UNIVERSITE DE POITIERS
U.F.R. Sciences Fondamentales et Appliquées

Année 2004-2005

Master Sciences et Technologies
Mention Biologie Santé Agronomie
Institut Universitaire Professionnalisé (I.U.P.)
Génie Physiologique Informatique

****

1ère année de Master1 I.U.P.
Rapport de stage

****

Statistical Tools For Mixed Effect Modeling Programming Two New Function in SPlus

Effectué à :
Aventis Pharma, *une entreprise du groupe* Sanofi-Aventis
65 926 Frankfürt am Main
ALLEMAGNE
Du 01/06/2005 au 12/08/2005

Sous la responsabilité de :
Heiner Speth, Informaticien

Présenté par
Guillaume Gorson-Tanguy

1 Summary

Presentation The training course took place from June to August 2005 within Sanofi-Aventis in Germany. I was not the only trainee to join the site of Frankfurt this year : Matthieu Malary joined the same working group.

The subject of my training course is in the continuity of the step of the DMPK Populations-Pharmacokinetic of automation of complex statistical tools. We have thus developed two new statistical tools : Variation of Onetheta and Simplefit.

1.1 Sanofi-Aventis

1.1.1 The Group

Sanofi-Aventis is the third leading pharmaceutical group in the world and the first in Europe. The Sanofi-Aventis group was born from the merge from Aventis Pharma by Sanofi-Synthelabo in August 2004. Its currency " Because health matters " clearly defines its goal.

In 2004, the whole of the activities of Sanofi-Aventis (if we add the results with the two companies before merge) generated a sales turnover of 25 Billion euros. The group counts approximately a hundred thousands of collaborators.

The Sanofi-Aventis group was born from successive fusions several large French and European pharmaceutical companies.

In January 2004, Sanofi-Synthélabo, second pharmaceutical group in France, launched a public offer of hostile purchase on its principal competitor, Aventis . With the resulting one from the OPA/OPE, Sanofi-Synthelabo held 98% of the capital of Aventis Pharma.

Aventis was the result of the merge of the French group the Rhone-Poulenc S.A. and the German group Hoechst AG in December 1999. Aventis was immediately essential like one of the world leaders of pharmacy and agriculture.

Sanofi-Synthelabo results from fusion into 1999 of Sanofi (then subsidiary of the oil group Elf) and of Synthelabo (then subsidiary company of the group of cosmetics Oréal).

With meadows of 4 billion euro, the budget of Research and Development of Sanofi-Aventis belong to the 3 first budjets of world pharmaceutical industry. Today, the research of the group has one of richest and innovating wallets of all the world pharmaceutical industry with 128 molecules under development including 48 in advanced phases (phase II and III). Present on 3 continents, 11 500 researchers work in more than 20 sites.

1.1.2 The department SMA Metabolism and PK Germany

The goal of department SMA Metabolism and PK Germany is to make statistical studies on the data resulting from various clinical trials in order to determine pharmacodynamic and pharmacokinetic models and thus to allow forecasts useful to later studies or to detect possible errors of with certain patients of the clinical study.

1.1.3 The PKPD Team

of DMPK Populations-Kinetic is made up of three people :

- **Dr. Willi Weber**, pharmacometrician
- **Dr. Diether Rüppel**, pharmacometrician
- **Heiner Speth**, computer scientist

These three people are charged to work on pharmacokinetic models starting from data of clinical trials. Their work consists in working out statistical tests in order to realize and improve the pharmacokinetic models

The purpose of that is also to detect skews of population or adaptations of model to carried out on precise patient. the result obtained will thus be used in order to improve the future studies from the data collected on the last studies.

1.2 Two Statistical Tools For Mixed Effect Modeling

1.2.1 Populations-Kinetic

This method from the pharmacokinetic data of some patients on a given drug, makes it possible to model the pharmacodynamics of this drug on one or more populations. That in particular makes it possible to evaluate the posology of the future drug.

1.2.2 NONMEM

The team works with FORTRAN program of mathematical regressions NONMEM. This last whose initial ones mean " NON linear Mixed Effect Modeling " was developed by S. Beal and L Sheiner, all the two members of the NONMEM Projetct Group of the University of California in San Francisco. It is marketed by the company Globomax LLC.

It uses the pharmacokinetic data contained in a data file to calculate the theoretical kinetics of the drug in the human body. It is based for that on the control file. This one is written by the pharmacometrician according to his experiment and to the knowledge which he has on the drug. The program tries to optimize the model by modifying the parameters in order to obtain a minimum for the objective function (OF). At the end a file containing the results is generated : the report file. All the files are compacted into a file archive.

1.2.3 The Programing of the tools

SPlus We learned the programming language SPlus, which is a language adapted to statistical calculation. It is used within the team of Frankfurt to analyze the results provided by NONMEM.

We continued the work of Justine Lahaye, Matthieu Chosseler and Baptiste Moulinier by creating two new tools. We indeed kept the same general structure of programming, in order to preserve the general coherence of the whole of the functions. We initially altered a little bit the functions of our predecessors, in order to make them a little more handy. We have separated launching from processes NONMEM of the generation of the reports. Thus if there would be failure of NONMEM, the reports are'nt generated for nothing. The purpose of this part which was not difficult was especially to teach us Splus and to render comprehensible themselves the work of our predecessors.

Variation Onetheta The pharmacokinetic models include parameters called theta. Variation Onetheta is interested in the influence of one of these parameters on the objective function of the model.

To this end a certain number of values are generated in an interval located around initial value of the theta. The pharmacometrician can choose itself the number of values and the size of the

interval. For each new value of the theta a new file of control is created in an under repertory. And in each one of them a new process NONMEM is launched.

When calculations are finished, the results are extracted from the archival files. Tables and curves are created starting from these data. A report is then generated automatically by using the LaTeX language.

Simplefit The purpose of this method is to check that one of the patients of the study does not induce a too great skew in the model. Indeed if a patient with very different results from the other patients, it influences the model. This method is close to the Jackknife method.

To this end the method realizes as much under population that there are patients in the study and place only one patient in each under population. To be able to model with only one individual, a new control file is necessary. For each individual, a process NONMEM is launched.

At the end of all the processes, a report is produced

My training course did not consist of a great project. But the development of these two tools was very interesting. I learned much about pharmacokinetics.