Streamlining the PK/PD data transfer process — 1 year later

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This paper is a follow-up to a paper in issue 3.1 of the *Pharmaceutical Programming Journal* where we provided an overview of the pharmacokinetics and pharmacodynamics (PK/PD) component of clinical trials as well as an initiative taken by the Biostatistics and Drug Metabolism and Pharmacokinetics (DMPK) departments at Biogen IDEC to develop more efficient processes for the handling and flow of PK/PD data in clinical trials. In this paper we describe the implementation of procedures developed in the initiative and the impact they have had on several clinical programs at Biogen. We have concluded that having a formal PK/PD data flow process has given the DMPK Scientists a place at the table when designing and conducting clinical trials as well as creating efficiencies for all involved functions.

Keywords: Pharmacokinetics, Pharmacodynamics, Modeling, Data Flow, NonMem, WinNonlin

Introduction

In issue 3.1 of the *Pharmaceutical Programming Journal*, we provided an overview of the pharmacokinetics/pharmacodynamics (PK/PD) component of clinical trials, as well as an outline showing how we planned to define and roll out a standard process to transfer data between statistical programmers and PK scientists.[1] This was a work in progress at the time. We have since developed a process and implemented it at Biogen Idec. The purpose of this paper is to show some more detail on the process, as well as give an update on how it is working at the company.

Background

As stated in the original article, three main motivations drove evaluation and revision of the data flow processes at Biogen Idec: transparency, quality, and support of the newer modeling and simulation (M&S) paradigm. First, by charting, documenting, and revising the necessarily complicated data flow practices of drug development, areas for modification and change could be identified that would increase efficiencies and reduce risks for delays in data readiness. This increases corporate transparency and provides a method to unify functional areas through common knowledge of how they worked together.

The paper described an initiative taken by the Biostatistics and Drug Metabolism and Pharmacokinetics (DMPK) departments within Biogen Idec to re-evaluate current practices and develop efficient processes for the handling and flow of PK/PD data in clinical trials that proactively supports model-based supported drug development. While we did not describe changes in trial design that would optimize data collection to support M&S, this is a critical element and readers are encouraged to consider these sorts of modifications for M&S support optimization. We described the prior process and explained how the new process was developed for building a more efficient PK/PD data flow across departments that supports timely M&S activities.

Starting a New Process

The new data flow process that was developed in the initiative described in the original paper has been fully implemented and has gained wide acceptance among members of all functional areas. The core components are that we have more involvement of PK scientists in study teams and all PK/PD analyses, whether traditional early stage PK/PD analysis using WinNonlin or M&S using NONMEM, is supported by a statistical programmer. All data flows through the statistical programmer and standard data structures and processes are used at all stages.

Training and communication have been the key to gaining such a high level of acceptance and implementation. All members of the Biostatistics and DMPK departments have been formally trained in the process and presentations have been given to members of several other departments which participate as members of study teams.

First Through the Gate

Scientists in our DMPK group have performed extensive modeling for an oncology drug program

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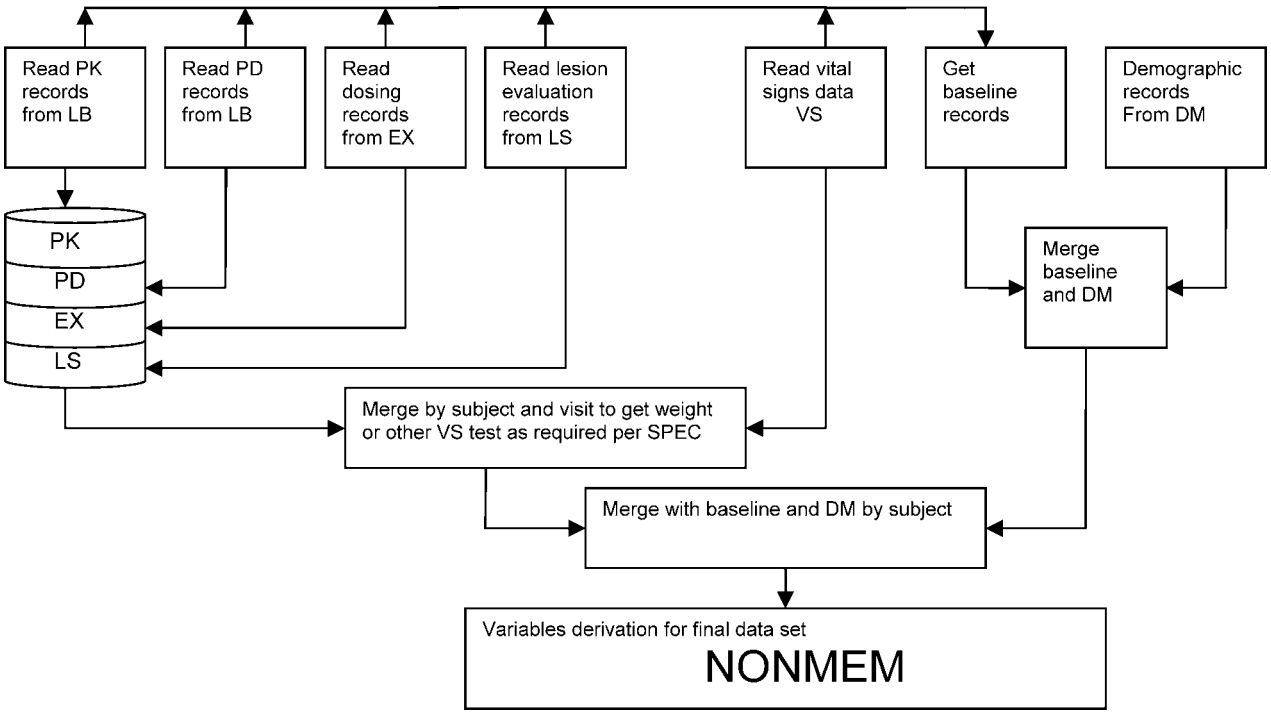

Figure 1 Flow diagram detailing the generation of the NONMEM dataset

with data derived from multiple studies. This modeling has been carried out with NONMEM software, supported by statistical programming. This team has created a document detailing their activities, which can serve as a guide to other teams as this model-based drug development paradigm continues to be adopted. Included above is a data flow diagram developed by the team (Fig. 1).

Mark Peterson, a DMPK scientist who was a co-author on the original paper, sees this model-based paradigm emerging across the pharmaceutical/biotech industry as a valuable and complementary scientific component of drug development. He feels that it provides strong rationale for study designs and reduces risk in the clinical decision-making process.

With a process in place and the need for this type of analysis seen as valuable inside the company, other project teams are now using this process to formalize a standard data flow for modeling PK/PD data.

Others to Follow

The two late stage programs in our Neurology therapeutic area have been considering using the new data flow to perform modeling with NONMEM in order to try to identify predictive biomarkers as well as to confirm optimal dosing regimens. In both cases, the PK scientists have been more active members of the study team and in one of the cases, the PK scientist has had input in the design of the case reporting forms (CRF) in order to facilitate their analysis.

The other late stage program team has chosen not to allow the PK scientist to be unblinded to the phase II study results prior to the database lock in order to develop models to inform decisions about dosing regimens for the phase III studies. This decision was made after much deliberation and careful consultation with the PK scientist, with concerns about the potential hazards of having study team members unblinded ultimately trumping the potential benefits that the modeling could bring.

This is an example of the careful consideration and weighing of pros and cons which must be carried out when looking at a paradigm shift of this sort and highlights the importance of bringing PK scientists into the fold so that the decision-making process is driven by as much information and diversity of viewpoints as possible.

Two other programs have used the new data flow for traditional early stage PK/PD analysis using WinNonlin. These two programs, which are in another therapeutic area, have been having successful data transfers, and both teams have reported increased efficiency and satisfaction with the process.

Conclusion

In conclusion, having a formal data flow process and specifically referring to PK analysis in process documents has placed a spotlight on it and has given the PK scientist a place at the table when designing and conducting clinical trials. The PK scientists themselves in several cases, have become more integral members of the study teams and that can only lead to collaboration which creates efficiencies as well as helping the company reach its objectives.

As a final note to underscore the value this can have, we have included an excerpt of the rationale from an internal document titled 'Statistical programming specifications for NONMEM data':

> *As the overall objectives of pharmacometrics are to quantitatively support the decision-making process*

regarding selection of dose levels, appropriate dose separations, dose regimen, and anticipated responses, as well as characterization of the stochastic nature of the pharmacokinetics (PK) and pharmacodynamics (PD), timely availability of the data is critical. It should be noted that development of predictive models and informative simulations (that are a function of the available data) requires substantially more time than traditional statistical analyses. This type of analysis provides insight on the probability of future events and can provide valuable information to the decision-making and trial design processes.

References

1 Collins A, Peterson M, Silva G. Streamlining the PK/PD data transfer process. Pharm Program 2010;**3**(1):24–8.