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Beyond the AUC: Rethinking Exposure Metrics in Modern Bioequivalence Assessment

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Abstract

Bioequivalence assessment has traditionally relied heavily on pharmacokinetic measures such as the area under the plasma concentration–time curve (AUC) and the maximum observed concentration (Cmax) to establish comparability between pharmaceutical products. These metrics have provided a practical and standardized foundation for regulatory decision-making; however, the increasing complexity of drug delivery systems, modified-release formulations, biologics, and patient-specific pharmacokinetic behaviour has highlighted limitations in relying on conventional exposure measures alone. Two products may demonstrate comparable AUC values while exhibiting clinically relevant differences in the timing, duration, fluctuation, or distribution of drug exposure. Contemporary pharmacokinetic evaluation therefore requires a broader perspective that considers the temporal characteristics of concentration–time profiles in addition to total systemic exposure. Metrics describing partial exposure, early exposure, time to peak concentration, exposure during specific therapeutic windows, and concentration variability may provide complementary information when conventional measures fail to adequately characterize formulation differences. Advances in pharmacometrics modelling, population pharmacokinetics, physiologically based pharmacokinetic modelling, and high-resolution sampling strategies further create opportunities to refine bioequivalence assessment. Rethinking exposure metrics does not imply abandoning AUC or Cmax; rather, it emphasizes their appropriate interpretation within a multidimensional framework.

Keywords: Bioequivalence; Pharmacokinetics; AUC; Cmax; Drug Exposure; Partial AUC; Pharmacometrics Modeming; Modified-Release Formulations; Pharmacokinetic Variability; Regulatory Science

Introduction

Bioequivalence has become an essential component of pharmaceutical development, providing the scientific basis for demonstrating that a test formulation and a reference product exhibit sufficiently comparable drug exposure. For many immediate-release products, conventional pharmacokinetic parameters have offered an efficient and reproducible framework for evaluating product similarity. Among these parameters, AUC is primarily associated with the extent of systemic exposure, whereas Cmax provides information regarding the peak concentration achieved after administration. Together with the time to maximum concentration, these measures have formed the foundation of numerous bioequivalence assessments.

Despite their established importance, conventional exposure metrics do not capture every characteristic of a pharmacokinetic profile. AUC compresses an entire concentration–time curve into a single measure of overall exposure. Consequently, two formulations can produce similar total exposure while differing substantially in how

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quickly the drug becomes available, how long concentrations remain within a particular therapeutic range, or how exposure is distributed across different phases of absorption and elimination. Such differences may become particularly important when the pharmacological effect of a medicine depends on maintaining concentrations above or below specific thresholds.

The evolution of pharmaceutical technology has made this issue increasingly relevant. Modified-release formulations, complex drug-delivery platforms, combination products, and formulations designed to produce controlled or delayed exposure can generate concentration–time profiles that are not adequately described by a small number of traditional parameters. In these circumstances, the question is no longer simply whether two products provide the same overall exposure, but whether they provide exposure in a sufficiently similar temporal pattern.

Conclusion

Bioequivalence assessment is entering a stage in which the concept of drug exposure can no longer be viewed solely through the lens of total systemic exposure. AUC and Cmax remain foundational pharmacokinetic measures, but increasingly complex pharmaceutical formulations demonstrate the importance of examining the timing, distribution, and variability of exposure.

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