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The Road Not Taken: SAS® for Pharmacometrics

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ABSTRACT

This paper aims to introduce SAS® specialists from diverse backgrounds to the exciting new world of Pharmacometrics and explores the limitless possibilities in this cutting edge field. Pharmacometrics is the science of using mathematical models to integrate knowledge of biology, pharmacology and physiology to quantify the relationship between exposure and response. Model Based Drug Development (MBDD) holds the key to personalized healthcare and is the clear future of Drug Research and Development. As you can imagine, data is the crux of any scientific endeavor. Preparing high quality datasets for Pharmacokinetic and Pharmacodynamic modeling is the primary remit of a PK Programmer. Other responsibilities include using innovative ways of data exploration (e.g. graphical analysis), ensuring the smooth transition of knowledge from SDTM/ADAM datasets to a modeling ready dataset. As a SAS® programmer, Pharmacometrics is not the first thing that comes to our minds as a career choice. But, with a basic understanding of pharmacology, an inclination towards mathematical methodologies and some hard work, one can easily transition to the specialized role of a PK Programmer. Are your ready to take “The Road Not Taken”?

INTRODUCTION

It is very likely that most of us consider changing career paths at some point. This could be driven by multiple factors. We hope to point out the potential upsides of a move to Pharmacometrics programming in this paper. This field provides programmers with excellent career development opportunities in an ever changing and challenging regulatory environment. It is a field that is often overlooked. We hope to sow this new idea in the reader’s mind so that the next time they find themselves in a career crossroad, they will stop and think about the “Road not Taken”.

WHAT IS PHARMACOMETRICS

Pharmacometrics is the science of using mathematical models to integrate knowledge of biology, pharmacology and physiology to quantify the relationship between exposure and response. In most companies, pharmacometric analyses are performed in the Modeling and Simulation, Clinical Pharmacology or Quantitative Pharmacology departments. These departments comprise of Modelers or Scientists who are trained in pharmacokinetics, pharmacodynamics and/or pharmacology. Increasingly, these groups are also actively looking for specialist PK programmers who could handle all the data related activities.

Pharmacometric models have many applications in drug development. They can be used to describe the pharmacokinetics of a drug, the nature of the compound and for optimal dose selection. They are used to explain the response, efficacy or safety of a drug by quantifying its relationship with the drug exposure.

THE ROLE IN A NUTSHELL

At first glance, the role of a PK programmer is similar to any programming role in the pharmaceutical industry. The crux of the job involves creating high quality analysis datasets for pharmacometric analyses. As of now, we do not have precise data standards for these analysis datasets like we do for the other domains (e.g. ADSL, ADPC etc.). Each dataset is different and is tailor made for a particular modeling exercise. The structure of the dataset is decided a priori in consultation with the modeler or pharmacometrician. Typically, this is similar to any standard programming specifications document. But the datasets should follow certain structural requirements as stipulated by the modeling software like NONMEM® or NLME®.

Along with the source data which is used as input into generating these PKPD datasets, the work plan and DAP (Data Analysis Plan) play a pivotal role in building up the specifications. The work plan details the scope of work and all the activities that will be involved in the project. The DAP is a Modeling and Simulation Analysis plan that details all objectives, data sources, data handling and methodology of analysis that will be performed.

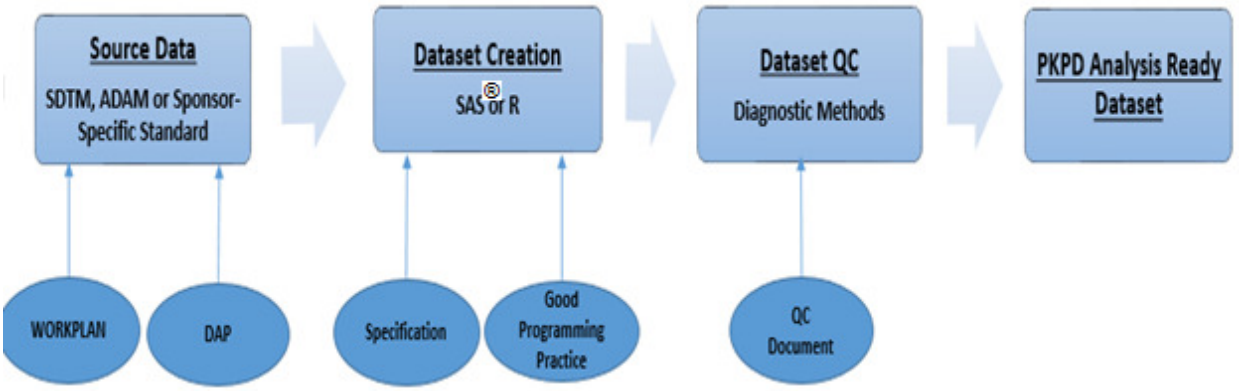

Figure 1: Flowchart with an overview of steps involved in PKPD dataset generation

A PK programmer acts as a conduit between the biostatistics and the clinical pharmacology departments and ensures smooth capture and transfer of datasets that are most important for modeling and simulation (e.g. DM, EX, PC etc.).

Making the connection between the exposure (EX) and the pharmacokinetic concentrations (PC) domains is the most interesting, challenging and the most complex part of this job. Dirty data is a part of life. PK programming is no different. Identification of issues that arise from the combination of drug exposure and concentration data is of utmost importance.

Datasets for modeling are longitudinal and contain information in a chronological order. For studies that are conducted over long periods of time, datetimes are typically not recorded for dosing. Creating an appropriate dosing history for a subject takes knowledge

of the drug and an understanding of basic PK concepts. This is a skill that all PK programmers will acquire over time.

Quality control processes of datasets in the pharmacometric space involve much more than just regular QC techniques. Innovative graphical displays are used to visualize data in different ways. More recently, dynamic data visualizations are being used.

OPPORTUNITIES AND POTENTIAL CAREER PATHS

For individuals who have an aptitude for Mathematics and that are willing to learn basic concepts of pharmacology and physiology, this field offers a wide variety of opportunities. Apart from being a specialist PK programmer, one can choose to perform NCA (non compartmental analysis), non-linear mixed effects modeling, leading all clinical pharmacology related study activities, create PK related TLG's and much more.

Although these roles require additional training in mathematics and pharmacology, these are very realistic career progressions that can materialize in 2-4 years and most companies encourage their programmers to choose one of the above routes.

AREAS OF IMPACT

The ultimate goal of a programmer is to produce quality datasets for analysis. To this end, there are multiple areas where we can create a positive impact. Apart from creating high quality analysis datasets, one can contribute to CRF design, provide input to make data collection and data management more efficient for PK analysis, write analysis plans, be involved in submissions to health authorities, provide input to label of the drug and dose selection and other critical areas in drug development. Programmers are a critical resource for building specialized databases for Disease modeling efforts.

CONCLUSION

As you can see from the above, programming in the field of pharmacometrics can be a very rewarding experience and an excellent career choice. As biostatistics programming gets saturated, we should all look for new innovative ways to utilize our programming expertise to make a significant contribution to drug development. Pharmacometrics certainly has a bright future and the hope is that model based drug development will not only inspire more adaptive clinical trial designs but also move us towards personalized healthcare.

REFERENCES

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