A Guide for Reporting the Results of Population Pharmacokinetic Analyses: A Swedish Perspective

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ABSTRACT

Population pharmacokinetic analyses are frequently part of regulatory submissions and are mainly used to provide information on special populations (effects of age, renal impairment, etc) and drug-drug interactions. A varying standard of population analysis reports has been received at the Medical Products Agency in Sweden, some very good and some unassessable. In the latter case, it may be that it is a report of an inadequate analysis or may be a report of a perfectly acceptable analysis, but too little detail has been provided in the report for the conclusions reached to be properly assessed. A sufficient level of detail must be present in these reports in order for them to be assessable and to allow the conclusions reached to be incorporated into the summary of product characteristics. The report should specify the goal(s) of the analysis, describe in detail the origin and nature of the data, clearly describe the model-building process, include a range of goodness of fit (GOF) plots to support decisions made during the model-building process, and demonstrate that the final model is a good description of the data. The use of color in GOF plots is encouraged so that key features are easily visible. Covariate effects in the final model should be clearly presented and their clinical relevance discussed. In the case of many covariates 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.

KEYWORDS: population analysis reports, NONMEM, regulatory aspects

INTRODUCTION

The efficacy and safety of a new chemical entity (NCE) is generally characterized in phase III studies in a well-defined, fairly restricted patient population. The pharmacokinetic (PK) information submitted to the regulatory

agency is then used to generalize the safety and efficacy findings in the well-defined patient population to the entire patient population who may receive the NCE in question. Consequently, many PK and PK/pharmacodynamic (PK/PD) questions have to be answered during the course of assessing a NCE. Today, both population PK and PK/PD analyses are a regular part of NCE submissions and form one way in which a drug developer can choose to provide PK and PK/PD information to regulatory bodies for the NCE evaluation process. Currently, results from population analyses are most frequently used to support dosing recommendations for special populations (elderly, gender, renally impaired, etc) and for characterizing drug-drug interactions. In order for the information resulting from a population analysis to be useful during the regulatory assessment, 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 so the results and conclusions ensuing from the population analysis are valid. A varying standard of population analysis reports has been received at the Medical Products Agency (MPA) in Sweden. In the case of poor quality reports, it may be that it is a report of an inadequate analysis or may be a report of a perfectly acceptable analysis, but too little detail has been provided for a conclusion about the standard of the analysis to be drawn. The latter case is disturbing, because it will mean that valuable information resulting from the population analysis may be disregarded during the assessment process and may result in a more restricted summary of product characteristics (which is equivalent to the drug label in the United States) than had been submitted by the developer.

This article aims to set out what the MPA looks for when assessing a population PK analysis. It is hoped that providing this information will help those who write the reports to provide a sufficient level of detail. Some points made herein can certainly be generalized to reports of population PK/PD analyses, although that is not specifically covered within this article.

The vast majority of analyses received by the MPA have been conducted using the NONMEM software.¹ If other programs have been or are to be used, then it is hoped that

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the reader can, again, generalize the points made in this paper to the software used in their particular analysis.

ANALYSIS PLAN

There should be a prospectively written analysis plan for the population PK analysis. The analysis plan should be provided 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, attributable in part to the exploratory nature of some population analyses. However, the analysis plan should present the goal(s) of the analysis, a brief description of the study (or studies) that the data originate from, the nature of the data to be analyzed (how many subjects, rich or sparsely sampled), and the procedures for handling missing data and outlying data. The analysis plan should include information regarding the structural models to be tested (if this has been decided) and should also define the covariates to be tested and describe the criteria to be used for building covariate models. The form of model evaluation/qualification/validation procedures to be used in an analysis should also be defined in the analysis plan.

It is recognized that much of the detail that should be present in the analysis plan will be repeated in the body of the report of the population PK analysis, resulting in an overlap of information. However, from a regulatory perspective, there is rarely too much information or a problem if information is repeated.

FINAL REPORT SUBSECTIONS

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

Introduction

The introduction to the report of the population PK analysis should provide some background information about the drug to be analyzed and should clearly state the goal(s) of the analysis in question. An example of a goal 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 goals may include using the model to perform simulations based on the final model.

Methods

The methods section should describe the methods used and should include the same components as in the analysis plan. If, during the analysis, any deviations from the anal-

ysis plan occur, then these should be clearly described in the methods section of the report. The report methods section should also include information regarding the bio-analytical method(s) used and the limit of quantification for each method. Information regarding software and method (eg, for NONMEM, First Order (FO), or First Order Conditional Estimation (FOCE) should be given. Assumptions made during the analysis should be stated and briefly discussed. The data used in the analysis should be well described, as described next. The procedures for building the covariate model (both forward and backward steps) should be clearly presented.

Data

The report should briefly describe the study or studies that the data included in the analysis originate from. The report should additionally state how many subjects and how many data points per subject have been analyzed. It is possible that not all of the subjects in a given study have been included in the population PK analysis; in such a situation, the justification for omitting certain groups of subjects should be provided. Plots of the raw data are very useful. It is up to the discretion of the data analyst/report author to determine the most appropriate way to present such plots.

Incomplete data can be an issue in population PK analyses; for example, not all of the subjects may have a full complement of covariate information. Other subjects may have missing dose and/or sample times. The problem of missing data can be addressed by 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.

Outliers, which are defined as data points in the dataset that appear to be outside the norm, are another issue that may have to be dealt with during the course of a population PK analysis. 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 the procedures that were taken in handling the outliers. If the outliers are omitted from the analysis, then the MPA recommends that the final model be rerun with the outlying data points reincluded and any potential differences in parameter values discussed in the final report.

Run Record

The report should include a run record or equivalent document that, at a minimum, clearly describes the major decisions taken during the building of the basic population model. Run records documenting decisions made during the model building process are often part of population PK reports but frequently use abbreviations or codes that are

not interpretable by a regulatory assessor; thus, such codes or abbreviations should be avoided when possible; if not, provide a clear key for each table. The run record should also clearly present the covariate model building (both forward inclusion and backwards deletion) steps, because the regulatory assessor may frequently be interested in both covariates that are included in the final model and those that were tested but were not retained in the final model.

It is not uncommon that an analysis commences before a final data set is available or that a data set changes because of the omission or reinclusion 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.

A run record could include a brief but interpretable description of the run, the objective function value, and information regarding whether the model converged successfully. It helps the assessor if the run record also includes parameter estimates (for key runs) and, when needed, a comment about the run.

Basic Model

The basic population model is usually a model with no covariates, although this may not always be the case, because it could be necessary to include covariates on the absorption process in order for the basic model to be a good description of the data. Such covariates could include formulation and presence/absence of food.

The report should clearly present a priori information available regarding the potential structure of the model and any major decisions taken during the building of the basic model. The forms of intersubject, intrasubject, and residual variability models should also be presented and supported by appropriate graphics. The parameter estimates should be presented for all of the parameters in the basic model, together with their SEs and/or confidence intervals.

Goodness-of-fit (GOF) plots should be presented for key stages during basic model development. The fundamental GOF plots that should be presented in the report include the following (all are presented as X versus Y): (1) predicted data versus observed data (PRED versus DV; a line of identity and a “trend” line should be included), (2) PRED versus weighted residuals (WRES; zero line and a trend line should be included), and (3) time versus WRES (a zero line and a trend line should be included). Time can be both time after dose and continuous time (time in the study). Both plots are useful from a regulatory perspective. A plot of time after dose versus WRES is a useful diagnostic of how well the structural model describes the data. A plot of time versus WRES is also a useful diagnostic of

how well the structural model describes the data but can additionally highlight possible time dependencies in the PKs of the drug being analyzed.

Additional fundamental GOF plots that should be presented in the report include PRED versus absolute WRES. A trend line should be included. This plot enables the appropriateness of the residual error model to be assessed.

Also included is a histogram and/or Quantile plot of the WRES. The normal Quantile plot graphically compares the distribution of a given variable (WRES in this case) to the normal distribution. This plot is useful to evaluate whether the assumption made in NONMEM analyses of normally distributed WRES has been violated.

An additional plot that may be useful when the FOCE method has been used is the individual PRED versus DV. A line of identity and a trend line should be included. Other useful plots could be the time versus DV, individual PRED, and population PRED concentrations (overlaid).

Obviously, many other plots to support the selection of various aspects of the basic model are possible. As many of 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 of the plots, which could be achieved by using color in the plots. In the case of very large data sets, including only a randomly selected percentage of the data may increase the ability of the assessor to see if there are any trends in the plot. The NONMEM input and output file for the basic run should be provided, preferably in an appendix.

Inspection of the many NONMEM analyses received by the MPA has revealed that it is not always the structural model with the lowest objective function value that is selected as the basic model. In such cases, the reasons for accepting the simpler model with the higher objective function value should be clearly presented and justified. Furthermore, GOF plots should be presented for both competing models in such an instance during the development of the basic model.

Covariate Model

The covariates to be tested should have been prespecified in the analysis plan. Summary statistics and histograms of the continuous covariates and frequencies of categorical covariates should be presented in the report to enable the regulatory assessor to judge if the range/frequency and distribution of covariate values are sufficient to permit valid

conclusions to be drawn. The correlation between covariates should be presented graphically in an appropriate fashion. Plots generated to screen for potential covariate relationships should be provided in the report (eg, plots of potential covariates versus Bayesian parameter estimates).

The criteria for covariate selection (forward and backward) should be presented. The MPA encourages the use of both statistical and clinical relevance (only effects larger than a certain predefined magnitude) criteria in the process of covariate model building, especially if the analysis is to be used as part of a regulatory submission. It is acknowledged that analyses performed earlier in the drug development may be exploratory to aid internal company decision processes and, as such, may use different, possibly less strict criteria for covariate selection/retention.

The magnitude of the statistical criteria used in the analysis will depend on the method used within NONMEM (FO or FOCE),² the number of subjects,³ and the number of data points. Selection of the level of statistical significance should have been prospectively defined in the analysis plan.

The results for the final covariate model should be presented as the parameter estimates and in graphical form as far as possible. The values of the affected parameter at the extremes 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, area under the curve.

In order for a claim of no effect of a covariate to be acceptable, the potential covariate must have been included and tested during covariate model building within NONMEM and a confidence interval for the (lack of) effect provided. A conclusion of no effect based solely on the inspection of graphical screening plots is not acceptable because of the issue of shrinkage to the mean caused when the data are sparse and that renders it impossible to see any trends in such screening plots.

Drug-Drug Interactions

As stated in the introduction, many presently submitted population PK analyses are used to provide information about drug-drug interactions. Population PK analysis is not the preferred approach for providing information about potential drug-drug interactions from a regulatory assessors perspective. The reasons for this include the fact that the results usually only provide interaction information in 1 direction (the potential effect of other drugs on the drug that is the subject of the analysis), and there is rarely information available about the dosing times and schedules of administration for interacting drugs (potentially interacting

drugs are checked as present during a screening visit, but no information is collected to show that the drug was administered continuously during the whole study duration). Furthermore, the number of patients on one specific drug is often low, and drug-drug interactions are frequently tested as different types of groupings (by mechanism of interaction, PD mechanism of action, combination of different dose levels, and combination of different dosing schedules). Groupings could be acceptable provided that the grouping is mechanistically based and adequately justified. However, such groupings may easily result in underestimation of the magnitude of a drug-drug interaction. All of these reasons make it difficult to accept a conclusion of no interaction in a population PK analysis, especially if such an interaction has been suggested by appropriate in vitro studies. However, when there are sufficient subjects receiving the potentially interacting drug or group of drugs, then, according to the Committee for Medicinal Products for Human Use guideline on drug-drug interactions,⁴ population PK analysis can be used to highlight unsuspected interactions and to confirm the absence of noninteractions.

Final Model

The form of the final model should be clearly described, and the parameter estimates for all of the parameters in the final model, together with their SEs and/or confidence intervals, should be presented. 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 of the η s, a scatter plot of the η correlation matrix, plots of η s 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. The NONMEM input and output file for the final model should be provided, preferably in an appendix.

The model evaluation/qualification/validation (subsequently referred to as model evaluation) procedures taken should be presented to demonstrate that the final model is a sufficiently good description of the data so that the goal(s) of the analysis can be met. Such model evaluation procedures may include simply using the GOF plots and parameter estimates, data splitting, bootstrapping or jackknifing techniques, or a posterior predictive check. The amount and type of model evaluation procedures will depend on the goal(s) of the analysis. Model evaluation procedures to support a goal that is basically to describe the data in hand and evaluate potential covariate effects could be simpler than those needed if the final model is to be used to perform simulations. In the latter case, more rigorous procedures should be applied.

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. It is the experience of the MPA that, for some submitted analyses, the parameter estimates of some final models may differ considerably from results obtained from other studies, indicating detection of previously unknown influences (eg, time dependency) or gross model misspecification. Another example that has been observed in the case of parameter estimates of final models differing considerably from results obtained from other studies is that of not recognizing when flip-flop situations have occurred.

EXAMPLE(S)

The examples given below highlight the role of population PK within the regulatory assessment of 3 different drugs approved in the European Union through the centralized procedure. Results from population PK analyses are often used in conjunction with specific studies in special populations and drug-drug interaction studies in the assessment of PK in these populations. In some cases, the complete information is derived from population analyses alone. Fuzeon (enfuvirtide), indicated for the treatment of HIV, is such an example. Given the indication for a fairly restricted population when it comes to age distribution and patients with renal and hepatic impairment, conclusions regarding PK in elderly (>67 years), severe renal impairment (glomerular filtration rate [GFR] < 35) and hepatic impairment could not be drawn because of a lack of data. In a population PK analysis, gender and weight were found to influence clearance (clearance 20% lower in women than males irrespective of weight, and clearance increased with increased body weight irrespective of gender; 20% higher in a 100-kg and 20% lower in a 40-kg patient relative to a 70 kg reference patient). However, these changes were of limited clinical relevance, and no dose adjustment was warranted.

The results from population PK analyses are more commonly presented as a description of the covariate effects (or lack of effect) in the PK section of the summary of product characteristics than as specific dosage recommendations. Caspofungin, however, is an example where a drug-drug interaction identified in the population PK analysis resulted in a specific recommendation of using an increased dose during concomitant administration of drugs that induce metabolic enzymes. Also, the recommendation of using an increased dose of caspofungin in patients weighing <80 kg was based on the population PK analysis. Another example is Arixtra (fondaparinux). Dosage recom-

mendations for the use of Arixtra in patients with renal impairment were based on a population PK analysis and subsequent simulations conducted by the company on a request from the regulatory authorities. The resulting data supported a reduced dose in patients with moderate renal impairment and a contraindication in patients with severe renal impairment.

CONCLUSION

The MPA encourages the submission of high-quality population PK analyses to support the regulatory assessment process. Such analyses that make use of both rich and sparse concentration data ensure that as much information as possible is extracted from all of the collected data.

In the future, it is envisaged that electronic submissions will allow the reports of population PK analyses to contain many more graphics, which will facilitate the assessment of whether the model is a good description of the data. The regulatory assessor will then be able to select which graphics to look at during the course of the assessment process.

The quality of reports of population PK analysis received by the MPA has been variable. It is hoped that the information presented in this article will help authors of population PK reports to include a sufficient level of detail in their reports so that these reports can be assessed by the regulators. This, in turn, will help ensure that valuable results from such analyses are not ignored, can form part of the regulatory assessment, and can contribute to the optimal use of the drug in each individual patient.

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