Clinical pharmacokinetic/pharmacodynamic and physiologically based pharmacokinetic modeling in new drug development: 
The capecitabine experience

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Key words: pharmacokinetic–pharmacodynamic (PKPD) modeling, physiologically-based (PBPK) modeling, 
capecitabine, oral prodrug, computer simulation, NONMEM

Summary
Preclinical studies, along with Phase I, II, and III clinical trials demonstrate the pharmacokinetics, pharmacodynamics, safety and efficacy of a new drug under well controlled circumstances in relatively homogeneous populations. However, these types of studies generally do not answer important questions about variability in specific factors that predict pharmacokinetic and pharmacodynamic (PKPD) activity, in turn affecting safety and efficacy. Semi-physiological and clinical PKPD modeling and simulation offer the possibility of utilizing data obtained in the laboratory and the clinic to make accurate characterizations and predictions of PKPD activity in the target population, based on variability in predictive factors. Capecitabine is an orally administered pro-drug of 5-fluorouracil (5-FU), designed to exploit tissue-specific differences in metabolic enzyme activities in order to enhance efficacy and safety. It undergoes extensive metabolism in multiple physiologic compartments, and presents particular challenges for predicting pharmacokinetic and pharmacodynamic activity in humans. Clinical and physiologically based pharmacokinetic (PBPK) and pharmacodynamic models were developed to characterize the activity of capecitabine and its metabolites, and the clinical consequences under varying physiological conditions such as creatinine clearance or activity of key metabolic enzymes. The results of the modeling investigations were consistent with capecitabine’s rational design as a triple pro-drug of 5-FU. This paper reviews and discusses the PKPD and PBPK modeling approaches used in capecitabine development to provide a more thorough understanding of what the key predictors of its PBPK activity are, and how variability in these predictors may affect its PKPD, and ultimately, clinical outcomes.

Background and introduction
Modeling and simulation have the potential to be important tools in all phases of drug development from preclinical through clinical and post-marketing phases, providing scientific evidence upon which to base key decisions during all stages of a product’s life cycle. Modeling and simulation rely on the use of mathematical and statistical models that are essentially simplified descriptions of complex systems under investigation. Although modeling and simulation have been carried out successfully within the pharmaceutical industry for some time, it was not until the early 1980s, when the notion of therapeutic drug monitoring gained attention Regulatory scientists in the FDA and other agencies became aware that registration packages for new chemical entities lacked pharmacokinetic (PK) and exposure
information in the target patient population and began requesting these types of data. This, along with advances in the application of estimation methods including maximum likelihood and particularly in the area of nonlinear mixed effects modeling in the 1970s, enhanced the importance of pharmacokinetic and pharmacodynamic (PKPD) modeling and simulation as a useful tool for new drug development. The release of the nonlinear mixed effects modeling software, NONMEM, in 1980 was a major milestone. Numerous successful applications demonstrated its utility in the analysis of PKPD data, especially when sparse data were collected in patients, giving rise to the notion of “population pharmacokinetics” or “the population approach.”

At the same time, methods for predicting human PK characteristics based on pre-clinical data were also being rapidly developed as important tools for identifying the best candidates for further development. In an environment of high throughput molecule identification, it is desirable to have methods that can rapidly and reliably predict human PK characteristics. Data including lipophilicity, ionization, solubility, ex vivo protein binding, metabolic stability in liver preparations and membrane permeability can be used as input data to predict characteristics such as fraction of dose absorbed, fraction metabolized and tissue distribution. These characteristics can be subsequently used to predict the time course of the clinical candidate’s plasma and tissue concentration profiles. Physiologically based pharmacokinetic (PBPK) models are increasingly being used in pre-clinical drug development to enhance understanding of the complex interactions of biological and physiologic parameters that affect drug behavior at the molecular level in multiple physiologic compartments. Compared to standard compartmental models, PBPK models aim at a more physiologically oriented description of the system under investigation with obvious advantages regarding the interpretation of results. Because of its complex design as a triple pro-drug of 5-FU, the clinical development of capecitabine benefited from both PKPD and PBPK modeling and simulation.

Capecitabine

Capecitabine (N\(^4\)-pentyloxycarbonyl-\(5'\)-deoxy-5-fluorocytidine, XELODA\(^{\text{TM}}\)), is a rationally designed, orally administered triple pro-drug of 5-fluorouracil (5-FU) that is approved for the treatment of breast and colorectal cancer. After oral administration, capecitabine is well-absorbed and sequentially metabolized to 5-FU in 3 steps (Figure 1):

1. Capecitabine is converted to \(5'\)-deoxy-5-fluorocytidine (\(5'\)-DFCR) by carboxylesterase;
2. \(5'\)-DFCR is converted to \(5'\)-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase (cyd deaminase);
3. \(5'\)-DFUR is converted to 5-FU by thymidine phosphorolase (dThdPase).

In a second set of 3 steps, the active moiety, 5-FU is first converted to dihydroxyfluorouracil (FUH\(_2\)) by dihydropyrimidine dehydrogenase (DPD). This is followed by conversion to 5-fluoro-ureido-propionic acid (FUPA) via ring cleavage with dihydropyrimidinease (DHP). The final step is conversion of FUPA to \(\alpha\)-fluoro-\(\beta\)-alanine (FBAL) by the enzyme \(\beta\)-ureido-propionase (BUP).

Carboxylesterase, cyd deaminase, and dThdPase, the three metabolic enzymes involved in the biotransformation of capecitabine to 5-FU show relatively specific expression in liver and tumor tissues (Figure 1) [1]. By design, the biotransformation of capecitabine to 5'-DFCR by carboxylesterase is intended to occur preferentially in the liver, in order to minimize the accumulation of 5-FU in blood and healthy tissues. Conversion of 5'-DFCR to 5'-DFUR by cyd deaminase occurs primarily in liver and tumor tissue. Conversion of 5'-DFUR to 5-FU occurs via dThdPase, which is more highly expressed in many types of human tumors than in healthy tissues [1] (Figure 1). In humans, 60–90% of 5-FU is catabolized by DPD to FUH\(_2\) and ultimately to FBAL [2], while 10–20% is excreted in urine in the unchanged form [3].

Capecitabine is therefore expected to allow preferential exposure to 5-FU in malignant tumors, limit levels of circulating 5-FU in plasma, and limit

![Figure 1. Metabolic pathway of capecitabine.](image-url)