4.1. Scope of the Work:

4.1.1. Scope of the Research Area – Pharmacogenetics:

Over the past two decades, the drug development process for a new drug has become increasingly expensive, with diminishing probability of success.\textsuperscript{136,137} In 2004, the USFDA launched The Critical Path Initiative (CPI) to promote innovative approaches, such as ‘Pharmacogenetics’ to overcome stagnation in drug development.\textsuperscript{138} In recent years, the application of pharmacogenetics within clinical development phases has experienced unprecedented growth.\textsuperscript{139}

Pharmacogenetics, the study of genetic differences causing the variability in drug response between individuals provides information for ‘personalized medicine’, giving a patient the right medicine at right dose. This approach enables the prescribers to administer drug treatment only to individuals who could able to process the drug in the desired way, and to tailor the treatment dosage in order to maximize the efficacy and to reduce the toxicity and ADRs.\textsuperscript{140}

The medical practitioners have started recognizing the importance of pharmacogenetics in decision making and selecting drug treatment to those more likely to benefit.\textsuperscript{26,141-142} Thus, pharmacogenetics has more potential in clinical research and practice to explain unexpected variability in safety and efficacy outcomes of a drug treatment. In earlier days, this variability has resulted in termination of either drug development program or treatment in the practice.\textsuperscript{143}
Though pharmacogenetics has been proved to be extremely valuable for optimizing the benefits and minimize the risks of some drugs in drug development, in clinical practice, the desire to achieve more effective treatment in patients, the success remains limited. To some extent, pharmacogenetics can be used as a tool to re-evaluate drug development plans or drug treatment plans when the outcome of the treatment is negative or ambiguous rather than being an integral part of personalized medicine plan.

However, pharmacogenetics remains an evolving science that requires further technological and methodological development to optimize the study designs. Indeed, the right combination of planning, data collection and analysis is likely to yield many more success for pharmacogenetics.

4.1.2. Scope of the Research Area – Population Pharmacokinetics:

A conventional pharmacokinetic model describes drug effect time course after administration. The same model can then be used mechanismically to predict the action of other doses. If this mechanistic extrapolation of an empirical pharmacokinetic model developed from the data collected from a single subject or many subjects is reasonable, then we can predict what will happen in further new subjects. But in reality, the next subject often does not match the prediction. Thus we do not expect all patients respond in a similar manner as there is something missing in the conventional pharmacokinetic model, a factor responsible for variation between patients.144

Population approaches to pharmacokinetic modeling integrate such variability factors into the model and explain these variations on the basis of differing biological
Thus, population pharmacokinetics is the study of variability in drug concentrations between individuals (healthy volunteers or patients). It comprises the assessment of variability within the population and accounts for the variability in terms of patient characteristics such as age, renal function, disease state, genetic polymorphism and etc. Among the various methods available, the non-linear mixed effects modeling approach has been increasingly used for population pharmacokinetics analysis.\textsuperscript{145} NONMEM® is the proprietary software most widely used computer package for the Pop PK analysis by the pharmaceutical industries.

4.1.3. Scope of integrating Pharmacogenetics in Population Pharmacokinetics:

It is understood that pharmacogenetic information of an individual or a population will explain the reason for variation in drug pharmacokinetics and response, and population pharmacokinetics is an effective tool to measure the impact of such variation and include it in to the mathematical model in order to individualize the model for a specific population/individual.

4.1.4. Scope of the Present Study:

In this background, the genetic polymorphism of CYP2C19 enzyme was selected for this study as it is more prevalent in the study population and the drugs sertraline and omeprazole were selected as they are primarily metabolized by this enzyme and known to show high interindividual variability.

The present study has got the following scopes:
A detailed literature review was done on the subject matters of this thesis and presented systematically for better understanding of the background of the study.

The theoretical aspects of emerging areas of biomedical science namely, ‘pharmacogenetics’ and ‘population pharmacokinetics’ were described in detail.

The practical aspects of these techniques were illustrated to enable the other researchers to understand and execute them in their research set ups.

The validated bioanalytical methods for the quantification of the study drugs in plasma were explained in detail.

The population pharmacokinetic models with the covariates influencing the primary pharmacokinetic parameters for the study drugs were proposed.

This is the first study to report population pharmacokinetics of sertraline and omeprazole in south Indian population.

This is also the first study to investigate the impact of pharmacogenetic polymorphism as a covariate in population pharmacokinetics model in this population.
4.2. Plan of Work:

**From Clinical Observations & Preliminary Studies:**
Variability in Pharmacokinetics and Clinical Response of Study Drugs: Sertraline, Omeprazole

**Formation of Study Question & Setting Aim and Objectives:**
Which factors influence the PK of study drugs including CYP2C19 Polymorphism?

**Formatting:**
Scope and Plan of Work
Methodology
Study Protocol
Data Collection Forms

**Methodical Literature Review:**
Using Primary, Secondary and Tertiary Resources

**Ethical Approval:**
Protocol Submission to IEC/IRB
Protocol Revision (if any)
Protocol Resubmission
Getting Ethical Approval

**Study Initiation:**
Identification of Study Sites
Screening for Potential Patients
Informed Consent Process
Patient Recruitment

**Sample & Data Collection:**
Blood Sample Collection
Plasma Separation and Storing
Data Acquisition from Case Sheets and Patients

**Sample & Data Analysis:**
Plasma analysis by RP-HPLC
DNA Isolation, RTPCR, RFLP, CYP2C19 Polymorphism
Preliminary Data Analysis

**Pop PK Analysis: NONMEM®**
Data File Formation
Model Building: Base, Covariate
Final Model: Validation
Results and Discussion

**Thesis & Publication**
Thesis Formatting
Presentations & Publications of the Results

**RP-HPLC:** Reverse Phase High Performance Liquid Chromatography; **RTPCR:** Reverse Transcriptase Polymerase Chain Reaction; **RFLP:** Restriction Fragment Length Polymorphism