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# Pharmacometric Analysis Plans & Technical Reports

## Effectively Communicating Pharmacometric Analysis Results & Implications

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# Overview of the Presentation

- The need for pharmacometric data analysis plans
- DAP content recommendations
- Various perspectives on analysis plans and reporting of pharmacometric work
- Pharmacometric technical report content
- How do DAPs, FTRs, and the issues surrounding communication of pharmacometric analyses impact the evolution and acceptance of model-based development paradigms?
- What more is needed?

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# The Issue in Context

- Population-based approaches and the use of M&S are exploratory, aren't they?
- What I am going to do all depends on the data anyway
- CPI, labeling statements, special populations, use of models to support simulations which in turn support dose selection and study design, etc.
- Are there right methods in certain circumstances, generally accepted standards, measures of acceptability for models, etc.?

# Art vs. Science Continuum

- The contextual nature of this argument
- Art implies “beauty is in the eyes of the beholder” and if this so, then, by definition, standards and rules cannot exist allowing for an objective characterization of these results
- Science end of this spectrum doesn’t mean there isn’t a role for experience and instinct

# Barriers to Model-Based Development

- Inability to frame the right question, identify, and/or manage the underlying assumptions and uncertainty, and willingness to iterate and accept the changing nature of the problem

  (Chien et al., AAPS J 2005; 7 (3) Article 55)

- Statistics versus pharmacometrics

  (Commentary – Brian Smith, AAPS J 2005; 7 (3) Article 65)

- Lack of early interaction with regulators, lack of collaboration and communication

  (Bhattaram et al., AAPS J 2005; 7 (3) Article 51)

# Analysis Planning: Basic Principles

- Development of a DAP prior to data lock, unblinding of the treatment codes, and/or analysis commencement is perceived to be good statistical practice to minimize potential bias and lend credibility to findings
- Consistency, repeatability of analyses
- Enough detail should be present in the DAP such that two independent analysts following the plan would come to essentially the same bottom-line conclusions

# Relevant Guidance per the ICH

- Per ICH guidelines on “Statistical Principles for Clinical Trials”
  - SAP should be a separate document from the protocol, drafted after protocol finalization
  - Possibly updated as a result of blind data review
  - Finalized before breaking the blind
  - Records should be kept of when the SAP was finalized and when the blind was broken

# EMEA CHMP Draft Guideline

- "Guideline on Reporting the Results of Population Pharmacokinetic Analyses"
  - Consultation/comment period: 06/29/2006 – 01/01/2007
  - To detail what European regulatory assessors look for in a population report – NOT how to conduct
  - "It is … vital that every assumption and decision made during model development is made clear for the assessor."

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# EMEA CHMP Draft Guideline (cont'd.)

- A fair amount of detail regarding recommended characterization of the data
- Methods should detail deviations from the plan
- A run record: overview of steps and description of major decisions

# Analysis Plan Content

- Purpose of the analysis
  - Intended use for the model and context for analysis in the development program
- Objectives
- Study design(s)
- Characterization of data to be modeled
- Data editing rules
  - Missing data
  - Outliers

# Analysis Plan Content

- Planned EDA and implications: feasibility of analysis plan
- Structural models to be tested, fixed & random effects
  - Evaluation of assumption verification
  - Alternative methods/models to be tested if assumptions are not met
- Covariate analyses
  - List of covariates to be considered
  - Methodology for statistical selection
  - Functional forms for sub-models
  - Which covariates on which parameters?
- Model refinement, evaluation, qualification, and/or validation planned and justification for method

# Analysis Plan Content

- Assumptions – stated implicitly or explicitly?
  - Karlsson, Jonsson, Wiltse, and Wade, JPB: 26(2) 1998.
    - Violations of assumptions may lead to inappropriate conclusions; routinely, only a few are stated and justified in reporting
    - 22 standard assumptions in various categories: method, data quality, structural sub-model, covariate sub-model(s), statistical sub-models, modeling process
      - Justification through experience, graphics, and/or modeling
    - Some well recognized and generally included for (attempted) completeness

# Standard Assumptions

[Karlsson et al., JPB: 26(2) 1998]

- Method
  - FO approximation
- Data quality
  - Dosing history
  - Sampling times
  - Covariate values
  - Data exclusions
  - Data imputations
- Structural sub-model
  - Adequate structural model
  - Same model for all subjects
- Covariate sub-model(s)
  - Adequate strategy
  - Appropriate functional forms
  - No interactions
- Statistical sub-models
  - $\eta$ and $\kappa$ normally dist
  - Variance models appropriate
  - Correlation between $\eta$ and $\kappa$
  - No interaction between $\eta$ and $\kappa$
  - IOV random
  - $\varepsilon$ dist symmetric w/ mean 0
  - $\varepsilon$ independent
  - $\varepsilon$ identically distributed
- Modeling process
  - Global minimum found
  - No influencing software bugs
  - Model can generate real world-like data

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# Assumption Verification

[Karlsson et al., JPB: 26(2) 1998]

- How rigorous do we need to be in verifying the appropriateness of assumptions?
- An extensive check cannot be expected to be routinely carried out; most will be inspected during model building
- However, if the model is to be used for clinical trial simulations:
  - Variability models and related assumptions may be most critical

# Typical Analysis Plan Pitfalls

- Lack of detail re: data editing, implications of missing data, rules for conmed flags, outliers
- Lack of EDA specifications
- Covariate analyses
  - Which factors on which parameters? Rationale for laundry list
  - How will correlated (if defined) covariates be handled?
  - How will clinically significant covariate effects be identified?
- What type, if any, of model qualification will be performed? What is the justification for the model qualification method selection?
- Internal inconsistencies

# Analysis Planning: Benefits

- Alignment/agreement on analysis which will support eventual claims
- Layout of workscope for resource planning, life cycle mgmt, and development program timelines
- A reduction in time to complete M&S projects, prepare summary reports, and therefore, a reduction in time to submission because programming and writing can begin earlier
- Consideration of possible explanations for findings and interpretation prior to availability of final results
- Improved accuracy and consistency of analyses and reports

# PM Analysis Plan Stakeholders: Who *Isn't* the Audience?

- Primary and supporting pharmacometricians (internal or external) in addition to supervisory/consulting pharmacometricians
- Regulators
- Programmers and analysts
- Statisticians
- Clinical scientists
- Medical writers
- Other team members
- Cross-functional collaboration on DAPs can eliminate redundancy and duplication of effort, encourage synergies

# DAP: Pharmacometrician Stakeholder

- The mere act of pre-specifying, in detail, the major analysis steps and contingencies will inevitably result in a discovery of some sort
- As an independent reviewer, the more thorough the plan, the higher the quality I anticipate from the analysis
  - Where there's smoke, there's fire: works both ways
- On the other hand, if there is clearly a major disconnect between the plan and the eventual analysis (FTR) and no reference to the nature and cause of this discrepancy, the analysis is potentially cast in an even worse light (e.g., compliance with a QMS)

# DAP: Pharmacometrician Stakeholder

- Since some issues are philosophical and subjective regarding which methods are better or preferable in certain circumstances, a philosophical disagreement should be able to co-exist with a reasonably high quality plan and analysis
  - I don't agree with what was done, but I see why it was done this way and the selection of the method is supported

# DAP: Regulatory Stakeholder

- Agencies are requesting preparation and review of DAPs, sometimes before analysis and at least as an appendix to the report
  - If prior to analysis, this review may result in a recommendation or discussion of M&S strategy or methodology *before* it's too late to make a correction
- Obtaining *a priori* agreement with reviewers on the plan will clarify expectations and (hopefully) reduce potential questions
- The mere existence of a DAP implies that the strategy for how M&S are to be utilized (and perhaps why and when) has been considered

# DAP: Programmer/Analyst Stakeholder

- Sharing of the big picture understanding of the overall goals and objectives allows for synergy
- A thorough DAP provides insight into what data items are more/less important
- Data editing rules can be improved with programmer involvement
- Repeated involvement/exposure may result in opportunities for standardization of code/processes

# DAP: Statistician Stakeholder

- Pharmaceutical statisticians don't believe that Columbus discovered America
- Tension between traditional statistical analyses and M&S efforts
  - Exploratory nature of M&S
  - Reliance on mechanistic models (Smith commentary)
  - Inference (and Bayesian thinking) versus empiricism
  - Pre-specification of population to be used and outlier criteria
    - Agreement between model-based findings and traditional findings
    - Territorial implications

# DAP: Clinical Scientist Stakeholder

- Model emphasis is better placed on parsimony and not perfection and/or chasing zebras
- Covariate selection: opportunity to get input on what matters
- More recent references to clinical relevance of covariate effects, but input here is critical and this input must be obtained in a way that facilitates collaboration
  - Too much emphasis on “pick a number” approach may not be productive
  - Need to facilitate understanding in both directions

# DAP: Clinical Scientist Stakeholder

- Drug-disease model development
  - Talk to a clinical disease specialist about time-course and knowledge of factors which might influence response

(Holford, 1999:www.ecpag.org/presentations/1999/presentations1/sld001.htm)

- Simulation planning should only be done with clinical input
  - Patient population characteristics and expectations about compliance, drop-outs, etc.
  - Design-wise, what is reasonable to simulate and what is completely out of the question?

# DAP: Medical Writing Stakeholder

- Early consideration of the message based on anticipated results
- Understanding of what will come from this type of analysis
  - What types of statements can be made (even before results are known)
  - What types of statements cannot be made (perhaps based on limitations of the data or the methodology)

  (McPhail et al., DIJ, vol 40, pp. 197-202, 2006.)

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# Analysis Planning: Team Benefits

- If well-constructed, the DAP will elucidate the major decision points in the analysis and some factors to be considered in making these decisions
  - These decision points then become appropriate stopping places to review, re-group, and get agreement on decisions *before* proceeding

# Pharmacometric FTR Content

- Typical report sections: Summary, Intro, Objectives, Data, Methods, Results, Discussion, Implications
- Rationale for the analysis and how it fits in with the current knowledgebase, development program, etc.
  - Why develop a model?
  - What is its intended use?
- Flowchart of the model building steps

  (FDA Guidance, Population PK 1999)
- Application of the model, use in making labeling statements, learn-confirm cycle, use in planned simulations, etc.

# Pharmacometric FTR Content

- Include the DAP (pop PK study protocol, per FDA Guidance) as an appendix to the report
- Include the un-edited control stream and output from base and final models
- Reference to discrepancies between the plan and the results
- Detailed listings of outliers and data edits
- Plots of the raw data, both as part of EDA and in support of main conclusions
- How many/which of the thousands of plots to include?

# Pharmacometric FTR Pitfalls

- There is a varying standard for reporting of pharmacometric analyses
  - Some reports of perfectly acceptable analyses provide far too little detail for the conclusions to be properly assessed

    (Wade et al., AAPS J 2005; 7 (2) Article 45)
- Only the base and final models are described in any detail, with little or no reference to other attempts to improve or investigate potential issues
- If there is a change in the methods from the DAP, the change should be justified, approved, and fully documented in the report

  (PSI Professional Standards Working Party, DIJ, vol 28, pp. 615-27; 1994.)

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# Pharmacometric FTR Pitfalls

- Audience is assumed to be an expert pharmacometrician with extensive experience using NONMEM or another software and a good grasp on the jargon and the relevant literature
- No support or evidence is provided for the more subjective claims or decision points

# PMTR: Medical Writing Perspective

- M&S is a black box with too much jargon (Greek symbols, acronyms, NONMEM-ese, etc.) and an over-emphasis on mathematical and statistical issues, estimation methods, etc.
- Only with collaboration and open communication can precise wording can be crafted to express a complicated modeling issue elegantly
- If the right message is found, the ultimate implications may be realized

# PMTR: Clinical Perspective

- If the findings are not expressed in such a way that the intended user of the knowledge understands, then has this really impacted the development program?
  - What can we learn from this model? How can it be used?
  - If there are implications for dosing regimen selection, can the strategy be simple and if not, what is sacrificed?
  - What really is the bottom line?
    - PK – dose selection and justification of strategy
    - PK/PD – intended use and expectations
  - Why does it matter if a CCV or additive plus CCV error model was used for RV?

# Recommendations

- Because timing is so critical, strategic and early planning is essential to successful implementation
  - Integrate analysis planning process and the development of analysis plan documents into timelines
  - Plan for and seek input and approval from appropriate stakeholders
- Paramount in both analysis plan development and later reporting of pharmacometric analyses (PK/PD M&S) is an explicit statement of the highest level purpose/intended use
  - This should guide the selection of methods in addition to the consideration of appropriate techniques and, if known, the assumptions requiring verification

# What more is needed? A Systematic Plan

- More evaluation of assumptions and further simulation studies exploring the impact of violations of these
  - What is the penalty for violation of an assumption?
  - Efficient and customized tools needed (Karlsson et al.)
- But we could be doing simulations forever
  - So, we need a systematic approach to developing a plan for these evaluations
- In the absence of simulation studies designed to answer a particular question, more discussion and consensus regarding what the standards are, or how to think about what the standards should be

# What more is needed? A Systematic Plan (cont'd.)

- How to compare the various methods now available and currently under development or emerging and what are the criteria for method selection?
  - What is the basis for comparison?
    - Intended use for model, data available and quality of data, knowledge of relevant issues, including mechanism, time available for analysis, future opportunities for iterations, potential for exploration of the sensitivity of the model to assumptions, etc.
  - When and where should each method be considered for application?

# What more is needed? Measures of acceptability

- Criteria for acceptance of a model as part of the critical path / a basis for evaluation of the quality of a model
  - Convergence characteristics, success of $COV step, # significant digits obtained, quantification of stability, evaluation of PRDERR output, need for NOABORT option, etc.
  - Value and interpretation of goodness of fit and other diagnostics
    - Precision of FPEs, interpretation of plots, reduction/increase in random effect estimates, etc.
- Simulations/PPC: how many replications is enough?
  - How to assess quality of outcome?
  - How to deal with unsuccessful runs?

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# Conclusions: Analysis Planning

- The development of sufficiently detailed and complete data analysis plans describing pharmacometric analyses is complicated, but essential
- In recognition of the fact that there are many, many decision points during dataset creation and pharmacometric analyses, each of which has the potential to influence the outcome, the preparation of a DAP provides an opportunity to recognize and state a plan for dealing with at least the major ones

# Conclusions: Reporting & Communication of Results

- Clear and effective communication of pharmacometric analyses, including methodology and implications, is required for the acceptance and continued evolution of these methods
- This evolution and the exponentially increasing usage of pharmacometric analyses for critical path decision-making will put ever more stress on pharmacometricians
  - Need for continued multi-disciplinary input and perspectives on M&S

# Conclusions: A Call for Standards

- The development of accepted (technical) standards for M&S is a critical step in the successful transition to a model-based development paradigm
  - Need for more and more thorough explorations of M&S issues
  - Need for better understanding and clarification of underlying assumptions
  - Need for clarity on consequences of these not being met
  - Need for development of and consensus on measures of acceptability for models

# Thank You

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