Introduction
The fraction of dose absorbed is affected by numerous factors which can be split into drug- and formulation-specific parameters and physiological parameters (the system). An integrated approach that considers the interplay between these factors is important for accurate prediction of the rate and extent of oral drug absorption. Physiological parameters (gastric emptying rate, intestinal transit and mobility, gastrointestinal fluid pH, secretion and reabsorption, intestinal blood flow, bile secretion, enterohypothalamic recirculation, and intake of food and fluids etc.) form an integral component of predictive tools which rely upon extensive databases storing the mean and population variability of such parameters, including, where available, their covariation. While such databases have been developed there remain significant gaps, some of which will be addressed in this task.

Areas Being Addressed
1. Circadian Variation
Many physiological processes follow circadian rhythms and the processes involved in determining the rate and extent of oral drug absorption are no exception. Gastric emptying rate and hepatic blood flow are known to be reduced significantly in the evening (night) compared to the morning (day) which may have an impact upon the rate and extent of absorption of acid-labile drugs, enterico-coated formulations and drugs with significant gut-wall and hepatic metabolism. Hence, when the GI transit of drug and blood flow to liver and villi reduces at night, the rate at which a drug is carried away from first-pass metabolism sites (gut-wall and liver) is lowered leading to higher first pass metabolism at night compared to the day time.

Figs. 1 and 2 indicate the impact (simulated and clinically observed) of circadian variations on the bioavailability and PK parameters respectively of CYP3A4 substrate and BCS/BDDCS Class II drug Nifedipine.

2. Viscosity of Physiologically Relevant Dissolution Systems
In order to simulate in vivo dissolution and disintegration of drugs, physiologically relevant dissolution media, mimicking gastric or intestinal juices are often employed. For such media, pH, surface tension, ionic strength, osmolarity parameters are usually considered. However, little attention has been paid to rheological attributes. The differential viscosity of luminal contents in the fasting and fed states can have a significant impact on dissolution and disintegration of oral dosage forms. The following components will be addressed building this database.

Fasting state condition
Database till date:
- Viscosity in stomach: Chinese and Japanese population
- Viscosity in intestine: Chinese
- Viscosity in colon: Chinese

Further work:
- Viscosity in stomach: Caucasian
- Viscosity in intestine: Japanese and Caucasian
- Viscosity in Colon: Japanese and Caucasian

Fed state condition
Database till date:
- In vitro viscosity of FDA breakfast
- In vivo viscosity of high viscosity fibres, example: - Dietary fibres and locust bean gum

Further work:
- In vivo viscosity of FDA breakfast
- In vivo and in vitro viscosity of high and low fat food
- In vivo and in vitro viscosity of high and low protein food

3. Animal PBPK Models (Beagle Dog, Sprague Dawley Rat, Generic Strain Mouse)
- Studies with preclinical species play an important role in drug development including studies with oral dosage forms. Modelling and simulation tools can, for example, be used to set appropriate dosing levels and to improve/confirmd understanding of drug behaviour before moving to human studies. Gastro-intestinal anatomical & physiological data for preclinical species are thus required. Data required include:
  - Small intestine and colon anatomy and physiology data (length, diameter, gastric emptying, transit time, pH, bile salt concentrations, villi morphology, unstirred boundary layer).
  - Regional small intestine, villus and colon blood flows during fasted and fed state.
  - Regional volumes of luminal fluids at steady state (influenced by secretion and re-absorption rates).
  - Regional pH and bile salt concentrations in the fasted and fed states.

4. Physiologically Relevant Buffer Systems
Development of dissolution media, closely simulating in vivo physiological conditions, is expected to enhance predictions of the in vivo performance of test formulations. Bicarbonate buffer plays a major role in the in vivo gut but provides significant practical difficulties in in vitro dissolution studies. However in terms of the mechanistic modelling and simulation of dissolution in the in vivo gut it is necessary to consider the properties of bicarbonate buffer.

Population data (mean and variability) describing luminal buffer capacity and related intestinal secretion rates of relevant fluids, together with consideration of the effect of food and potentially disease state will be collected. This will then be coupled with mechanistic models for oral absorption prediction, including the modelling of surface (local) pH effects and the dissolution of pH sensitive polymers (enteric-coated formulations).