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DRAFT

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 PK analysis, in order to provide a level of details that will enable a secondary evaluation. 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 (background)

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 entire 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. In order for the information resulting from a population analysis to be useful during the regulatory assessment, the report should include sufficient detail to enable a secondary evaluation by a reviewer. 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 population report and the main components to be included in a report of a population PK analysis. The guideline does not provide guidance on how to conduct a population PK analysis, but rather provides guidance on how to present the results from such an analysis, in order to provide a level of detail which will enable a secondary evaluation. 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 and PK/PD studies.

The vast majority of population analyses received by the EU regulatory agencies have been carried out using nonlinear mixed effects modelling with the software NONMEM [1]. 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 paper to the software used in their particular analysis.

In essence this guideline is 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. *AAPS Journal*. 2005; 07(02): Article 45.

3. LEGAL BASIS

This guideline applies to all new Marketing Authorisation Applications for human medicinal products submitted in accordance with Art 8(3) of Directive 2001/83/EC as amended.

This guideline has to 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.

4. MAIN GUIDELINE TEXT

4.1 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 present:

- 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
- which structural models to be tested (if this has been decided)
- which covariates to be tested
- the criteria to be used for model building and inclusion of covariates (e.g. Objective function value, goodness of fit plots, standard error, interindividual variability, clinical relevance)
- the types of variability models to be tested
- the form of model evaluation/qualification/validation procedures to be used

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

4.2 Final Report sub-sections

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

4.2.1 Summary

The summary should provide an overall summary of the population PK study. It should include sufficient information on the context of the study and the main findings and conclusions of the population PK study.

4.2.2 Introduction

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

4.2.3 Objectives

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

4.2.4 Data

The report should briefly describe the study or studies from which the data included in the analysis originate. The report should further state how many subjects and how many data points per subject have been analyzed. Information regarding number of samples per visit should be given. In case there is a large range of number of samples per subject, a histogram of the distribution of the number of samples per subject and visit should be included. A histogram of the distribution of sample times should be provided. Plots of the raw data are very useful, and should be provided on linear and log-linear scale. Lines connecting the data points could be included for part of the subjects to visualise the data. If relevant, the type of data transformation used should be described and justified. If used, data

input checking procedures should be described as well. Data from internal or external validation datasets should be presented separately. Information regarding drop-outs during the study should be provided (number of drop-outs and time point in relation to PK sampling).

Summary statistics and histograms of the continuous covariates and frequencies of categorical covariates should be presented in the report. If relevant, this covariate data could be presented stratified over subpopulations or validation sets.

Handling of incomplete data should be described. For example not all subjects may have a full complement of covariate information. Other subjects may have missing dose and/or sample times. The consequences of missing data may be either imputation of the missing information or deletion of the affected data points and/or subjects. 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 as such 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. If the outliers are omitted from the analysis it is recommended that the final model should be rerun with the outlying data points re-included and any potential differences in parameters values discussed in the final report. Outliers should be specified in a separate appendix to the report, with all data available. Subjects removed from the analysis should be listed with relevant patient characteristics.

4.2.5 Methods

The methods section should describe the methods used and should include the same components as the analysis plan (even if there is some repetition). If, during the analysis, any deviations from the analysis plan occur, then these should be clearly described in the methods section of the report. This section should also include information regarding the bioanalytical methods used and the limit of quantification for each method. The choice of parametric or non-parametric analysis and the choice of estimation method should be stated and justified. Assumptions made during the analysis should be stated and briefly discussed. The level of statistical significance should have been defined prospectively in the analysis plan. The actual significance level obtained from the LRT (ΔOFV in NONMEM) could be markedly different from the nominal. Depending on which 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, which should be taken into account [2, 3]. The software and version used should be stated.

Basic (or structural) model

The basic population model is usually, but not always, a model with no covariates. The report should clearly present *a priori* information available regarding the potential structure of the model and any major decisions taken during the basic model development. The report should include an overview of the steps taken during model development (a run record) that, at a minimum, clearly describes the major decisions taken during the building of the basic 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.

It is not uncommon that an analysis commences before the final data set is available, or that a data set changes due to the omission or re-inclusion of outlying data points. 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.

A run record 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.

Covariate model

The covariates to be tested should have been pre-specified in the analysis plan. Any use of transformation of covariates with skewed distribution should be described. The correlation between covariates should be presented graphically.

The criteria for covariate selection (forward and backward) should be presented. It is recommended to use both statistical significance and clinical relevance (only effects larger than a certain pre-defined magnitude) in the process of covariate model building.

The covariate model building steps (both forward inclusion and 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 the run record. The criteria on which the decision was based, e.g. objective function values, should be outlined as well.

4.2.6 Results

Basic model

The parameter estimates should be presented in a table for all parameters in the basic model, together with their standard errors and/or confidence intervals. The forms of inter-subject, intra-subject and residual variability models should also be presented and supported by appropriate graphics. The value of different diagnostic graphics (goodness of fit (GOF) plots) is dependent on the situation (type of data; rich or sparse, type of estimation method etc. [7]). Simulations can be used for diagnostic purposes and can also be used to support the value of different GOF plots.

GOF plots should be presented for key stages during basic model development [4, 5]. 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.
- 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 Weighted Residuals or Conditional Weighted Residuals versus Predicted Data ($|$WRES$|$ or $|$CWRES$|$ vs PRED) and when relevant 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 [6].
- Observed (DV), Individual Predicted (IPRED) and Population Predicted (PRED) concentrations versus Time (overlayed).

The trend line used in e.g. DV vs PRED plots should preferably be a regression line, and in WRES plots preferably a smooth line. The selection of GOF plots included in the report should be justified. The report should include interpretation of the provided GOF plots. Obviously, other plots to support the selection of various aspects of the basic model are possible. These should be included or substituted as needed to support the validity of different aspects of the basic 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 model

Plots generated to screen for potential covariate relationships should be provided in the report (for example, plots of the posterior Bayes estimates of the parameters versus potential covariates, or the posterior Bayes estimates of the etas versus potential covariates). Any use of automatic or statistical methods for covariate selection (e.g. step-wise covariate model building procedures [8]) should be described.

The results for the final covariate model should be presented on terms of parameter estimates and in graphical form as far as possible. 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 is claimed to have no effect, the covariate should have been included and tested during covariate model building within the nonlinear mixed effects modelling procedure and preferably a confidence interval for the estimated effect should be provided. This confidence interval may be obtained from estimated standard errors, bootstrapping or log-likelihood profiling [8, 9]. A conclusion of no effect based solely upon inspection of graphical screening plots is usually not acceptable, because when the data are sparse, there is a risk of shrinkage of the individual estimates towards the population mean, which renders it very difficult to see any trends in such screening plots.

Final Model

The form of 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 (obtained from bootstrapping, log-likelihood profiling etc [8, 9]) 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 basic model should also be supplied. Additional GOF plots for the final model could include:

- the distributions (e.g. histograms) of the etas,
- a scatter plot of the eta correlation matrix,
- plots of etas versus the covariates in the final model (to ensure that the form of the covariate model is most appropriate) and
- individual plots that illustrate how well the model describes the data for any given subject.

These plots should also be provided in case the final model does not include covariates (and is identical to the basic model).

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

The NONMEM input and output files for the basic and final models should be provided, preferably in an appendix.

The model evaluation/qualification/validation (subsequently referred to as model evaluation) procedures taken should be presented in order to demonstrate that the final model is robust and is a sufficiently good description of the data so that the objective(s) of the analysis can be met. The model evaluation procedures may include different methods such as simply using the GOF plots and parameter estimates, visual predictive checks (plot comparing 95% prediction interval with observed data), bootstrapping or jack-knifing techniques, a posterior predictive check or external validation with

data not included in the current analysis. The amount and type of model evaluation procedures will depend upon the objective(s) of the model development. Model evaluation procedures to support an objective that is to basically 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. In the latter case a more rigorous procedures should be applied. Simulations should be described in detail, including description of the demographics (e.g. covariate distribution and variability) of the simulation data set. Any measures taken for evaluation of influential individuals should be described.

4.2.7 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.

DEFINITIONS

Nomenclature

GOF: Goodness of Fit

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

PRED: Predicted Data based on population parameter estimates

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

WRES: Weighted Residuals

CWRES: Weighted Residuals evaluated at individual conditional estimates

|WRES| : Absolute Weighted Residuals

|IWRES| : Absolute Individual Weighted Residuals

TAD: Time After Dose

QQ: Quantile-quantile

Eta: Difference between individual posterior Bayes estimate of the parameter and the typical population parameter estimate

FO: First Order methods implemented in NONMEM are based on first order Taylor series linearization of the predictions, with respect to the dependence of the parameters. The derivative of the function is evaluated at the typical value in the population.

FOCE: First Order Conditional Estimation method .The derivative is evaluated at the individual conditional estimate. The residual error magnitude is modeled as dependent on the population prediction.

INTER: When the residual error is heteroscedastic the residual error magnitude can be modeled as dependent on the individual prediction i.e., the interaction between interindividual variability and residual error is taken into account.

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

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.

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