By contrast, physiologically based pharmacokinetics (PBPK) modeling starts with an explicit representation of the organism (Willmann et al. 2005). Organs and sub-compartments such as the vascular, the interstitial, and the cellular space are represented individually and connected in way that reflects blood flows and diffusion process or active transport mediated by drug transporters in a 1:1 manner. PBPK models for different animal species and humans differ in the respective model parameters such as organ volumes, blood flow rates, and enzyme and transport protein expression levels. Likewise, models for different human populations such as adults and children also only differ in the respective model parameters representing the dimensions and properties of the bodies (Edginton et al. 2006). Common to all organism parameters is that they are set based on prior information independent of the PK experiments. Typical sources of this information are epidemiological databases such as the National Health and Nutrition Examination Survey (NHANES, http://www.cdc.gov/nchs/nhanes.htm) or the Cancer Genome Anatomy Project (CGAP, http://cgap.nci.nih.gov/) as well as highly specific, dedicated studies of individual properties such as the geographic distribution of different cytochrome P450 2D6 genotypes (Sistonen et al. 2007). In a similar fashion, properties of the drug that is administered are also represented in a 1:1 manner. Solubility, lipophilicity, protein binding, and metabolic stability can be determined in in vitro assays and are represented by individual parameters (Willmann et al. 2005). Consequently, a PBPK model can provide a prediction of the PK of a drug in a given organism before any in vivo experiment has been performed. Once experimental data is available, the PBPK model can be calibrated to better describe the observed PK. As with classical approaches, this is done by adjusting parameter values. The main differences are that organism parameters are usually not touched and parameters representing drug properties are modified only within plausible ranges previously determined in in vitro surrogate assays. In this way, deficiencies of in vitro systems are compensated and, e.g., an in vitro solubility measured in water or intestinal fluid-simulating media is corrected to better reflect in vivo solubility in the gastrointestinal tract.

Simulation, i.e., prediction of new PK experiments, with PBPK models is relying on prior drug-independent information again. For example, organism parameter values representing adult patients are replaced by parameter values describing the different organ volumes and compositions, blood flows, and enzyme expression levels in children to predict PK in pediatrics. In population modeling, new experiments are also simulated. Since parameters are not explicitly representing individual biological or chemical properties but lump drug and organism features,

Fig. 2 (continued) both approaches follow the same procedure. Model parameter values are modified to adjust the model-based representation to new situations such as a new group of patients of different age and body weight and the model is used to calculate the expected PK profiles. In PBPK modeling, the parameters are modified based on prior independent information about patients (e.g., tabulated organ volumes in children and adults) while population modeling uses regression models identified from the PK data for the drug of interest linking so-called covariates such as body weight with one or several of the model parameters