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Toward Smarter Bioequivalence Studies: Integrating Pharmacokinetics, Formulation Behaviour, and Patient Variability

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Abstract

Bioequivalence (BE) assessment is a fundamental component of generic drug development and is traditionally established by comparing pharmacokinetic measures of systemic exposure between a test and reference product. Although this approach provides a practical framework for demonstrating comparable drug exposure, interpretation of bioequivalence can become challenging when formulation characteristics, gastrointestinal conditions, and patient-related variability interact. Differences in drug release, dissolution, solubility, permeability, gastric emptying, intestinal transit, metabolism, and transporter activity may influence the relationship between formulation performance and observed pharmacokinetic profiles. In addition, intra-individual variability can affect the precision of pharmacokinetic comparisons, particularly for highly variable drug products. Recent advances in bioequivalence methodology, including harmonized regulatory guidance, physiologically based biopharmaceutics modelling, mechanistic dissolution approaches, and improved statistical study designs, provide opportunities to make BE assessment more informative and efficient.

Keywords: Bioequivalence; Pharmacokinetics; Formulation Performance; Drug Dissolution; Patient Variability; Intra-individual Variability; Bioavailability; Physiologically Based Biopharmaceutics Modelling; Generic Drugs; Drug Development

Introduction

Bioequivalence studies are designed to determine whether two pharmaceutical products provide comparable systemic exposure when administered under defined conditions. Pharmacokinetic parameters such as area under the concentration–time curve (AUC) and maximum plasma concentration (Cmax) are commonly used to characterize the extent and rate of drug exposure. Current international guidance has further harmonized approaches for bioequivalence assessment of immediate-release solid oral dosage forms, with ICH M13A providing recommendations for study design and analysis. The guideline became effective in the European [1].

However, pharmacokinetic similarity is influenced by more than the administered dose. The formulation determines how rapidly and completely the active pharmaceutical ingredient is released, dissolved, and made available for absorption. At the same time, the gastrointestinal environment and characteristics of the individual receiving the formulation can modify drug absorption. Consequently, observed pharmacokinetic variability may reflect a combination of formulation-related and physiological factors.

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A smarter bioequivalence strategy should therefore consider these factors as interconnected components. Integrating formulation behaviour, pharmacokinetic response, and patient variability may provide a more mechanistic understanding of why two products appear similar or different in a BE study [2].

Conclusion

Dissolution testing provides an essential link between pharmaceutical formulation and biological performance, but the relationship between in vitro drug release and in vivo exposure is neither automatic nor universal. Drug solubility, permeability, gastrointestinal physiology, formulation characteristics, and presystolic processes can all influence the transition from dissolution to systemic exposure.

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