ROLE OF T_{max} IN BIOEQUIVALENCE ANALYSIS

The FDA does not ask ANDA applicants to use statistical procedures to compare the time to drug peak plasma concentrations (T_{max}) for the test and reference products.[26] Although theoretically a relatively sensitive measure of absorption rate, T_{max} is thought to have shortcomings as an indirect measure of the rate of drug absorption.[27,28] For example, ANOVA analysis cannot be applied to T_{max}, because T_{max} is a discrete measure dependent on frequency of blood sampling.[29] In addition, most pharmacokinetic studies typically employ irregular sampling schemes to collect T_{max} data, and as a result, these data are not routinely amenable to proper statistical evaluation.[30] Nonetheless, the FDA believes that T_{max} should be considered in bioequivalence decision-making and routinely examines T_{max} data in bioequivalence studies as supportive data to verify that the test and reference products have the same rate of absorption.[31]

PARTIAL AUC

In certain circumstances, the FDA recognizes that it is appropriate to use a partial AUC (pAUC) as an exposure metric to ensure that a generic and reference product have comparable therapeutic benefit.[32,33] The pAUC is an exposure metric determined by truncating the area under the plasma concentration versus time profile at a designated early time after dosing. The choice of truncation time is most appropriately based on the pharmacokinetic/pharmacodynamic or efficacy/safety data for the drug under examination.[34]

The FDA requests inclusion of pAUC metrics in bioequivalence studies of generic versions of multiphasic modified-release reference formulations designed to produce rapid drug action followed by a sustained effect. The desired outcome of rapid early response followed by sustained response is achieved by formulating the reference product as a combination of immediate-, delayed-, and/or extended-release components.[33] An additional criterion that must be satisfied to appropriately apply pAUC metrics is that the drug does not accumulate to steady-state under the multiphasic product's recommended dosing regimen.

For such products, the FDA recommends use of both an early pAUC measure to compare drug exposure responsible for early onset of response, and a late pAUC to compare drug exposure associated with the second sustained release of drug. These two metrics replace AUC_{0-t} in bioequivalence evaluation. Thus, the metrics used are AUC_{0-T} (where T is the early sampling truncation time), AUC_{T-t} (where t is the time of the last measurable plasma drug concentration), C_{max}, and AUC_{∞}. It is not necessary for the generic version to contain the same ratios of immediate- and delayed- or extended-release components as the multiphasic modified-release reference. A generic version is considered therapeutically equivalent to a corresponding multiphasic modified-release reference drug product if the two are shown to be bioequivalent based on the parameters AUC_{0-T}, AUC_{T-t}, AUC_{∞}, and C_{max}.

Figure 10.2 illustrates the application of the pAUC and other bioequivalence metrics in the case where a multiphasic reference product is formulated to release drug in such a manner as to achieve an early onset of response followed by a sustained