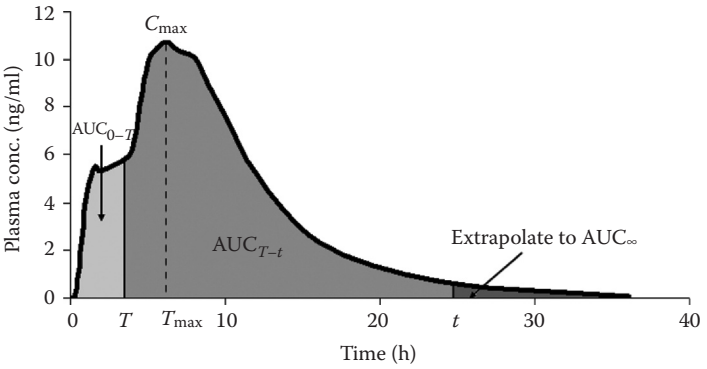

FIGURE 10.2 pAUC refers to the AUC between two specified, clinically relevant, time points on the drug plasma concentration versus time profile. pAUC metrics should meet bioequivalence limits for generic versions of multiphasic modified-release oral dosage formulations, which are formulated both to rapidly release drug from an immediate-release portion to achieve rapid onset of response and to slowly release drug from a delayed- or extended-release portion to sustain the response. An additional criterion for using the pAUC metric for such formulations is that the drug should not accumulate when administered under the appropriate dosing regimen. The geometric mean test/reference ratios of the four metrics C_{max}, AUC_{0-T}, AUC_{T-t}, and AUC_∞ should fall within the limits of 80% to 125%. The metric C_{max} is the peak plasma drug concentration. The sampling time for the pAUC determination (T) is selected based on the pharmacokinetic/pharmacodynamic properties of the active ingredient. The first pAUC, AUC_{0-T}, compares test and reference systemic exposure responsible for early onset of the therapeutic response. The second pAUC, AUC_{T-t}, where t is the last sampling time point with measurable drug concentration, compares test and reference systemic exposure responsible for sustaining the therapeutic response. The metric AUC_∞ is the AUC extrapolated to infinity, representing total drug systemic exposure after a single dose.

response. To date, the FDA includes the pAUC in bioequivalence evaluation of multiphasic modified-release formulations of zolpidem,[35,36] methylphenidate,[37] dexmethylphenidate,[38] and mixed amphetamines.[39] These four products meet the criteria described above for pAUC application. For these four products, the FDA scientists selected the pAUC truncation times based on the relationship between drug plasma pharmacokinetic profiles and the time course of the associated pharmacodynamic response.

GENERAL BIOEQUIVALENCE STUDY DESIGN RECOMMENDATIONS

There are several types of designs suitable for in vivo bioequivalence studies. The preferred design for most orally administered dosage forms is a two-way crossover, two-period, two-sequence, single-dose study, in healthy subjects, performed under fasting conditions. Each study subject receives each treatment, test and reference, in random order. Plasma or blood samples are collected for three or more pharmacokinetic half-lives for determination of the rate and extent of drug release from the dosage form and absorption by each subject. A washout period is scheduled between