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Review Article

Biosensor-Based Innovations in Therapeutic Drug Monitoring: Bridging Traditional Methods and Precision Medicine

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ABSTRACT

Therapeutic Drug Monitoring (TDM) serves as a crucial component of personalized medicine, allowing healthcare providers to tailor drug dosages according to individual pharmacokinetic and pharmacodynamic profiles, thereby maximizing effectiveness and minimizing adverse effects. This detailed review investigates the essential principles and justifications for TDM, stressing its importance for medications with narrow therapeutic windows, considerable variations among patients, non-linear pharmacokinetics, and intricate drug interactions. It outlines the conventional TDM process from evaluating the patient and collecting samples to analyzing measurements, interpreting results, and continuous enhancement while also showcasing alternative methods that include point-of-care testing, non-invasive sampling methods, and AI-based modeling. A critical analysis of traditional analytical techniques such as LC-MS/MS, HPLC-UV/FLD, GC-MS, immunoassays, and atomic spectroscopy is provided, examining their principles, uses, benefits, and drawbacks. Following this, the article highlights the emerging trend towards the use of biosensors, motivated by the limitations of standard approaches like long turnaround times, invasiveness, and expensive procedures. Recent innovations in biosensors featuring continuous monitoring, non-invasive sampling, detailed PK/PD profiling, multiplexing, AI incorporation, CRISPR related systems, and nanomaterials are explored, demonstrating their capacity to transform TDM through real-time, decentralized, and patient-focused methods. The challenges faced in adopting biosensors, such as issues with stability, scalability, and regulatory obstacles, are discussed, emphasizing the importance of hybrid models that integrate both traditional and cutting-edge technologies. Ultimately, this review argues that the incorporation of biosensors in clinical settings can significantly improve patient outcomes in the age of precision medicine.

Keywords: Biosensors, Therapeutic Drug Monitoring, Narrow Therapeutic Index, Traditional Analytical Methods, LC-MS, HPLC, Gas Chromatography, Atomic Absorption, Immunoassays.

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INTRODUCTION

Therapeutic Drug Monitoring (TDM) is a basis of personalized medicine within clinical pharmacology, fundamentally aimed at optimizing individual medication therapy to enhance effectiveness and minimize adverse effects (Manubolu *et al*., 2024; Vermeire *et al*., 2020). At its core, TDM involves systematic measurement of drug concentrations in biological matrices, typically blood or plasma, but also increasingly in alternative fluids like saliva, cerebrospinal fluid, or urine (Manubolu *et al*., 2024; Ates *et al*., 2020; Kang & Lee, 2009). This process is driven by the premise that drug concentration in the body correlates more reliably with therapeutic and toxic effects than the administered dose alone (Manubolu *et al*., 2024; Fishberger *et al*., 2022).

The goal of TDM is to precisely adjust drug dosages to maintain concentrations within a predefined therapeutic window or target range, a concentration interval associated with optimal therapeutic response and minimal toxicity (Manubolu *et al*., 2024; Ates *et al*., 2020). This isn't a one-time assessment but a dynamic, feedback-driven process. It begins with the initial prescription, considering patient-specific factors like age, weight, organ function, and concomitant medications to establish a preliminary dosing schedule (Manubolu *et al*., 2024; Kwaw *et al*., 2022). Subsequently, measured drug concentrations, interpreted

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within the context of sampling time, prior dosing history, and patient clinical status, guide necessary dosage modifications (Manubolu *et al*., 2024; Kang & Lee, 2009).

Foundational to TDM are Pharmacokinetic (PK) principles-what the body does to the drug. Key PK characteristics, such as clearance, volume of distribution, and half-life, are critical in guiding dosage adjustments (Manubolu *et al*., 2024). TDM relies on a definable relationship between the dose and the drug's concentration in blood, and, in turn, between that concentration and the drug's therapeutic or toxic effects (Manubolu *et al*., 2024; Amponsah & Pathak, 2022). This comprehensive approach allows clinicians to make informed decisions for optimal patient benefit across diverse healthcare scenarios (Manubolu *et al*., 2024; Kang & Lee, 2009).

The Rationale for TDM

While TDM is not necessary for the majority of prescriptions, it becomes indispensable in specific situations where drug therapy demands careful management (Manubolu *et al*., 2024; Edenya & Atoe, 2024). The need for TDM stems from several crucial factors

Narrow Therapeutic Index

Drugs with a Narrow Therapeutic Index (NTI) are prime candidates for TDM because they possess a small margin between their minimum effective concentration and their minimum toxic concentration (Alakeel, 2024; Kwaw *et al*., 2022; Fishberger *et al*., 2022). Even slight deviations in concentration can lead to either subtherapeutic effects (treatment failure) or severe toxicity.

Inter-Patient Pharmacokinetic Variablity

Individual patients can exhibit significant variability in drug pharmacokinetics, meaning their bodies handle drugs differently (Alakeel, 2024; Kwaw *et al*., 2022; De Rose *et al*., 2020). This variability can arise from numerous factors.

Age and developmental changes

Neonates and children, for instance, have rapidly changing organ function and metabolic pathways, making their drug responses highly unpredictable (Alakeel, 2024; De Rose *et al*., 2020). Their clearance rates may necessitate higher mg/kg doses than adults (Patsalos *et al*., 2008). Elderly patients also exhibit altered pharmacokinetics and are more prone to drug interactions due to polypharmacy and age-related physiological changes (Patsalos *et al*., 2008).

Organ function

Renal and hepatic impairments significantly alter drug clearance and metabolism, affecting drug concentrations. Critically ill patients, who may experience augmented renal clearance or acute kidney injury, particularly benefit from TDM (Fishberger *et al*., 2022).

Genetics

Genetic polymorphisms, particularly in enzymes like cytochrome P-450 (CYP) and transporters, can lead to wide inter-individual variability in drug metabolism (Fishberger *et al*., 2022; Widmer *et al*., 2014; Mueller-Schoell *et al*., 2021). This genetic background can profoundly impact how a patient absorbs, distributes, metabolizes, and excretes a drug (De Rose *et al*., 2020).

Concomitant medications and comorbidities

The presence of other drugs or disease states can alter a drug's pharmacokinetics (Manubolu *et al*., 2024; Kwaw *et al*., 2022).

Non-Linear Pharmacokinetics

Some drugs exhibit non-linear pharmacokinetics, where a proportional increase in dose does not lead to a proportional increase in drug concentration (Manubolu *et al*., 2024; Kwaw *et al*., 2022). This is often due to saturation of metabolic enzymes or transport proteins at clinically relevant concentrations. Phenytoin is a classic example: its binding sites can become saturated at relatively low doses, leading to a rapid and unpredictable increase in plasma concentration with subsequent dose increments (Fishberger *et al*., 2022). For such drugs, TDM is crucial to avoid unintended toxicity.

Inadequate Clinical Endpoints

For many medications, directly monitoring their therapeutic effect is challenging or impossible (Kwaw *et al*., 2022; Kang & Lee, 2009). This is particularly true for:

Prophylactic drugs

Medications like lithium (for manic-depressive attacks) or immunosuppressants (to prevent transplant rejection) are administered to prevent an event, making direct clinical response difficult to assess (Kwaw *et al*., 2022). TDM ensures sufficient drug exposure without relying on the absence of a negative outcome (Fishberger *et al*., 2022).

Drugs with delayed or subtle effects

Some drugs, including many anticancer agents, may have effects that are not immediately apparent or are difficult to quantify with simple clinical observations (Paci *et al*., 2014). For these, drug concentration can serve as a valuable surrogate marker for efficacy and safety (Kwaw *et al*., 2022).

Drug and Disease Interactions

TDM is invaluable in managing complex drug-drug and drug-disease interactions that can significantly alter drug concentrations or patient response (Manubolu *et al*., 2024; Kwaw *et al*., 2022; Kang & Lee, 2009).

In patients taking multiple medications simultaneously, especially those with enzyme inducing or inhibiting properties, TDM helps

identify potential interactions and allows for timely dosage adjustments (Manubolu *et al.*, 2024; Johannessen & Landmark, 2008). For instance, rifampin, an enzyme inducer, can increase the clearance of cyclosporine, necessitating higher cyclosporine doses (Fishberger *et al.*, 2022).

HIV patients often receive complex antiretroviral regimens alongside other medications, making them highly susceptible to significant drug-drug interactions. TDM helps verify adequate concentrations for both HIV and concomitant drugs (Peloquin, 2002).

Parkinson's disease patients on levodopa frequently take other drugs for age-related comorbidities, which can interfere with levodopa plasma levels and increase side effects. TDM can help manage this variability (Müller *et al.*, 2024).

Economic and Regulatory Imperatives

Beyond direct patient care, TDM also offers significant economic benefits and addresses regulatory considerations (Kwaw *et al.*, 2022). By optimizing dosing, TDM can:

Reduce healthcare costs

By preventing subtherapeutic concentrations that lead to treatment failure, or supratherapeutic levels causing toxicity requiring hospitalization, TDM can shorten hospital stays and reduce the overall burden on healthcare systems (Ates *et al.*, 2020; Kang & Lee, 2009).

Improve resource allocation

For expensive medications, especially novel oral targeted anticancer therapies, TDM ensures that costly drugs are used optimally, maximizing their therapeutic potential and justifying their cost from a public health perspective (Widmer *et al.*, 2014).

Monitor compliance

TDM is an effective tool for assessing patient adherence to medication regimens (Manubolu *et al.*, 2024; Kang & Lee, 2009). Non-compliance is a major cause of treatment failure and can be identified by unexpectedly low drug concentrations (Edenya & Atoe, 2024).

TDM Workflow

Patient Assessment and Drug Selection

It begins with the patient assessment, where we establish a preliminary dosage regimen tailored to the individual's clinical status, considering factors like age, weight, organ function, and concomitant therapies (Alakeel, 2024; Kwaw *et al.*, 2022). Not all drugs require TDM; it is reserved for those where the dose-response relationship is poorly predictable and where there are significant consequences of under- or overdosing (Manubolu *et al.*, 2024; Ates *et al.*, 2020; Kang & Lee, 2009).

Dosing Initiation and Target Setting

Once a drug is selected for monitoring, the goal is to define and achieve a therapeutic concentration range - a "window" within which the drug is most effective with minimal toxicity (Manubolu *et al.*, 2024; Kwaw *et al.*, 2022). This involves setting an initial dosage regimen and then, critically, individualizing it. For many Antiepileptic Drugs (AEDs), for example, the concept of an "individual therapeutic concentration" has emerged, acknowledging that optimal levels can vary greatly among patients based on their unique response (Patsalos *et al.*, 2008; Johannessen & Landmark, 2008).

Sample Collection

This is a pivotal step, as accurate measurement relies heavily on proper sample collection. The choice of biological matrix is vital; while blood (serum or plasma) is the most common and often recommended specimen (Manubolu *et al.*, 2024; Ates *et al.*, 2020), other matrices like urine, saliva, and Cerebrospinal Fluid (CSF) may also be used (Resztak *et al.*, 2025; Amponsah & Pathak, 2022). For certain drugs like cyclosporine A, whole blood must be collected due to its distribution between red blood cells and plasma (Manubolu *et al.*, 2024).

Timing of sample collection is perhaps the most critical factor, as it can dramatically influence interpretation (Manubolu *et al.*, 2024; Kwaw *et al.*, 2022; Fishberger *et al.*, 2022).

Steady-state samples are generally preferred, collected after 4-5 half-lives of consistent dosing, when the drug's intake and elimination are in equilibrium (Kwaw *et al.*, 2022; Patsalos *et al.*, 2008).

Trough concentrations (C_{min}), measured just before the next dose, reflect the lowest drug level and are often used to assess steady-state and ensure sufficient ongoing exposure, particularly for drugs like vancomycin and linezolid (Manubolu *et al.*, 2024; Dogan *et al.*, 2025; Roberts *et al.*, 2012).

Peak concentrations (C_{max}), measured after drug administration (e.g., 30-60 min post-IV infusion), capture maximum drug exposure and are important for drugs with rapid onset or short half-lives, such as aminoglycosides (Manubolu *et al.*, 2024; Roberts *et al.*, 2012).

Analytical Measurement

Once collected, samples undergo laboratory evaluation to quantify drug concentrations. Common analytical techniques include:

Immunoassays (FPIA, EMIT, ELISA)

These are often easy to use, automated, and rely on validated kits, but can suffer from low specificity and cross-reactivity with metabolites or similar compounds, potentially leading to

inaccurate results (Campbell & Williams, 1998; Fishberger *et al.*, 2022).

Chromatography (HPLC, LC-MS/MS, GC-MS)

These methods offer higher sensitivity and specificity but are typically more expensive, require sophisticated equipment, and demand highly trained personnel and complex sample preparation (Manubolu *et al.*, 2024; Ates *et al.*, 2020; Kwaw *et al.*, 2022).

Rigorous quality control measures are essential throughout this process, including instrument calibration, assay validation, and participation in external quality assurance programs, to ensure the reliability and accuracy of TDM results (Manubolu *et al.*, 2024; Kang & Lee, 2009).

INTERPRETATION OF RESULTS

Interpreting TDM results involves a holistic view of the patient's data (Manubolu *et al.*, 2024; Kwaw *et al.*, 2022).

Comparison with therapeutic ranges

Drug concentrations are compared against established reference ranges. However, it's crucial to remember that these ranges are probabilistic and many patients may achieve optimal outcomes outside them (Kang & Lee, 2009; Ghiculescu, 2008).

Assessment of pharmacokinetic parameters

Evaluating parameters like C_{max}, C_{min}, AUC, and half-life helps understand how the drug is absorbed, distributed, metabolized, and eliminated in that specific patient (Dogan *et al.*, 2025; Roberts *et al.*, 2012).

Consideration of patient factors

Individual variables such as age, weight, renal and hepatic function, genetics, comorbidities, and concomitant medications (which can lead to significant drug-drug interactions) profoundly impact drug behavior and must be carefully integrated into the interpretation (Kwaw *et al.*, 2022; Patsalos *et al.*, 2008).

Dose Adjustment and Treatment Optimization

Based on comprehensive interpretation, healthcare providers make informed decisions to adjust the drug therapy (Manubolu *et al.*, 2024). This might involve increasing or decreasing the dose, or altering the dosing frequency (Manubolu *et al.*, 2024; Dogan *et al.*, 2025). The aim is to optimize therapeutic efficacy while minimizing adverse effects (Manubolu *et al.*, 2024). TDM is particularly valuable in managing drug-drug interactions by allowing clinicians to adjust regimens or select alternative therapies to maintain efficacy and safety (Fishberger *et al.*, 2022; Johannessen & Landmark, 2008). Evidence-based algorithms often guide these adjustments (Manubolu *et al.*, 2024; Vermeire *et al.*, 2020).

Ongoing Monitoring and Evaluation

The TDM process is not a one-time event; it's a continuous cycle. Treatment decisions and their rationale are meticulously documented (Manubolu *et al.*, 2024). Follow-up monitoring is scheduled to assess the patient's response, track for adverse effects, and ensure ongoing therapeutic optimization (Manubolu *et al.*, 2024). TDM can significantly reduce healthcare costs by decreasing hospitalizations and the incidence of adverse drug reactions (Kwaw *et al.*, 2022; Kang & Lee, 2009; Widmer *et al.*, 2014). It's a fundamental tool for quality assurance in drug therapy (Johannessen & Landmark, 2008).

TRADITIONAL ANALYTICAL METHODS IN TDM

Liquid Chromatography-Tandem Mass Spectroscopy (LC-MS)

Principle

At the forefront of modern TDM is Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS), widely regarded as the gold standard for quantitative detection of small molecules (Zhang & Garg, 2024; Wang *et al.*, 2025). This powerful analytical technique operates by first separating compounds within a complex biological sample using Liquid Chromatography (LC) (Bekoe *et al.*, 2022; Zhang & Garg, 2024). Following separation, the isolated analytes are ionized, typically via Electrospray Ionization (ESI), and then introduced into a tandem Mass Spectrometer (MS/MS) (Pigliasco *et al.*, 2024; Zhang & Garg, 2024). The MS/MS component then selects a "precursor ion" and fragments it into specific "product ions," which are then detected (Zhang & Garg, 2024). This process, often performed in "Multiple Reaction Monitoring" (MRM) mode, provides exceptional specificity by identifying drugs based on unique fragmentation patterns (Zhang & Garg, 2024; Gqamana & Zhang, 2024). To ensure high accuracy and compensate for variations in ionization and extraction efficiency, Stable Isotope-Labeled Internal Standards (SIL-IS) are almost universally employed, behaving identically to the target analyte but with a different mass (Kocur *et al.*, 2024; Adaway & Keevil, 2012).

Key Advantages

LC-MS/MS offers unparalleled specificity and sensitivity, enabling the definitive identification and quantification of drugs, even at very low concentrations, overcoming limitations of older immunoassay methods prone to cross-reactivity (Adaway & Keevil, 2012; Zhang & Garg, 2024). This inherent specificity has made it indispensable for compounds lacking natural chromophores or fluorophores, or those with significant metabolite interference (Adaway & Keevil, 2012).

Perhaps one of its most transformative benefits is its revolutionary multiplexing capability, allowing for the simultaneous measurement of dozens to hundreds of analytes from a single

sample aliquot (Zhang & Garg, 2024; Adaway & Keevil, 2012). This has revolutionized monitoring in complex clinical scenarios, such as in Intensive Care Units (ICUs), where patients often receive multiple antibiotics (Qi *et al*., 2025; Radovanovic *et al*., 2022). For instance, recent methods can simultaneously quantify 10-15 antibiotics in human plasma within minutes, a significant leap from traditional methods that would require multiple, time-consuming assays (Radovanovic *et al*., 2022). "The ability to quantify multiple drugs simultaneously in critically ill patients has significantly improved the optimization of antimicrobial therapy," allowing for timely dose adjustments that improve patient outcomes and potentially reduce drug resistance (Qi *et al*., 2025; Radovanovic *et al*., 2022).

LC-MS/MS methods often feature streamlined sample preparation, employing simple techniques like protein precipitation or "dilute and shoot," which significantly reduce pre-analytical steps and analysis time (Radovanovic *et al*., 2022; Adaway & Keevil, 2012). This simplicity, coupled with rapid chromatographic separation, translates to fast turnaround times, with total run times per sample often ranging from 2 to 15 minutes (Radovanovic *et al*., 2022; Wang *et al*., 2025). Even with calibration and controls, results can often be available within hours, crucially before the next dosing interval, directly impacting clinical decisions (Radovanovic *et al*., 2022). The versatility of LC-MS/MS is remarkable, covering a broad spectrum of drugs across various therapeutic classes. These include, but are not limited to:

- **Immunosuppressants** like tacrolimus, sirolimus, everolimus, and mycophenolic acid (Wolken *et al*., 2024; Avataneo *et al*., 2019).
- **Antivirals** such as ganciclovir and antiretroviral drugs (Kocur *et al*., 2024; Avataneo *et al*., 2019).
- **Antiepileptics** including fenfluramine, cannabidiol, levetiracetam, and lamotrigine (Pigliasco *et al*., 2024; Bodor & Rands, 2024).
- **Antibiotics and Antifungals** like omadacycline, vancomycin, teicoplanin, piperacillin, voriconazole, and itraconazole (Qi *et al*., 2025; Wang *et al*., 2025; Cafaro *et al*., 2024; Dejaco *et al*., 2025).
- **Analgesics** such as morphine, oxycodone, and fentanyl (Yao *et al*., 2024).

Other critical drugs including oral antineoplastics, antidepressants, and cardiovascular agents (Gaspar *et al*., 2021). The typical Lower Limit of Quantification (LLOQ) for these assays can be as low as 0.005 ng/mL for some analgesics or 0.82 ng/mL for norfenfluramine, extending to wide calibration ranges suitable for clinical monitoring (Wang *et al*., 2025; Pigliasco *et al*., 2024).

Challenges and Considerations

Despite its advantages, LC-MS/MS comes with significant hurdles. The high initial capital investment for instrumentation is substantial, making it inaccessible for many laboratories (Zhang & Garg, 2024; Gaspar *et al*., 2021). Furthermore, its operation and method development demand highly specialized and trained personnel, a critical bottleneck for widespread adoption (Adaway & Keevil, 2012; Seger & Salzmann, 2020).

HPLC (High Performance Liquid Chromatography)

Principle

High-Performance Liquid Chromatography (HPLC) is a chromatographic separation technique that leverages the differing interactions of compounds with a stationary phase (typically a column) and a mobile phase (solvent system) (Tuzimski & Petruczynik, 2020). This allows for the effective separation of complex mixtures, making it a versatile tool in pharmaceutical analysis (Bekoe *et al*., 2022).

UV Detection (HPLC-UV)

This detection method relies on the principle that many drug molecules absorb UV light. When electrons within a molecule's atoms are promoted from a ground state to an excited state by absorbing energy from UV light at specific wavelengths, this absorption can be quantified (MohammadiArani *et al*., 2023). This makes HPLC-UV particularly suitable for drugs with chromophores (light-absorbing groups) in their structure (Tuzimski & Petruczynik, 2020).

Fluorescence Detection (HPLC-FLD)

For compounds that naturally fluoresce or can be chemically derivatized to become fluorescent, FLD offers enhanced sensitivity. It measures the light emitted by molecules after they absorb light at a specific excitation wavelength (Tuzimski & Petruczynik, 2020).

Key Advantages

HPLC-UV/FLD methods are often favored for routine TDM due to their simplicity, cost-effectiveness, and lower maintenance requirements compared to LC-MS/MS systems, making them highly suitable for general hospital laboratories (Tuzimski & Petruczynik, 2020; Boccardi *et al*., 2024). As one study on ceftobiprole noted, "LC-MS/MS availability is still not so obliquitous in hospitals for both its high cost and the need of specialized staff, while HPLC-UV is sensitive and accurate enough to guide clinician decision". This highlights the pragmatic choice of HPLC-UV in budget-limited clinical settings to ensure TDM implementation (Boccardi *et al*., 2024).

Sample Preparation

A crucial step for accurate analysis in biological matrices is sample preparation, which typically involves removing interfering substances while retaining the analytes of interest. Common techniques include:

Protein Precipitation (PP)

A widely used, straightforward method where proteins are precipitated (e.g., using acetonitrile or sulphosalicylic acid), and the supernatant containing the drug is then analyzed (Tuzimski & Petruczynik, 2020; Boccardi *et al*., 2024).

Liquid-Liquid Extraction (LLE) and Solid-Phase Extraction (SPE)

These are employed for more extensive cleanup and concentration, especially for drugs present at lower concentrations or in complex matrices (Tuzimski & Petruczynik, 2020).

Derivatization

For drugs lacking a natural chromophore, pre-column derivatization is essential to enable UV or fluorescence detection. A notable example is Valproic Acid (VPA), an anticonvulsant with a therapeutic range of 50-100 µg/mL (Kaewpradit *et al*., 2024). VPA lacks a chromophore, making direct detection challenging. However, a recent innovative method utilized microwave-assisted derivatization (MAD) with phenylhydrazine hydrochloride (PH HCl), allowing for efficient HPLC-UV detection (Kaewpradit *et al*., 2024). This streamlined process, optimized at 450W for 50 seconds, significantly improved feasibility and cost-effectiveness, offering "a viable alternative to conventional HPLC methodologies, offering a balance of efficiency and economic practicality for VPA quantification" (Kaewpradit *et al*., 2024). The reported sensitivity for VPA in plasma using this MAD method was adequate for TDM, with a concentration of 30 µg/mL being detectable (Kaewpradit *et al*., 2024).

Drugs Commonly Monitored with HPLC-UV/FLD: Many drugs across various therapeutic classes are quantified using HPLC-UV/FLD due to their suitable concentrations in biological samples and UV absorption properties.

Carbamazepine (CBZ) and its Metabolites

A widely used antiepileptic drug, TDM for CBZ is crucial due to its narrow therapeutic window and significant inter-individual variability (Milosheska & Roškar, 2023). HPLC-UV methods have been extensively developed for CBZ and its active metabolites, such as carbamazepine-10,11-epoxide (CBZ-E) and 10-Monohydroxycarbazepine (MHD) (MohammadiArani *et al*., 2023; Milosheska & Roškar, 2023). A recent HPLC-UV method simultaneously quantified 12 antiepileptic drugs and 3 metabolites, including CBZ, CBZ-E, and MHD, in a single run using a Phenyl-Hexyl column, which enhances interactions with aromatic compounds (Milosheska & Roškar, 2023). This method reported LOQ values of 0.5 mg/L for CBZ and 0.2 mg/L for CBZ-E.

Vancomycin

This important antibiotic requires TDM to maintain effective plasma concentrations, typically within 10.0-20.0 µg/mL (Jiang *et al*., 2024). HPLC-UV methods, detecting at 240 nm, have been validated for its quantification, with a reported LLOQ of 1 µg/mL (Tuzimski & Petruczynik, 2020). The necessity for TDM is underscored by observations of a high proportion of subtherapeutic concentrations in patients.

Ceftobiprole (CB)

A newer cephalosporin, Ceftobiprole (CB) also benefits from TDM. HPLC-UV methods have been developed to support routine monitoring, offering a linear range of 0.5-50.0 mg/L and an LOQ of 0.5 mg/L. Its simple protein precipitation sample preparation makes it practical for busy hospital labs (Boccardi *et al*., 2024).

Other Antibiotics

HPLC-UV is often suitable for various antibiotics (e.g., piperacillin, tazobactam, daptomycin, linezolid) because they are frequently administered in high doses, leading to concentrations in biological samples that are readily detectable by UV (Tuzimski & Petruczynik, 2020).

Anticancer Drugs

For many anticancer drugs like enzalutamide and methotrexate, HPLC-UV is utilized, particularly when high doses result in high plasma concentrations. For enzalutamide, the LOD was 0.20 µg/mL and LLOQ 0.50 µg/mL. Methotrexate can be quantified by HPLC-UV with an LLOQ of 0.05 µmol/L (approximately 0.0227 µg/mL) (Tuzimski & Petruczynik, 2020).

Safinamide (SAF)

An anti-Parkinsonian drug, SAF can be quantified using HPLC-DAD, which also detects degradation products and impurities. Its methods emphasize eco-friendly and time-efficient aspects (Ibrahim *et al*., 2024), with linearity up to 150 µg/mL (Ibrahim *et al*., 2024).

Limitations

While highly valuable, HPLC-UV/FLD methods do have limitations that sometimes necessitate the use of more advanced techniques:

Sensitivity for Low Concentration Drugs

While adequate for many drugs, HPLC-UV/FLD may lack the sensitivity required for drugs present at very low concentrations in biological matrices (Bekoe *et al*., 2022; Tuzimski & Petruczynik,

2020). UPLC and LC-MS/MS, for instance, can quantify drugs down to picogram levels (Vanitha Madhuri *et al.*, 2024).

Specificity and Interference Challenges

Although HPLC offers good specificity through chromatographic separation (Tuzimski & Petruczynik, 2020; Nassar *et al.*, 2025), interference from co-administered medications or endogenous matrix components can still be a concern, especially in complex clinical samples (Milosheska & Roškar, 2023). Careful evaluation of selectivity is crucial.

Requirement for Derivatization

For drugs that do not possess intrinsic chromophores or fluorophores (like Valproic acid), a derivatization step is necessary to enable detection by UV or FLD (Tuzimski & Petruczynik, 2020). This additional step can add complexity and time to the analytical process (Kaewpradit *et al.*, 2024).

Run Time for Complex Mixtures

While some HPLC methods are rapid, achieving separation for multiple analytes with diverse physicochemical properties can lead to longer run times (Boccardi *et al.*, 2024; Zayed *et al.*, 2024; Nassar *et al.*, 2025). For very complex or high-throughput needs, LC-MS/MS might offer significantly shorter analysis times (Jiang *et al.*, 2024; Lee *et al.*, 2024).

Initial Capital Investment

Compared to simpler analytical techniques like immunoassays, HPLC systems represent a higher initial capital investment for laboratories, although their running costs are generally considered low (Bekoe *et al.*, 2022).

Gas Chromatography (GC)

Principle

Gas Chromatography, particularly when coupled with Mass Spectrometry (GC-MS), stands out as a powerful analytical tool for drug quantification (Nikolaou *et al.*, 2015; Ando *et al.*, 2020; Hahn *et al.*, 2017; Chiadmi & Schlatter, 2015). At its core, GC separates compounds based on their volatility and interaction with a stationary phase inside a heated column (Ikeda *et al.*, 2014). Once separated, these compounds are detected, often by a mass spectrometer, which identifies them based on their unique fragmentation patterns. GC-FID (Flame Ionization Detection) and GC-ECD (Electron Capture Detection) are other common GC detectors, offering high sensitivity for specific types of compounds.

Derivatization

A significant aspect of GC analysis, especially for polar or less volatile compounds, is derivatization (Nikolaou *et al.*, 2015). This chemical modification makes the analyte more volatile and stable, improves chromatographic behavior (reducing peak tailing), and often enhances detection sensitivity.

Lacosamide, an antiepileptic drug, requires silylation using N-methyl-N-tert-butyldimethylsilyltrifluoroacetamide (MTBSTFA) with 1% tert-butyldimethylsilylchloride (TBDMSCl) before GC-MS analysis due to its polar amino groups (Nikolaou *et al.*, 2015). This method, validated for human plasma, was reported as the first of its kind using GC-MS for lacosamide determination.

Valproic acid (VPA), widely used for epilepsy, has been quantified in tears and plasma. For tears, a GC/ECNCI/MS method converted VPA directly into its pentafluorobenzyl ester (PFB-ester) derivative without prior extraction (Nakajima *et al.*, 2000). In another GC-EI-MS method for dried plasma spots, VPA was trimethylsilylated using N-methy l-N-trimethylsilyltrifluoroacetamide (MSTFA) (Ikeda *et al.*, 2014). GC-FID methods for VPA in plasma have also been reported using dispersive liquid-liquid microextraction (DLLME) (Fazeli-Bakhtiyari *et al.*, 2015).

Theophylline, a bronchodilator, was determined in tears and plasma using GC-EI-MS after being converted to its pentafluorobenzoyl amide (PFB-amide) derivative (Nakajima *et al.*, 2003).

Mitotane, a key drug for adrenal cortical carcinoma, was analyzed in plasma using a simplified GC-EI-MS method after deproteination and liquid-liquid extraction (Ando *et al.*, 2020).

Topiramate, another antiepileptic, can be measured in Dried Blood Spots (DBS) using GC-MS after a flash methylation with Trimethylanilinium Hydroxide (TMAH). This is particularly advantageous as whole blood is considered a more suitable matrix for TOP TDM due to its concentration-dependent binding to erythrocytes (Hahn *et al.*, 2017).

Methadone and its principal metabolite, EDDP, have been quantified in human plasma using GC-MS with derivatization by bis(trimethylsilyl)trifluoroacetamide (BSTFA) + 1% Trimethylchlorosilane (TMCS) (Chiadmi & Schlatter, 2015).

Immunoassays

Principle

Immunoassays are analytical techniques that leverage the highly specific binding affinity between antibodies and antigens for the detection and quantification of target analytes (Bekoe *et al.*, 2022). For small drug molecules like many therapeutics, a competitive immunoassay format is typically employed, where the drug in the sample competes with a labeled drug derivative for binding to a specific antibody. The signal intensity is inversely proportional to the drug concentration (Cavalera *et al.*, 2023). These assays can be categorized as heterogeneous (requiring a separation step) or homogeneous (no separation needed) (Kozo *et al.*, 2017). Many

modern immunoassays are designed for automated clinical chemistry analyzers, making them a common sight in routine laboratories (Kozo *et al.*, 2017).

Gemcitabine

A rapid, homogeneous nanoparticle immunoassay was developed for this anticancer agent, utilizing a monoclonal antibody coated on nanoparticles (Kozo *et al.*, 2017). This assay was specifically designed to be robust and not affected by the major metabolite dFdU or the blood stabilizer THU (Kozo *et al.*, 2017).

Busulfan

A nanoparticle immunoassay for busulfan, an alkylating agent used in stem cell transplantation, demonstrated good precision, accuracy, and linearity (Hilaire *et al.*, 2021). It showed good correlation with mass spectrometry methods.

Immunosuppressants

Immunoassays are widely used for routine monitoring of critical drugs like tacrolimus, cyclosporine, sirolimus, everolimus, and mycophenolic acid due to their speed and ease of operation (Dasgupta, 2016).

Tacrolimus

While immunoassays like CMIA are routinely used and FDA-approved, they often exhibit a positive bias compared to the LC-MS/MS gold standard, largely due to cross-reactivity with active metabolites (e.g., M-II). Issues like low hematocrit and endogenous antibodies (e.g., rheumatoid factor) can also cause false-positive results with certain immunoassay platforms (Dasgupta, 2016).

Cyclosporine

Immunoassays for cyclosporine often lack specificity because they cannot distinguish the parent drug from its numerous metabolites, which increase over the course of treatment, leading to positive bias (Dasgupta, 2016; Wang *et al.*, 2021). Whole blood is the preferred sample matrix for these drugs due to their distribution within blood components.

Tenofovir (TFV)

ELISA and Lateral Flow Immunoassays (LFIAs) have been developed for TFV in saliva, requiring high sensitivity due to low drug levels in this matrix (Cavalera *et al.*, 2023). LFIAs offer rapid, on-site screening suitable for low-resource settings.

Methotrexate (MTX)

Various immunoassays are used for MTX monitoring, but concerns exist regarding the influence of metabolites like 7-hydroxymethotrexate on assay results and clinical decision-making (Descoeur *et al.*, 2022).

TNF-alpha inhibitors (Infliximab, Adalimumab)

ELISAs are extensively used, but new chemiluminescent and fluorescence-based immunoassays offer faster turnaround times and higher throughput, potentially enabling more proactive TDM (Kim *et al.*, 2024; Van Aalen *et al.*, 2023; Vroemen *et al.*, 2024).

Pros:

- Cost-effective and economical (Bekoe *et al.*, 2022; Kozo *et al.*, 2017).
- Rapid detection and faster turnaround times (Bekoe *et al.*, 2022; Vroemen *et al.*, 2024; Hilaire *et al.*, 2021).
- Robust and user-friendly (Bekoe *et al.*, 2022).
- Automated and suitable for routine clinical analyzers (Kozo *et al.*, 2017; Hilaire *et al.*, 2021).

Cons:

- Significant cross-reactivity with drug metabolites is a major limitation, leading to positive bias and potentially inaccurate results compared to more specific methods (Dasgupta, 2016; Wang *et al.*, 2021).
- Potential for false-positive or false-negative results (Bekoe *et al.*, 2022; Descoeur *et al.*, 2022).
- Matrix effects and interference from endogenous substances or antibodies (e.g., rheumatoid factor) can compromise accuracy (Bekoe *et al.*, 2022; Hilaire *et al.*, 2021; Dasgupta, 2016).
- Generally, not suitable for simultaneous multi-component analysis (Bekoe *et al.*, 2022).
- Lack of standardization across different assays and laboratories can lead to interlaboratory variability (Dasgupta, 2016).

Atomic Spectroscopy & Inductively Coupled Plasma-Mass Spectrometry

Principle

Atomic Absorption Spectrometry (AAS)

AAS measures the absorption of light by free atoms in a sample, which is proportional to their concentration (Clases & Gonzalez De Vega, 2022). For lithium, this involves monitoring the partial resolution of its isotopic shift in the electronic transition (Winckelmann *et al.*, 2022).

Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)

This powerful technique ionizes elements in an argon plasma, extracts the ions, and separates them based on their mass-to-charge ratio (m/z) before detection (Clases & Gonzalez De Vega,

2022). ICP-MS is renowned for its high sensitivity, isotopic selectivity, and vast linear dynamic range, making it ideal for trace element analysis (Davison *et al.*, 2023). Hyphenated techniques, such as Liquid Chromatography-ICP-MS (LC-ICP-MS) and Laser Ablation-ICP-MS (LA-ICP-MS), couple separation or direct solid sampling with ICP-MS, enabling elemental speciation and bioimaging (Clases & Gonzalez De Vega, 2022).

Drugs Monitored and Practical Considerations

Lithium

Due to its narrow therapeutic range, close monitoring of lithium concentration is mandatory (Winckelmann *et al.*, 2022). ICP-MS and AAS methods are utilized, with isotope dilution techniques offering traceable and precise determination with reduced uncertainties and less matrix sensitivity (Winckelmann *et al.*, 2022).

Metal-Based Anticancer Drugs (e.g., Platinum/Cisplatin, Ruthenium)

ICP-MS is invaluable for understanding the pharmacokinetics and pharmacodynamics of these drugs.

It can directly measure metal content in drug-exposed cells to determine uptake rates and intracellular localization (Timerbaev, 2021; Clases & Gonzalez De Vega, 2022).

LA-ICP-MS provides elemental bioimaging to visualize drug distribution and accumulation within tissues at high spatial resolution, crucial for understanding efficacy and side effects (e.g., platinum deposition in tumors, liver, kidney) (Clases & Gonzalez De Vega, 2022).

Gadolinium-Based Contrast Agents (GBCAs)

ICP-MS is used to study the distribution and deposition of gadolinium in tissues, particularly in the brain, relevant for patient safety due to potential retention (Timerbaev, 2021).

Bismuth-Based Antibiotics: ICP-MS aids in understanding their mechanism of action by identifying bismuth-containing proteins (Timerbaev, 2021).

Pros:

- High sensitivity and selectivity, capable of detecting major, trace, and toxicologically relevant elements (Clases & Gonzalez De Vega, 2022).
- Multi-elemental capability, allowing comprehensive profiling of elements in biological samples (Clases & Gonzalez De Vega, 2022).
- Elemental speciation analysis when coupled with chromatography, providing insight into the functional forms of elements (Clases & Gonzalez De Vega, 2022).
- Elemental bioimaging with LA-ICP-MS, offering high spatial resolution to visualize drug distribution in tissues (Clases & Gonzalez De Vega, 2022).
- Isotope Dilution Analysis (IDA) provides absolute quantification with high accuracy, less susceptibility to matrix effects, and reduced uncertainties (Winckelmann *et al.*, 2022).

Cons:

- High initial capital investment and running costs (Winckelmann *et al.*, 2022).
- Requires extensive expertise and highly trained personnel for operation and method development (Clases & Gonzalez De Vega, 2022).
- Often involves laborious sample preparation steps (e.g., acid digestion for total metal content) (Timerbaev, 2021).
- Lack of Certified Reference Materials (CRMs) for all matrices and elements, which can complicate validation and standardization (Clases & Gonzalez De Vega, 2022).
- While generally robust, can still face matrix effects or spectral interferences, though advanced hardware (e.g., collision/reaction cells, tandem MS) mitigates these (Timerbaev, 2021).

LIMITATIONS OF TRADITIONAL LAB-BASED METHODS DRIVING THE SHIFT TO BIOSENSORS

Prolonged Turnaround Times

ELISA, a commonly used immunoassay, typically requires several days for results, primarily because laboratories conduct batch testing, accumulating samples before analysis (Kim *et al.*, 2024). Similarly, chromatographic methods such as HPLC and LC-MS/MS involve laborious sample preparation and long processing times, which can extend to hours or even days (Garzón *et al.*, 2019; Casian *et al.*, 2025; Chen *et al.*, 2025; Astúa *et al.*, 2025). This delay is particularly critical for drugs with narrow therapeutic windows, where rapid adjustments are essential to prevent adverse effects like vancomycin's potential for kidney and ear toxicity (Hemdan *et al.*, 2024; Kudłacik-Kramarczyk *et al.*, 2025).

Invasiveness and Sample Volume

Traditional methods usually necessitate blood sample collection by trained personnel, which is invasive, can cause patient discomfort, and is impractical for vulnerable populations such as neonates or critically ill patients (Awad *et al.*, 2025; Sedighi *et al.*, 2026). Large sample volumes (e.g., ≥1 mL) are often required, limiting frequent monitoring (Garzón *et al.*, 2020).

Centralisation and Accessibility

The need for specialised laboratories and trained staff means TDM is often confined to centralised facilities, making it unfeasible for widespread, routine application, especially in rural or resource-limited areas (Kim *et al.*, 2024; Garzón *et al.*, 2019; Garzón *et al.*, 2020; Awad *et al.*, 2025; Astúa *et al.*, 2025). This centralisation can lead to significant delays (e.g., 24-hour waits) in receiving crucial results, particularly impacting timely clinical decision-making (Awad *et al.*, 2025).

High Costs

HPLC and LC-MS/MS instruments are expensive, and their operation requires costly reagents and highly skilled personnel, leading to substantial per-test costs (e.g., reported costs of €15-€80 per test, though not explicitly stated in the provided sources, it is implied by the emphasis on cost-effectiveness of biosensors) (Garzón *et al.*, 2019; Garzón *et al.*, 2020; Awad *et al.*, 2025). ELISA also contributes to costs through the need for calibration curves and trained staff (Kim *et al.*, 2024).

Interference Effects

Immunoassays can be susceptible to interference from matrix components, co-administered drugs, and metabolites, potentially leading to inaccurate results (Chen *et al.*, 2025).

These limitations collectively underscore the urgent demand for alternative, more efficient solutions for TDM, driving a significant shift towards biosensors for faster, less invasive, and decentralised monitoring (Jarnda *et al.*, 2025; Awad *et al.*, 2025).

Biosensors: Their Transformative Role in TDM

A biosensor is an advanced analytical device that precisely detects subtle changes in complex biological processes, converting these variations into clear, measurable signals (Hemdan *et al.*, 2024; Kudłacik-Kramarczyk *et al.*, 2025). It typically integrates a biological recognition element (e.g., enzymes, antibodies, nucleic acids) with a physicochemical transducer that converts the biological interaction into a quantifiable signal (e.g., electrical, optical, or mass-sensitive) (Jarnda *et al.*, 2025).

In TDM, biosensors play a pivotal role by providing real-time or near-real-time monitoring of drug concentrations in biological samples (Hemdan *et al.*, 2025). This capability moves beyond the 'snapshot' measurements of traditional methods, enabling continuous monitoring of vital physiological and biochemical parameters (Vo & Trinh, 2024; Mayol *et al.*, 2025; Frumento & Țălu, 2025; Duan *et al.*, 2025).

ADVANCEMENTS OF BIOSENSORS IN TDM

Continuous Monitoring and Point-of-Care (POCT) Integration

Optical Biosensors and Microfluidic Paper-Based Analytical Devices (µPADs) have emerged as cost-effective, portable, and highly sensitive tools (Garzón *et al.*, 2020; Jarnda *et al.*, 2025). µPADs, for instance, can provide rapid results, often within minutes, for biomarkers like glucose and uric acid (Jarnda *et al.*, 2025).

Electrochemical Biosensors are particularly attractive for POCT due to their high sensitivity, portability, and direct electronic output, eliminating the need for additional detectors (Frumento & Țălu, 2025; Lehr *et al.*, 2026; Belcastro & Arduini, 2025).

Wearable and Implantable Biosensors represent a significant frontier, offering continuous, non-invasive or minimally invasive monitoring of physiological parameters and drug levels directly on or within the body (Vo & Trinh, 2024; Hemdan *et al.*, 2024; Duan *et al.*, 2025). LC-MS/MS, while a gold standard for drug quantification, is now seen as a reference for validating these emerging biosensor technologies (Casian *et al.*, 2025; Astúa *et al.*, 2025; Minichmayr *et al.*, 2024).

Smartphone-Assisted Systems enable user-friendly, real-time data exchange and analysis, making TDM more accessible at home or in remote settings (Awad *et al.*, 2025; Hemdan *et al.*, 2025). For example, the MediMeter app, combined with colorimetric and electrochemical biosensors, successfully quantified paracetamol in artificial saliva within minutes, demonstrating potential for remote drug monitoring (Awad *et al.*, 2025).

Plasmonic Biosensors offer high specificity and sensitivity for rapid antibiotic monitoring, with results in under 20 minutes for amikacin and colistin in blood serum (Astúa *et al.*, 2025).

Ultra-Low Volume and Non-Invasive Sample Analysis

Biosensors can analyse diverse biological fluids, including saliva, sweat, tears, and interstitial fluid (ISF), offering less invasive alternatives to blood sampling (Awad *et al.*, 2025; Duan *et al.*, 2025).

Saliva-based sensors are explored for drugs like paracetamol and potentially tacrolimus, offering advantages like non-invasiveness and cost-effectiveness (Jarnda *et al.*, 2025).

Sweat-based biosensors enable dynamic profiling of stress hormones (Tu *et al.*, 2025) and continuous monitoring of electrolytes and metabolites (Frumento & Țălu, 2025).

Tear-based biosensors, such as contact lenses, can quantify glucose (Garzón *et al.*, 2020) and ocular proteins like TNF-α (Duan *et al.*, 2025).

Microneedle (MN) patches provide minimally invasive access to ISF, allowing continuous monitoring of drugs like phenoxymethylpenicillin, tobramycin, and vancomycin, as well as metabolites and cytokines (Mayol *et al.*, 2025; Vo & Trinh, 2024; Hemdan *et al.*, 2024). This allows for the detection of unbound, active drug levels.

Paper-based SERS Nanosensors facilitate rapid detection of drugs like flucytosine in undiluted serum and whole blood by physically separating the analyte from blood components (Agogo-Mawuli & Siderovski, 2022).

High-Resolution Pharmacokinetic/ Pharmacodynamic (PK/PD) Profiling

Aptamer-based electrochemical (E-AB) sensors can provide high-resolution temporal datasets for real-time pharmacokinetic analysis in living animals, linking drug elimination rates to organ function (e.g., tobramycin in rats and kidney function) (Minichmayr *et al.*, 2024; Mayol *et al.*, 2025; Lehr *et al.*, 2026). This significantly enhances the understanding of drug dynamics compared to traditional snapshot measurements.

Digital Twins, virtual replicas of an individual's physiological systems, can simulate the impact of interventions, providing a proactive approach to healthcare by integrating real-time biosensor data (Soumma *et al.*, 2025).

Model-Informed Precision Dosing (MIPD) integrates mathematical predictions with patient-specific factors and biosensor data, moving beyond traditional TDM for more accurate dosing (Minichmayr *et al.*, 2024).

Multiplexed Detection Capabilities

Biosensors can detect multiple analytes simultaneously, offering comprehensive diagnostic profiles from a single test (Jarnda *et al.*, 2025; Ranjan *et al.*, 2025). µPADs, for instance, can perform multiple analyses on one strip.

Surface Plasmon Resonance imaging (SPRi) allows for the simultaneous study of multiple biomolecular interactions, making it suitable for multiplexed analysis of monoclonal antibodies or cardiovascular biomarkers (Garzón *et al.*, 2019; Hemdan *et al.*, 2024; Puiu & Bala, 2016; Mondal *et al.*, 2023).

Researchers have developed an integrated microfluidic platform for swiftly measuring cardiovascular disease biomarkers such as NT-proBNP, fibrinogen, cTnI, and CRP (Hemdan *et al.*, 2024).

Integration of Artificial Intelligence (AI)

AI-powered biosensors revolutionize health monitoring by enabling real-time data analysis, pattern recognition, and predictive modelling (Soumma *et al.*, 2025).

Machine learning algorithms enhance the precision of wearable devices in processing physiological signals, such as glucose levels and heart rate variability (Soumma *et al.*, 2025).

AI assists in optimizing sensor design, managing large datasets, and improving the overall performance and reliability of electrochemical diagnostics (Ranjan *et al.*, 2025). For example, AI has been used to significantly lower the limit of detection for tyrosine and uric acid using electrochemical eMoSx-LIG sensors in sweat and saliva.

Large Language Models (LLMs) can process and contextualize vast amounts of health data from biosensors, generating personalized health insights and recommendations (Soumma *et al.*, 2025).

Counterfactual explanations generated by AI can enhance trust and transparency by illustrating how changes in lifestyle or medication would affect health outcomes, offering actionable insights (Soumma *et al.*, 2025).

AI can overcome challenges related to signal complexity, noise, and data interpretation, identifying specific patterns often undetectable by traditional methods (Frumento & Țălu, 2025; Ranjan *et al.*, 2025).

Advanced Biorecognition and Transduction Mechanisms

Aptamer and Oligonucleotide-Based Biosensors

Aptamers, known as "nucleic acid antibodies," offer high specificity, stability, and versatility for a wide range of targets beyond what natural antibodies or enzymes can detect (Mayol *et al.*, 2025; Frumento & Țălu, 2025; Chen *et al.*, 2025). They enable rapid, label-free, and real-time detection of various biomarkers for diagnostics, including metabolites and therapeutic drugs like vancomycin and imatinib (Mayol *et al.*, 2025).

CRISPR-Cas Systems

These systems have been adapted for ultrasensitive detection of nucleic acids and, more recently, protein biomarkers (Sheng *et al.*, 2021). The MARPLE platform, for instance, leverages antibody induced proximity effects to activate CRISPR-Cas13a-mediated signal amplification, enabling femtomolar detection of clinically relevant antibodies such as trastuzumab and anti-MUC1 in human serum under one-pot conditions (Spezzani *et al.*, 2025). An immunocapture magnetic bead-enhanced biosensor also uses CRISPR-Cas13a for rapid, ultrasensitive SARS-CoV-2 nucleic acid detection (Han *et al.*, 2023).

Nanomaterials

The integration of nanomaterials (e.g., gold nanoparticles, carbon nanotubes, graphene, quantum dots) significantly enhances biosensor sensitivity, selectivity, and durability, allowing for the detection of analytes at ultra-low concentrations (Jarnda *et al.*,

2025; Vo & Trinh, 2024; Hemdan *et al.*, 2024; Kudłacik-Kramarczyk *et al.*, 2025; Hemdan *et al.*, 2025). They are crucial in improving the electrochemical performance of biosensors due to their high surface-to-volume ratios.

Bridging Elements and Future Directions

While biosensors promise to revolutionize TDM, traditional analytical methods like LC-MS/MS remain crucial as "gold standards" for validation (Casian *et al.*, 2025; Astúa *et al.*, 2025; Minichmayr *et al.*, 2024; Lehr *et al.*, 2026). The future of healthcare will likely see hybrid diagnostic models, where biosensor-based POCT devices act as first-line triage, providing rapid, on-site insights, with confirmatory testing or more complex analyses still performed by centralized laboratories using conventional methods when necessary (Frumento & Țălu, 2025; Lehr *et al.*, 2026). This collaboration ensures both speed and definitive reliability. Despite considerable advancements, several challenges persist in the widespread adoption of biosensors for TDM:

Sensor Stability and Biocompatibility

Ensuring long-term stability of reagents and sensor materials in complex biological environments, along with overcoming issues like biofouling and immunological degradation, remains critical (Kudłacik-Kramarczyk *et al.*, 2025; Sedighi *et al.*, 2026; Jarnda *et al.*, 2025; Mayol *et al.*, 2025).

Miniaturization and Manufacturing Scalability

While significant progress has been made, further miniaturization is needed for seamless integration into the body without disrupting physiological processes (Jarnda *et al.*, 2025; Kudłacik-Kramarczyk *et al.*, 2025). Scaling up production from lab prototypes to mass manufacturing while maintaining consistent performance is also a hurdle (Hemdan *et al.*, 2025).

Calibration and Interference Effects

The need for precise calibration and the mitigation of interference from other compounds or sample matrix components are ongoing challenges (Chen *et al.*, 2025; Jarnda *et al.*, 2025; Kudłacik-Kramarczyk *et al.*, 2025).

Data Integration and Regulatory Approval

Seamless data interoperability with Electronic Health Records (EHRs) and telemedicine platforms is crucial (Awad *et al.*, 2025; Jarnda *et al.*, 2025). Navigating stringent regulatory frameworks (e.g., FDA, EMA) for medical device approval is a complex and time-consuming process (Frumento & Țălu, 2025; Hemdan *et al.*, 2025).

Ethical Considerations

As biosensors become more pervasive and AI-driven, addressing data privacy concerns and ensuring informed consent for continuous monitoring are paramount (Sedighi *et al.*, 2026; Hemdan *et al.*, 2025; Soumma *et al.*, 2025).

CONCLUSION

Therapeutic Drug Monitoring (TDM) has advanced significantly, from its foundation in how drugs behave in the body to the integration of modern biosensors for personalized medicine. Traditional methods, while highly accurate, often involve delays, invasive procedures, and high resource demands that can hinder prompt patient care especially in cases with narrow safe dose ranges and vulnerable patients. Biosensors offer an effective solution, providing real-time, minimally invasive, and adaptable monitoring that better suits the demands of clinical practice. However, as with emerging technologies, challenges remain maintaining sensor stability in complex biological settings, achieving cost-effective mass production, reducing measurement errors, ensuring smooth integration with electronic health systems, and addressing ethical issues related to data privacy and patient autonomy.

ABBREVIATIONS

AEDs: Antiepileptic Drugs; **AI:** Artificial Intelligence; **AAS:** Atomic Absorption Spectrometry; **AUC:** Area Under the Curve; **BSTFA:** Bis(trimethylsilyl)trifluoroacetamide; **CB:** Ceftobiprole; **CBZ:** Carbamazepine; **CBZ-E:** Carbamazepine-10,11-epoxide; **CMIA:** Chemiluminescent Microparticle Immunoassay; **CRISPR:** Clustered Regularly Interspaced Short Palindromic Repeats; **CRM:** Certified Reference Material; **CSF:** Cerebrospinal Fluid; **C_{max}:** Maximum Concentration; **C_{min}:** Minimum (Trough) Concentration; **CRP:** C-Reactive Protein; **cTnI:** Cardiac Troponin I; **CYP:** Cytochrome P-450; **DBS:** Dried Blood Spots; **dFdU:** 2′,2′-Difluorodeoxyuridine; **DAD:** Diode Array Detector; **DLLME:** Dispersive Liquid-Liquid Microextraction; **E-AB:** Electrochemical Aptamer-Based; **ECD:** Electron Capture Detection; **EDDP:** 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; **EHRs:** Electronic Health Records; **EI:** Electron Ionization; **ELISA:** Enzyme-Linked Immunosorbent Assay; **EMA:** European Medicines Agency; **EMIT:** Enzyme Multiplied Immunoassay Technique.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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