for human medicinal products submitted in accordance with Directive 2001/83/EC as amended. This guideline should be read in conjunction with the Introduction and general principles paragraph (4) and Part I, Module 5 of the Annex I to Directive 2001/83 as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations especially those on:

- Pharmacokinetic Studies in Man (3CC3A, 1987)
- The Investigation of Drug Interactions (CPMP/EWP/560/95)
- Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Renal Function (CPMP/EWP/225/02)
- Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function (CPMP/EWP/2339/02)
- Guideline on the Role of Pharmacokinetics in the development of Medicinal Products in the Paediatric Population (CPMP/EWP/147013/2004)
- Guideline on Clinical Investigation if the Pharmacokinetics of Therapeutic Proteins (CPMP/EWP/89249/04)

4. MAIN GUIDELINE TEXT

4.1 Nomenclature[JYD1]

AIC: Akaike's information criteria. Statistical criteria used in model selection.

CWRES: Weighted Residuals evaluated at individual conditional estimates

DV: Dependent variable, i.e. the Observed Data

eta: Random effect describing the deviation of the individual empirical Bayes estimate of the parameter from the typical population parameter estimate

FO: First Order estimation method in NONMEM. NONMEM is a parametric maximum likelihood method. The likelihood of the observations, given model parameters and input variables, is the product of all individual likelihoods expressed as an integral over all possible values of eta. Most often, no closed form solution of the integral exists for nonlinear mixed-effects models, thus necessitating an approximation of the expression being integrated. The FO method is based on the first order Taylor series approximation to the model, with the model linearised about the mean of the random parameters (at the expected value of etas, which is 0, i.e. at the typical value). For residual error models with dependency on model predictions (heteroscedastic models), the prediction corresponds to the population prediction.

FOCE: First Order Conditional Estimation method in NONMEM. In this method the model is linearised about the individual conditional estimates of etas (at the empirical Bayes estimates of eta, i.e. at the individual value). For residual error models with dependency on model predictions (heteroscedastic models), the prediction corresponds to the population prediction.

GOF: Goodness of Fit

INTER: First Order Conditional Estimation method (see FOCE) with interaction in NONMEM. As FOCE with the following difference: For residual error models with dependency on model predictions (heteroscedastic models), the prediction corresponds to the individual

prediction, i.e. the interaction between inter-individual variability and residual error is taken into account.

IPRED: Individual Predicted Data based on individual empirical Bayes parameter estimates

IWRES: Absolute Individual Weighted Residuals

LRT: Likelihood Ratio Test. Test for statistical significance. The difference in -2LL between two nested models approximately follows a chi squared distribution, where the degrees of freedom is the difference in the number of estimated parameters.

NONMEM: Software used for nonlinear mixed effects modelling

OFV: Objective Function Value, approximately proportional to minus twice the log-likelihood (-2LL)

PRED: Predicted Data based on population parameter estimates

QQ: Quantile-quantile

TAD: Time After Dose

WRES: Weighted Residuals

WRES: Absolute Weighted Residuals

4.2 Analysis plan

There should be a prospectively written analysis plan for the population PK analysis. The analysis plan should be presented and could form an appendix in the report of the population PK analysis. It is acknowledged that the level of information in the analysis plan may be less detailed than in a standard clinical protocol, due in part to the exploratory nature of some population analyses. However, the analysis plan should at least include:

- the objective(s) of the analysis
- a brief description of the study (or studies) from which the data originate
- the nature of the data to be analyzed (how many subjects, rich or sparsely sampled)
- the procedures for handling missing data and outlying data
- the general modelling aspects (e.g. software, estimation methods, diagnostics)
- the overall modelling procedure/strategy
- the structural models to be tested (if this has been decided)
- the variability models to be tested
- the covariates and covariate models to be tested together with a rationale for testing these covariates based on, for example, biological, pharmacological and/or clinical plausibility.
- the algorithms/methods to be used for covariate model building
- the criteria to be used for selection of models during model building and inclusion of covariates (e.g. objective function value, level of statistical significance, goodness of fit plots, standard error, inter-individual variability, clinical relevance)
- the model evaluation/qualification procedures to be used

References to specific methodologies used should be given, and when relevant included in the documentation submitted.

4.3 Final Report sub-sections

Recommendations for information to be included in key report sections are provided below.

It is not necessary to append documents that are already included in other parts of the submitted documentation (as study protocols, analytical reports etc.). Clear cross-references should be given to these documents and preferably with hyperlinks in an eCTD application.

4.3.1 Summary

The summary should provide an overall summary of the population PK analysis. It should include sufficient information on the context of the study, objectives, study design, data (number of subjects and samples), methods, results and the main findings and conclusions of the population PK analysis.

4.3.2 Introduction

The introduction in a population PK report should provide some background information about the drug to be analyzed and the intent of the analysis. It should include sufficient background information to place the population PK analysis in its proper context within the drug's clinical development and indicate any special features of the population PK analysis.

4.3.3 Objectives

The objectives of the analysis should be stated. An example of an objective may be to build a model that describes the data and to test the possible influence of various specified covariates on the parameters of the model. Other objectives may include performing simulations based upon the final model, e.g. for dose recommendations in special populations.

4.3.4 Data

The report should briefly describe the study or studies from which the data included in the analysis originate. Information regarding nominal number of samples per subject per visit and sampling times in each study should be given.

The method for calculation of derived covariates (e.g. creatinine clearance, ideal body weight, body mass index) should be stated.

When relevant, the type of data transformation used should be described and justified. This applies both to the dependent variable and other variables.

Handling of missing data should be described. For example not all subjects may have complete covariate information and other subjects may have missing dose and/or sample times. The procedures taken in the case of missing data should be fully described in the report. The handling of data below the limit of quantification should also be described and possible consequences discussed (censoring problems).

Outliers are usually identified on initial visual inspection of raw data, and/or inspection of the output from initial model building runs. The report should describe and justify the procedures that were taken in handling outliers, e.g. description of rules applied for omitting data completely or for re-inclusion.

Electronic files of the analysis datasets should be provided as comma separated and space delimited text files.

It is recommended to include a specification of the data sets used, clearly describing the differences between various data sets used, and to be referenced in the run record.

4.3.5 Methods

The methods section should describe the methods used and should include the same components as the analysis plan. If, during the analysis, any deviations from the analysis plan occur, these should be clearly emphasised in the methods section of the report.

This section should also include information regarding the type of bioanalytical methods used and the limit of quantification for each analyte in each method.

The choice of analysis (e.g. parametric maximum likelihood, non-parametric maximum likelihood, Bayesian) and the choice of estimation method (e.g. FO, FOCE, FOCE INTER) should be stated and justified. The software and version used should be stated. Assumptions made during the analysis should be stated and briefly discussed [6].

The criteria to be used for selection of models during model building and inclusion of covariates (e.g. objective function value, level of statistical significance, goodness of fit plots, standard error, inter-individual variability, clinical relevance) should be described. It is recommended to justify the statistical criteria used, e.g. LRT, AIC or other. For example, when using the LRT the actual statistical

significance level (ΔOFV in NONMEM) could be markedly different from the nominal. Also, depending on the estimation method used (FO, FOCE with or without INTER) the number of subjects, number of samples per subject, residual error magnitude etc. may influence the actual significance level [7].

Structural model

The report should clearly present *a priori* information available regarding the potential structure of the model. A description of models evaluated should be given.

Covariate model

The covariates to be tested for inclusion in the model should be presented together with a rationale for testing these covariates based on, for example, biological, pharmacological and/or clinical plausibility. The parameterisation of the covariate model should be specified.

The covariate model building procedure (e.g. step-wise covariate model building procedures [8]) should be described. The criteria for covariate selection (e.g. statistical significance and clinical relevance) should be presented.

Variability models / Stochastic models

Models applied to describe inter-individual, residual and, when relevant, inter-occasion variability should be described.

Model evaluation

The amount and type of model evaluation/qualification (subsequently referred to as model evaluation) procedures will depend upon the objective(s) of the model development. Model evaluation procedures to support an objective that is to describe the data and evaluate potential covariate effects could be simpler than those needed if the final model is to be used to perform simulations, e.g. in support of dosage recommendations. For the latter case more rigorous procedures may be required. Further, some model evaluations may have other purposes, for example to evaluate the robustness or sensitivity of the model.

The model evaluation procedures should be described and may include both graphical evaluation and statistical procedures. The report should contain justification for the model evaluation procedures and tools used for the specific evaluation. Several tools and procedures are available for use in model evaluation whereof the following are examples: i) assessment of goodness-of-fit (GOF) plots, ii) plausibility of parameter estimates and their precision, iii) bootstrapping techniques [9, 10], iv) log-likelihood profiling [11, 12], v) case-deletion diagnostics [13], vi) jack-knife techniques [13], vii) visual predictive checks (plot comparing 95% prediction interval with observed data) [14], viii) posterior predictive check [15], ix) external evaluation on data not included in the current analysis or x) evaluation of influential individuals [16].

In the case of substantial simulations based on the model, these should be described in detail, including description of the demographics (e.g. covariate distribution and variability) of the simulation data set.

4.3.6 Results

Data

The report should include the following description of the data:

- The total number of subjects
- The total number of observed concentrations used in the analysis.
- The distribution of samples presented in an appropriate way that might include tables or graphics (e.g. histograms) presenting the actual number of samples per subject sorted by study, treatment group, visit etc.
- Plots of the raw data provided on linear scale and usually also on log-linear scale. Lines connecting the data points could be included for part of the subjects to visualise the data.
- Separate presentation of data from internal or external validation datasets.

- Information regarding drop-outs during the study (number of drop-outs, time point in relation to PK sampling, and when relevant, reason for drop out).
- Summary statistics and histograms of the continuous covariates and frequencies of categorical covariates. If relevant, this covariate data could be presented stratified over subpopulations or validation sets.
- Correlation between covariates.
- Missing data (missing dosing and sample times, missing covariates).
- Outliers specified with all relevant data available.
- Subjects removed from the analysis listed with relevant patient characteristics.

Base model

The report should describe any major decisions taken during the base model development and should include an overview of the steps taken during model development (a run record) that, at a minimum, clearly describes important decisions taken during the building of the base population model. The run record may be presented in a separate appendix. The use of abbreviations or codes in the run record that are difficult to interpret should be avoided.

The run record should describe the changes from the previous model and the decisions taken and could include a brief, but interpretable, description of the run, the objective function value and information whether the model converged successfully. Preferably, the run record should also include parameter estimates (for key runs) and, when needed, a comment about the run. If the data set alters during the course of the analysis then the run record is a good tool to document which data sets have been used for which particular runs. The numbers of subjects and observations used in each run can be given in the run record.

All parameter estimates in the base model, together with their standard errors and/or confidence intervals, should be presented in a table. The inter-individual and residual variability models, and when applicable inter-occasion (intra-individual) variability models, should also be presented and supported by appropriate graphics.

GOF plots should be presented for the base model, and when relevant for key stages during base model development [17, 18]. It is recommended to choose GOF plots appropriate for the analysis, as the value of different GOF plots may be dependent on the situation (e.g. rich or sparse data, type of estimation method [19]). When appropriate, simulations can be used for diagnostic purposes and used to support the value of some GOF plots. Examples of GOF plots that could be presented in the report, depending on situation, include (all are presented as Y vs. X):

- Observed Data versus Predicted Data (DV vs. PRED).

  A line of identity and a trend line should be included.

  The plot should preferably be provided in both linear and log scale.

- Observed Data versus Individual Predicted Data (DV vs. IPRED).

  A line of identity and a trend line should be included.

  The plot should preferably be provided in both linear and log scale.

- Weighted Residuals or Conditional Weighted Residuals versus Predicted Data (WRES or CWRES vs. PRED)

  A zero line and a trend line should be included.

- Weighted Residuals or Conditional Weighted Residuals versus Time (WRES or CWRES vs. TIME).

  A zero line and a trend line should be included. Time can be both Time After Dose (TAD) and continuous Time (time in the study).

- Absolute Individual Weighted Residuals versus Individual Predicted Data (IWRES vs. IPRED).

  A trend line should be included.

- A histogram and/or QQ plot of the Weighted Residuals.
- Observed (DV), Individual Predicted (IPRED) and Population Predicted (PRED) concentrations versus Time (overlayed and/or side by side).

The selection of GOF plots included in the report should be justified [20]. The report should include interpretation of the provided GOF plots. Obviously, other plots to support the selection of various aspects of the base model are possible. These should be included or substituted as needed to support the validity of different aspects of the base model. For plots other than those described herein, the report could include an accompanying note that informs the assessor what the key features in the plot are, and how any trends or lack of trend should be interpreted. It should be ensured that any lines of identity, zero lines or trend lines are clearly visible in all plots, which could be achieved by e.g. using colour in the plots. In the case of very large data sets, including only a randomly selected percentage of the data may increase the ability to detect trends in the plot. This plot could be provided in addition to the plot including all data.

If a structural model is selected that does not have the lowest objective function value, the reasons for accepting the simpler model with the higher objective function value should be clearly presented and justified (for example including graphics describing the difference or lack of difference in GOF).

Covariate selection

Plots generated to screen for potential covariate relationships should be provided in the report (for example, plots of the empirical Bayes estimates of the parameters versus potential covariates, or the empirical Bayes estimates of the etas versus potential covariates). The value of using empirical Bayes estimates should be presented, e.g. an assessment of the shrinkage of the individual estimates towards the population mean [21].

The covariate model building steps (e.g. both forward inclusion and/or backwards deletion) to illustrate covariates that are included in the final model and those that were tested but were not retained in the final model should be clearly presented in a separate run record. The criteria on which the decision was based, e.g. objective function values, should be outlined as well.

The results for the final covariate model should be presented in terms of parameter estimates and in graphical form. The values of the affected parameter at the extremes and/or the 5-95 percentiles of the covariate range could also be presented. If many covariates have been included in the final model it may be useful to perform some simulations to illustrate the effect of various covariate combinations for a series of different ‘typical’ subjects on, for example, AUC.

If a covariate, in the labelling, is claimed to have no effect, adequate and convincing support of such claim should be presented. For example, a confidence interval for the estimated effect should be provided, preferably obtained using methods that do not assume symmetrical distribution of the confidence interval, e.g. bootstrapping or log-likelihood profiling [9, 10, 11, 12]. A conclusion of no effect based solely upon inspection of graphical screening plots using empirical Bayes estimates of the parameters is usually not acceptable, as shrinkage of the individual estimates towards the population mean may hide true relationships [21].

Final Model

The final model should be clearly described and the parameter estimates for all parameters in the final model, together with their standard errors and/or confidence intervals should be presented. It should be stated to what extent inter-individual variability and inter-occasion variability are decreased by inclusion of covariates in the model. The fundamental GOF plots as defined for the base model should also be supplied. Consider also to present GOF plots for relevant sub-populations. Additional GOF plots for the final model could include:

- the distributions (e.g. histograms) of the empirical Bayes estimates of the parameters and/or eta,

- a scatter plot matrix of the empirical Bayes estimates of the parameters and/or etas
- plots of empirical Bayes estimates of etas versus the covariates in the final model
- individual plots that illustrate how well the model describes the data for any given subject

In case the final model does not include covariates (and is identical to the base model), the GOF plots provided for the base model can be referred to in the report. Titles should indicate that the plots are for both base and final models.

GOF plots for the base and final model could be given in parallel to present the improvement by covariate inclusion.

Evaluation of the effect of omitted data (outliers) should be presented according to the procedures planned to be taken for these data.

The NONMEM input and output files for the base and final models should be provided, preferably in an appendix. These files should also be provided electronically as text files.

Model evaluation

The outcome of the model evaluation procedures taken should be presented in a manner appropriate to demonstrate that the final model is robust and a sufficiently good description of the data so that the objective(s) of the analysis can be met.

Any simulations performed should be presented in detail making it possible to assess conclusion made based on it, for example the simulation to support a dosing recommendation in a specific sub-populations.

4.3.7 Discussion

The discussion of a population PK report should address how well the final model describes the data and the clinical relevance of any covariate influences. The discussion could also consider how well the results of the population PK analysis agree with previously obtained information. A discussion of how the results of the analysis will be used (e.g., to support labelling, individualize dosage, or define additional studies) could be provided. In case of a large number of drop-outs during the study, the report should include a discussion whether this may have affected the results of the analysis.

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