models to estimate the efficacious exposure can be further enhanced by integration of target engagement markers or subsequent MoA readouts and by attempting to establish a temporal link between the expression of pharmacological activity upon target binding with more "distant" efficacy endpoints such as tumour stasis or regression (Yamazaki 2013; Yamazaki et al. 2015; Venkatakrishnan et al. 2015).

Besides the confidence in the relevance and translatability of the results from animal models to the human situation, the relevance of unbound plasma concentrations for the concentrations in the effect compartment needs to be understood. For targets residing in the body's periphery with unrestricted proximity to the blood circulation, the time course of the unbound plasma concentrations most likely will correspond to the unbound concentration at the target site. This can be demonstrated experimentally by plotting the time course of total plasma vs. total target tissue concentrations. If they run in parallel, the unbound concentrations will be the same in both compartments, i.e. the unbound plasma concentration fully represents the free concentration of the compound at the target site. This information on plasma-target site equilibrium is very important for clinical studies where generally only plasma concentrations are accessible. If the target site in the body is not in direct correspondence with the plasma compartment, a possible exposure difference and/or time delay should be evaluated (Gabrielsson et al. 2009, 2011). For targets which are not in proximity to the general blood circulation or even locate behind a physiological barrier, e.g. CNS, additional data are needed to translate unbound plasma concentrations into relevant effect compartment concentrations (Reichel 2009, 2014, 2015).

PK/PD modelling based on popPK approaches combining different, independent experiments and using the data points from individual animals is very powerful to reduce noise and to extract experiment-independent parameters for the predictions.

The predicted therapeutic exposure in humans has also to be consistent with the existing knowledge of the target biology. Predictions carry particularly high confidence if they are based on experimental evidence for target engagement and expression of pharmacological activity (MoA) in an animal model which is relevant for the intended indication and patient population.

2.4.3 Prediction of Human Therapeutic Dose

Conceptually, human dose estimation is simple (Fig. 7): The predicted PK, i.e. dose–exposure relationship in humans from above, is used to estimate a dose/dosing schedule for humans which is anticipated to mimic the unbound concentration–time profile that is expected to be efficacious as well as safe in humans (Heimbach et al. 2009; Venkatakrishnan et al. 2015).

The accuracy of the predicted dose depends as much on the prediction of the human PK as it does on the estimated therapeutic exposure. The estimation of the human therapeutic dose often results in a range originating from different scenarios that reflect the most relevant uncertainties in the current understanding and set of data available. These may relate to both the prediction of the human PK and the estimation of the human therapeutic exposure. The use of PD or disease models in different preclinical species helps in eliminating any species differences between