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Commentary

# Clinical Importance of Therapeutic Drug Monitoring in Generic Drug Development

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## DESCRIPTION

Therapeutic Drug Monitoring (TDM) is a clinical practice used to measure drug concentrations in a patient's blood to optimize pharmacotherapy. It ensures that drug levels remain within a therapeutic range, minimizing toxicity while maximizing efficacy. While TDM is primarily applied to individualize treatment in patients, it also holds significance in the scope of Bioequivalence (BE) studies. TDM can play a critical role in refining and validating bioequivalence assessments, especially for complex drugs or those with Narrow Therapeutic Indices (NTIs).

Therapeutic drug monitoring involves the measurement of drug concentrations at designated intervals, aiming to maintain a drug's plasma levels within a target range that balances therapeutic benefits and adverse effects. TDM is particularly valuable for drugs with the following characteristics. Small differences in drug concentrations can lead to therapeutic failure or toxicity. Examples include warfarin, digoxin and cyclosporine. Drugs with significant inter-individual or intra-individual variability in absorption, distribution, metabolism, or excretion. Drugs for which clinical endpoints are challenging to measure, such as antiepileptics or immunosuppressants. Drugs where a small dose increase results in disproportionately high plasma concentrations. TDM guides dose adjustments based on individual pharma- cokinetics and ensures optimal treatment outcomes. In the context of bioequivalence, it provides a tool for comparing the pharmacokinetics of generic and reference innovator drugs in greater depth.

Bioequivalence studies aim to demonstrate that a generic drug delivers the same active ingredient to the site of action as the innovator drug, with comparable rate and extent of absorption. TDM can augment this process by offering insights into complex pharmacokinetics, validating PK parameters, and addressing specific challenges. For NTI drugs, small variations in plasma drug concentrations can result in significant clinical consequences. Regulatory agencies often impose tighter bioequivalence criteria for these drugs, requiring narrower acceptance ranges for PK parameters like maximum plasma concentration and area under the concentration-time curve.

Bioequivalence studies are often conducted in small, homogenous populations to minimize inter-individual variability. However, variability in drug absorption, distribution, metabolism, and excretion can still complicate the assessment of bioequivalence. TDM allows for more precise measurement of plasma drug levels, enabling researchers to quantify variability more accurately. For highly variable drugs, population pharmacokinetic approaches informed by TDM data can provide a robust framework for evaluating bioequivalence.

Complex drug formulations, such as Extended-Release (ER) tablets, transdermal systems, or liposomal drugs, present unique challenges in bioequivalence studies. These formulations often exhibit delayed or sustained drug release, requiring extended monitoring to capture their complete pharmacokinetic profiles. TDM facilitates detailed evaluation of these profiles, ensuring that the test and reference formulations exhibit similar release and absorption patterns over time. This is particularly important for drugs with multiple absorption phases or non-linear kinetics.

TDM can be integrated into the design of bioequivalence trials by including scheduled blood sampling to measure plasma drug levels over time. These measurements help establish detailed PK profiles for both the test and reference drugs. Additionally, TDM-based adjustments can be employed to refine trial protocols, ensuring accurate and reliable data.

*In vitro* dissolution studies are commonly used to predict the *in vivo* performance of oral formulations. However, *in vitro* tests may not fully capture the complexities of drug absorption in a physiological environment. TDM serves as a bridge between in vitro and in vivo data, validating dissolution profiles with real-world PK measurements. This approach strengthens the predictive power of in vitro studies and enhances the reliability of bioequivalence assessments.

PBPK modeling simulates drug absorption, distribution, metabolism, and excretion based on physiological and biochemical parameters.

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TDM provides real-world data that can be used to refine and validate these models, improving their predictive accuracy for bioequivalence studies. For instance, TDM data can be incorporated into PBPK models to simulate drug behavior under different physiological conditions, such as altered gastric pH or enzyme activity.