EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Modelling and Simulation examples that failed to meet regulator's expectations

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Disclaimer

The views expressed in this presentation are the views of some experts from some of the European regulatory agencies and EMA, but do not necessarily reflect the official EMA position or that of its committees or working parties.

Overview

What are regulators' expectations?

Guideline on reporting population PK analyses

Examples from recent applications

What are regulators' expectations?

- M&S encouraged in several guidelines
- No guideline on how to do M&S
- Guideline on reporting results of population PK analyses (CHMP/EWP/185990/06)
  - describes expectations
    - analysis plan
    - report

Guideline on reporting population PK analyses – Regulatory expectations

- The report should 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.
- 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.

Guideline on reporting population PK analyses – Regulatory expectations: Analysis plan

- Prospectively written, presented in report appendix
- Components
  - Objectives of analysis
  - Identification and justification of assumptions
  - Description of studies and nature of data (including omissions)
  - Procedures for handling missing data and outliers
  - General modelling aspects (software, estimation methods, diagnostics, model evaluation/validation/qualification procedures etc)
  - Details of model building (general procedure, models to be evaluated, prespecification of covariates to be evaluated and the algorithm to be used for covariate model building)

Guideline on reporting population PK analyses – Regulatory expectations: Report

- Introduction – put the analysis in perspective of other clinical data
- Objectives of analysis
- Description of data
- Methods – deviations from analysis plan clearly stated
- Results
  - Detailed description of the raw data tabulated and graphically including covaraites, missing data and outliers
  - Description of key modelling results including detailed description of covariate selection together with goodness-of-fit information and model qualification

Guideline on reporting population PK analyses – Regulatory expectations: Report

Discussion

- Companies should critically assess the analyses
  - How well does the final model describe the data?
  - What are the limitations of the analysis?
  - Assumptions should be discussed and justified
  - What is the clinical relevance of covariate influences?
  - Are covariate effects biologically plausible?
  - How well do the results agree with previously obtained information?
  - How will the results of the analysis be used (e.g support labelling, for dose individualisation, for optimising future studies)?

Guideline on reporting population PK analyses

- The amount and type of model evaluation/qualification 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.

Guideline on reporting population PK analyses

- The report should contain justification for the model evaluation procedures and tools used for the specific evaluation.
- 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.

Guideline on reporting population PK analyses

- Guideline adopted in June 2007
- "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."

Level of assessment depends on importance of analysis

- PopPK only source for evaluation of intrinsic factors or used for dose adjustment in sub-groups
  - → high level of scrutiny
- other data available to support evaluation of intrinsic factors and potential dose adjustments in sub-groups
  - → popPK lower importance
  - → lower level of scrutiny

Reasons for failing expectations

- Deficiencies in
  - quality of report
    - insufficiently detailed
    - missing information
    - very detailed but contains irrelevant information and lacks important information
  - quality of analysis
  - underlying data
- Criticism of conclusions drawn

Example A

Oncology product, cytotoxic agent

- BSA-based dosing applied in clinical studies
- Dose reduction based on safety

No specific studies evaluating intrinsic or extrinsic factors

Effects of intrinsic factors evaluated in

- integrated evaluation of non-compartmental data
- population PK analysis of 2 phase II studies, dated Feb 2009

Example A (cont)

Population PK analysis

- Data from 2 phase II studies, n=154
- Objectives:
  - To estimate POPPK parameters including inter-individual and residual variability in cancer patients.
  - To estimate the covariate effects
- Company used data from the PopPK together with integrated evaluation of non-compartmental data to evaluate effects of intrinsic factors on PK

Example A – assessors comments

Exclusion of data:

- Exclusion of data below the quantification limit may lead to biased parameter estimates if the proportion deleted comprises a considerable part of the data. There is no information available on the number of samples excluded for this reason.
- For the samples excluded due to being unrealistically high, a reasonable approach would have been to re-estimate the final model with these samples included to judge how they would affect the model estimates.

Example A – assessors comments

Use of individual empirical Bayes esimates:

- There are several plots employing the individual empirical Bayes estimates of the parameters. The quality of these plots are low since the shrinkage toward the typical population values were rather high for all parameters (ranged from 29% for CL to 65% for Q3), and conclusions made on the basis of graphics are uncertain and inconclusive.

Model misspecification

- high concentrations have not been adequately captured, indicating model misspecification.

Example A – assessors comments

Model development

- Weight: models including body size measures were introduced initially, but did not result in a reduction of the objective function value. Either these models are local minima or otherwise these results point toward that body size is not an important predictor for the systemic exposure. Thus, one may question the body weight based dosing.

Assessor's conclusion

- The confidence for this model is at present low and if the model will be used in any responses to questions made by the Rapporteur, the issues identified in this assessment need to be addressed properly and the models need probably re-development

Example A – regulator's concerns

- Weak support from data for relation between CL and BSA
- Risk for underdosing low weight patients and overdosing high weight patients with BSA based dosing
- Question raised
  - *The non-compartmental covariate analysis indicated no relationship between drug A clearance and body weight or body surface area, and the results concerning this aspect were inconclusive in the population PK analysis. Therefore, the Applicant should discuss the risk for under- and overdosing in low-weight and high-weigh patients, respectively, at the proposed dosing based on body surface area, and how to ensure an adequate dose also in the low and high BSA extremes. Please note, that if the response to this question would involve the use of the population PK model, the issues regarding this model identified in the Day 80 Critical Assessment Report on Human Pharmacokinetics need to be addressed properly*
- ⇒ Example of deficiency in quality of analysis

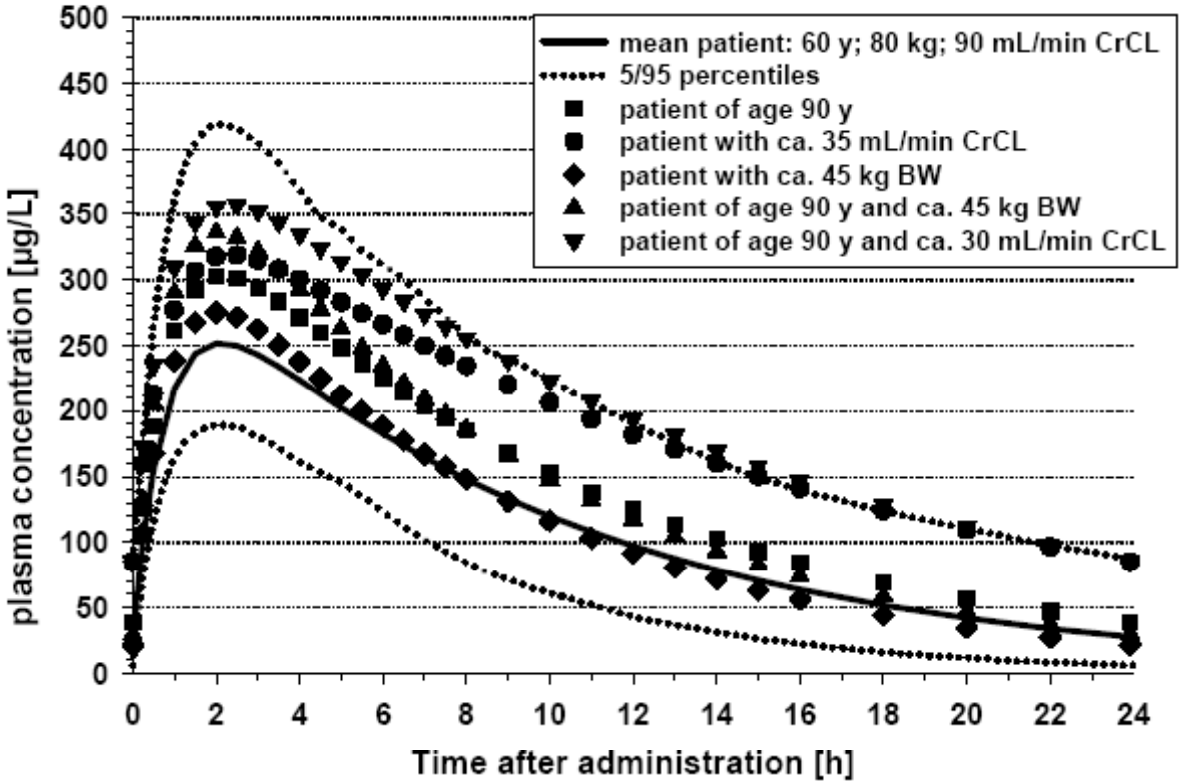
Example B

- Population PK analysis, report dated May 2010
  - Data from 2 phase II studies, 870 patients, 4634 conc
- Objectives:
  - To define structural PK and PK/PD models
  - To characterize the inter- and intra-individual variability
- Identified covariates
  - Age and serum creatinine on CL/F
  - Age and Lean body mass on V/F

Example B – company conclusions

- Company used data from the PopPK together with other data to evaluate effects of intrinsic factors on PK
- Company conclusions
  - Covariates effects seem to be moderate and within the observed variability of plasma-concentration time profiles of phase III patients.
  - The effects are in line with the results from the separate, dedicated clinical-pharmacological studies specifically investigating the influence of these covariates.

Population mean and 5/95 percentiles: posthoc prediction of 20 mg qd at steady-state



Example B – assessors comments

- GoF plots
  - high concentrations not well described
    CWRES vs time after dose etc not provided (as expected when using FOCEI)
- Shrinkage not provided
- VPCs
  - did not include percentiles (5th, 50th, 95th) of observed data
  - were not stratified for covariates of importance
- *If the model* will be used for simulations in response to questions posed, the applicant would need to provide improved information on predictive properties

Example B – assessors comments (cont)

- Simulations
  - Appropriate simulations should include also variability in the different subgroups and the 90% prediction interval of the sub-group be compared to the 90% prediction interval of the overall population.
  - The evaluation is insufficient to claim that no dose adjustment is needed in different sub-groups.

Example B – company response and assessor's conclusions

- CWRES plots, shrinkage, prediction-corrected visual predictive check were acceptable
  - The model was considered to describe the data well
- discussion on effects of age and renal function with comparison to results from dedicated clin pharm studies
  - Dose adjustment in moderate and severe renal impairment
- ⇒ Example of deficiency in quality of report and criticism of conclusions drawn

Example C

- Population PK analysis, report dated Oct 2010
  - Data from 2 phase I studies and 3 phase III studies, 1223 patients
- Objectives:
  - characterize the systemic exposures in patients, identify covariates, and quantify sources of variability
- Used to evaluate effects of intrinsic factors on PK and inform content of SPC
  - Covariates identified in PK analysis: creatinine clearance and gender on CL/F, body weight on Vc/F

Example C – assessor's comments

Covariate distribution

- Renal function: patients had mainly normal renal function or mild renal impairment. Thus, the effect of renal function may not be adequately characterised
- Age range does not include truly elderly subjects, 95th percentile was 71 years

Example C – assessor's comments

Model evaluation/qualification

- The visual predictive check is difficult to interpret since only the percentiles of the simulated data are included in the plots. An improved presentations of these plots would have been appreciated including the 5th, 50th and 95th percentiles for the observed data and the confidence intervals for the prediction intervals (5th, 50th and 95th) of the simulated data.
- VPCs stratified by dose as done is appreciated, but the applicant may also consider other stratification for sub-populations of interest or alternatively apply population prediction corrected visual predictive check

Use of empirical Bayes estimates

- To rely on empirical Bayes estimates obtained for the individuals included in the study, the shrinkage toward the typical population values should be calculated and presented.

Example C – assessors conclusion

- Effect of intrinsic factors was evaluated also in specific phase I studies and in a pooled analysis of Phase I data (n=431)
- The popPK analysis considered supportive
- Therefore, no questions raised on popPK analysis despite identified shortcomings
- SPC revised

- ⇒ Example of deficiency in quality of report, underlying data and conclusions drawn

Example D

- Indication: Replacement therapy
- New modified release formulation
- Current treatment
  - immediate release product b.i.d. or t.i.d
  - dose titrated based on response

Example D - PK data in patients

- Clinical study with sequential cross-over design
  - dose individually titrated based on clinical response (using IR formulation) resulting in varying clinical doses; 20, 25, 30, 40 mg daily
  - switch to corresponding daily dose of MR formulation
- AUC similar at 25, 30 and 40 mg dose levels
- Population PK analysis
  - Objective
    - describe PK
    - simulate other treatment regimens
    - develop dosing nomograms based on patient weight or concentration
- Data used to support dosing recommendations

Example D – assessor's concerns

- Population PK analysis
  - nonlinear exposure was modelled as nonlinear bioavailability
    - decrease in F with increased dose
- Study design
  - titration of dose based on clinical response
    - resulting in similar AUC in dose range 25-40 mg
  - patients with higher oral clearance likely titrated to higher dose levels
    - not taken into account in model
- Conclusion drawn
  - estimated dose – biovailability relationship not reliable
  - simulations of increased doses unreliable
  - dosing nomograms based on this model not accepted
- ⇒ Example of deficiencies in underlying data

Example of comments for other products

- Shrinkage not reported
- VPCs
  - 5th, 50th 95th percentiles of observed data missing
  - Confidence intervals around model predictions (eg. predicted 5th, 50th and 95th percentiles) are missing
  - not stratified for important covariates
- Limitations in data
  - Range and distribution of covariates may be insufficient, e.g. age, renal function, race
  - Insufficient information regarding dose levels and duration of dosing for concomitantly administered drugs

Final comments

- Many PopPK analyses are of good quality
- Several reasons for "failing" regulator's expectations
  - Often related to insufficient quality of report
  - Handled by questions raised
- Better quality of analyses and reports would make the review process more efficient
  - Assessment of analysis can be made based on report provided with MAA
  - No need for questions
  - Less burden on companies and regulatory authorities

Recommendations

- Reports should be sufficiently detailed
  - include relevant components
  - model qualification very important
  - enable a secondary evaluation by a regulatory assessor
- Companies should critically assess the analyses
  - How well does the final model describe the data?
  - What are the limitations of the analysis?
  - Are assumptions discussed and justified?
  - What is the clinical relevance of covariate influences?
  - How well do the results agree with previously obtained information?
  - How will the results of the analysis be used (e.g support labelling, for dose individualisation, for optimising future studies)?