# Senior Training Fellowship



1. Name: Dr Binu Susan Mathew

2. Department: Clinical Pharmacology

3. Year of STF: 2015

4. Objectives stated in the application for STF:

   a) Pharmacometrics – for population pharmacokinetics and BESTDOSE® application

   b) LC-MS/MS interpretation of analysis related to inborn errors of metabolism .

5. Center visited for STF & Mentor :

   a) Laboratory of Applied Pharmacokinetics, University of Southern California : Dr Michael Neely
   b) Children's Hospital, Cincinnatti, Dr Kenneth Setchell, Director of Mass Spec

6. Short description of training:

My training started in the beginning of March, in the Laboratory of Applied Pharmacokinetics (LAPK). This, being a part of the Children's Hospital, is situated in the heart of Los Angeles (Sunset Boulevard). But this Laboratory is currently situated in a separate office away from the Children's hospital. The team at the LAPK is a very diverse one, consists of the current head, Dr Michael Neely (a paediatrician with a pharmacology degree), mathematicians, statisticians and Dr Roger Jelliffe who has pioneered the work related to the importance of dose individualization, years ago. The team also includes a NASA scientist who introduces the theory of trajectories used in rocket science, into the Pmetrics programme and Best Dose programme.

Pmetrics is a library package for R to perform non-parametric pharmacokinetic-pharmacodynamic population and individual modeling and simulation. It is primarily designed for work related to pharmacometrics. The Pmetrics package has been compiled and created by Dr Micahel Neely.

In India, there are very few centres/ professionals involved in pharmacometrics. Almost all centres who have pharmacokinetic data, send their data to experts abroad for purpose of PK modeling. During my 6 week stay, I was able to understand the purpose

and practical application of using Pmetrics . I trained in writing commands, executing commands and to an extend in interpreting error messages during a run.

Nonparametric approach on modeling is superior in that they establish the most likely distribution of the entire population parameter distribution, while those based on parametric do not. Non parametric approach will also help to identify any subpopulations within the study population and take this into account while making the model.

I was trained , mainly by Dr Michael Neely, to use Pmetrics,which included writing commands, creating models, validating models and performing simulations. The purpose of modeling in clinical use, would be to predict concentrations (not measured), using the developed models. Also in difficult to treat patients, it is even possible to estimate the exposure in patients (not responding to treatment) by predicting the adequacy of the exposure(concentration prediction). In extreme situations, this can also be used in drugs (where assays not yet developed) but literature available as to the PK parameters and where treatment is not producing the expected outcome, the concentrations can be predicted.

And I had some training on applying this model into a second programme called as the BEST DOSE. This would help to predict the right dose for each individual based on the predicted concentrations.

My second visit was to Cincinnatti Children's, where I spent two weeks. Dr Denny Fleming had the opportunity to join for this visit to Cincinnati. Most of the time was spent in the Mass Spec Lab, where we saw a manual method (lab developed and validated method) for the estimation of acyl carnitines. And this centre shared their SOP for this assay with us. In India, wherever this test is being done, the Perkin Elmer Kit is being used, which is too expensive . These centres, unless they are high thoroughput areas , do not prefer to use kit methods (owing to the exhorbitant prices of the kits). The laboratory faculty was kind enough to drive us to a centre (2 hrs away) to look at a commercial lab doing the acylcarnitine screen . For the test on amino acids, we also visited a HPLC lab in Cincinnatti Children's and spent a day there, to have an exposure to the amino acid test done using HPLC. In addition, we had a meeting with the Genetics team (Dr Nancy Leslie) on the aspects of diagnosis, treatment and she explained programmes available online to understand better the inborn errors of metabolism and to facilitate in understanding the normal ranges of these acylcarnitines. In addition we spent a couple of days at the Clinical Pharmacology Unit in Cincinnatti, where we met a team of dedicated people working mainly on pharmacometrics and saw the benefit and application of pharmacometrics in a clinical setting.

7. Plans to implement objectives on return to CMC:

a) Pharmacokinetic data is produced for many drugs in our Unit. However the next step of predictions using modeling is not being practiced. We hope to develop PK models, PK PDmodels for many drugs where drug concentration prediction will have an influence on the outcome. As part of clinical service/ research, we hope to do these models in the Unit(and not sent it else where for analysis).
b) Eventually , following these model development, we wish to initiate a best dose prediction programme for the clinicians, where we will be in a position to suggest doses most suitable for each patient, with the help of the models and other data available for each patient.
c) We hope that we will be able to facilitate dose predictions in OutPatient services (for example with anticonvulsants,etc),to facilitate dose individualization .
d) I hope to train others in the Unit in the use of Pmetrics (both faculty and post graduates).
e) We hope to be able to develop the assay (with a lesser cost) to be used as an acylcarnitine screen in newborns (as required by the neonatologist / gynecologist).With the help of a paediatrician, biochemist,geneticist to facilitate in the interpretation of the acylcarnitine values., both in newborns and in older children.

Date: 1.06.2015 Signature