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Integrating computational methods, IVIVC, and real-world evidence for bioequivalence assessment in transitional markets: A perspective

Mohamed Khalil Tamim *

Director Regulatory Affairs Strategy, Quality and Regulatory Affairs, Alcon Pharmaceuticals Limited, Fribourg, Switzerland.

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Abstract

Current bioequivalence (BE) assessment methods for generic drugs face notable constraints - substantial costs, lengthy timelines, and narrow population representation. This perspective examines how integration of computational methods with In Vitro-In Vivo Correlation (IVIVC) and Real-World Evidence (RWE) might address these challenges, particularly for transitional regulatory environments. Markets enforcing BE requirements during marketing authorization renewals for products with years of clinical use but without formal BE studies, represent a unique case where this approach proves especially relevant. Rather than advocating replacement of traditional assessment, we suggest this tripartite framework as complementary methodology to potentially minimize unnecessary testing while maintaining scientific validity. Applications across Biopharmaceutics Classification System classes appear variable; implementation would logically follow a graduated pathway. We acknowledge current limitations while identifying specific research priorities to advance this approach.

Keywords: Bioequivalence; Computational Methods; IVIVC; Real-World Evidence; Generic Drugs; Regulatory Science

1. Introduction

The scientific benchmark of generic drug approval worldwide remains bioequivalence (BE) assessment, the process that verifies similarity between generic products and their reference listed drugs (RLDs) [1]. Conventional regulatory pathways typically require comparative pharmacokinetic (PK) studies involving healthy volunteers, with subsequent statistical analysis confirming key parameters fall within regulatory acceptance criteria [2, 3].

Despite its established track record in ensuring therapeutic equivalence, this conventional approach presents several notable limitations. Among these, financial barriers remain significant – BE studies typically incur costs between $1-4 million [4]. Time requirements extend from 6-24 months for study execution and analysis. Furthermore, limited healthy volunteer cohorts offer narrow insights into likely performance across diverse patient populations. Additional considerations include occasional inconsistencies between studies of identical formulations, raising questions about reproducibility [5].

A particularly challenging scenario has emerged in transitional pharmaceutical markets, Morocco representing the perfect example. Such regions have begun implementing or strengthening BE requirements for previously marketed generics during marketing authorization renewals. These products often have extensive histories of clinical use spanning years or decades but lack formal BE studies consistent with contemporary standards. This regulatory evolution creates substantial compliance challenges for manufacturers while risking continuity of medication access.

* Corresponding author: Mohamed Khalil Tamim

Three distinct yet complementary methodological approaches offer potential to enhance BE assessment in such contexts:

- Computational methods capable of recognizing complex patterns in pharmaceutical datasets
- In Vitro-In Vivo Correlation (IVIVC), which establishes mathematical relationships linking dissolution behavior to absorption characteristics [6]
- Real-World Evidence (RWE), providing empirical insights from clinical practice where products have established safety and efficacy profiles [7]

While pharmaceutical research has explored these approaches independently, their systematic integration specifically addressing BE assessment remains unexplored territory with considerable potential merit, particularly for transitional regulatory frameworks.

2. Conceptual Framework

The tripartite framework builds upon established scientific principles of biopharmaceutics. Fundamentally, drug absorption mechanisms reflect complex interplays between physicochemical properties, formulation characteristics, and physiological variables relationships amenable to mathematical representation [8, 20]. Contemporary computational approaches facilitate pattern recognition within multidimensional datasets extending beyond capabilities of conventional statistical methods [9]. Furthermore, similar formulations typically demonstrate comparable bioavailability characteristics, allowing reasonable extrapolation between related compounds [10].

Our proposed framework comprises four integrated functional elements:

2.1. Computational Component

This aspect would utilize structured data preparation processes using established modeling architectures tailored to pharmaceutical datasets [11]. Particularly relevant are transfer learning methodologies that would enable the migration of knowledge from well-characterized compounds to less studied formulations. Rigorous cross-validation across multiple datasets would establish reliability parameters and define confidence boundaries.

2.2. IVIVC Component

This element would establish connections between in vitro performance and in vivo behavior through comprehensive dissolution testing across biorelevant media, development of Level A correlations, and integration with physiologically-based pharmacokinetic models (PBPK) [12, 13]. Particular attention to dissolution method selection and media composition would ensure physiological relevance.

2.3. RWE Component

This distinctive element would leverage existing clinical experience with generic products that have established market presence in transitional environments now instituting formal BE requirements. For such markets, where products possess established usage histories but lack contemporary BE studies, RWE provides a critical evidence source [14]. Implementation would incorporate appropriately de-identified health records, prescription data, and documented clinical outcomes from settings where these formulations have extensive use histories. This approach is particularly useful during marketing authorization renewals in transition countries, which have recently strengthened BE standards for already approved generics. Established epidemiological methodologies, including propensity score matching, would address potential confounding factors [15].

2.4. Integration Component

This synthesizing element would combine outputs from preceding components to generate concentration-time profiles, conduct statistical analyses using established regulatory approaches, and articulate transparent explanations of predictions with uncertainty quantification [16]. Cross-validation between components would strengthen overall confidence in conclusions.

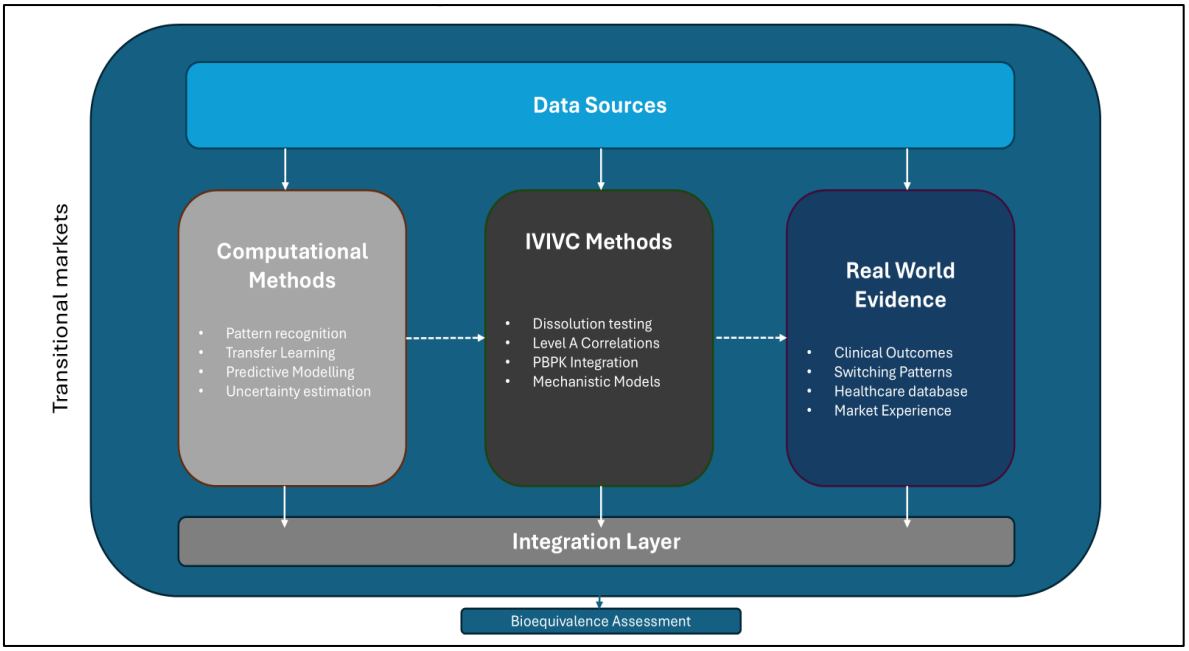

Figure 1 Conceptual framework and information flow between components

2.5. Applications Across BCS Classification System

Applicability varies notably across Biopharmaceutics Classification System (BCS) categories:

2.6. BCS Class I (High Solubility, High Permeability)

For compounds exemplified by metoprolol tartrate, this approach could enhance confidence in biowaiver decisions through sophisticated dissolution profile analysis coupled with formulation-specific insights. Potential expansion to modified-release formulations and multi-active products represent a significant opportunity, particularly given established regulatory precedent for biowaivers in this class [17].

2.7. BCS Class II (Low Solubility, High Permeability)

For dissolution-limited compounds such as ibuprofen, the framework offers potential capabilities for formulation optimization and food effect prediction [18]. Practical applications include formulation development guidance, BE study outcome forecasting, and mechanistic understanding of failure modes.

2.8. BCS Class III (High Solubility, Low Permeability)

For permeability-limited compounds like metformin, the approach could elucidate excipient effects on intestinal permeability and transporter interactions, informing excipient selection strategies and population-specific predictions [19]. This class particularly benefits from the RWE component demonstrating therapeutic equivalence despite permeability limitations.

2.9. BCS Class IV (Low Solubility, Low Permeability)

For compounds facing multiple absorption barriers, the integrated approach could support risk assessment for BE study design, guide targeted formulation optimization, and potentially reduce costly study failures through preliminary screening.

Table 1 Application potentials across BCS classes.

BCS Class	Primary Challenge	Potential Applications	Anticipated Limitations	Expected Utility
Class I	Demonstrating relevance beyond established biowaivers	Extension to modified-release formulations	Limited improvement over established approaches	High
Class II	Capturing dissolution variability	Food effect prediction, formulation optimization	Representing supersaturation dynamics	Moderate, High
Class III	Characterizing transporter effects	Population-specific predictions, excipient selection	Complex permeability mechanisms	Moderate
Class IV	Multiple absorption barriers	Risk assessment, targeted formulation strategies	Multiple limiting factors	Limited, Moderate

3. Implementation Considerations

3.1. Methodological Requirements

Successful implementation demands rigorous methodological approaches. Data collection must encompass comprehensive historical BE study results, thorough physiochemical characterization, and relevant real-world clinical data. Quality assessment procedures including completeness verification and consistency evaluation remain essential prerequisites.

Model development logically proceeds through stratified validation, beginning with well-characterized BCS Class I compounds before progression to more complex cases. Performance assessment requires multiple complementary metrics, including prediction accuracy measures, BE-specific classification parameters, uncertainty quantification, and independent validation against distinct BE studies.

3.2. Regulatory Pathway

Regulatory acceptance represents a critical consideration, particularly for transitional markets implementing new BE requirements. A phased implementation pathway appears most pragmatic:

3.2.1. Phase 1: Evidence Compilation and Risk Assessment

Initial efforts would focus on compiling and evaluating available evidence for previously marketed generic products, categorizing them by confidence level regarding bioequivalence based on integrated analysis. This would enable prioritization of products requiring immediate formal BE studies versus those where existing evidence might suffice during defined transition periods.

3.2.2. Phase 2: Targeted Clinical Study Optimization

Following sufficient validation evidence, the approach could support study size reduction for well-characterized drugs and potentially expand biowaiver applications. For products with extensive market presence and positive RWE, authorities might reasonably accept reduced clinical data requirements.

3.2.3. Phase 3: Alternative Assessment Frameworks

Subject to comprehensive validation, qualified models might eventually provide virtual BE assessment options for select drug categories, particularly benefiting products with established clinical histories and challenging study requirements. This would prove especially valuable in resource-constrained environments.

Implementation would require clear definition of appropriate use contexts, predetermined performance metrics, comprehensive validation protocols, and transparent documentation practices reflecting established quality standards.

3.3. Limitations and Research Priorities

Several notable limitations warrant acknowledgment. Data availability and quality remain significant challenges, particularly regarding complete BE study datasets and proprietary formulation specifications. Regulatory acceptance will require robust prospective validation studies and establishment of appropriate standards for evidence evaluation. Technical limitations include computational complexity for certain drug categories and incomplete mechanistic understanding of complex formulation interactions.

3.3.1. Advancing this approach requires focused research in several areas:

- Development of standardized BE study data repositories with consistent reporting formats
- Advanced model architectures incorporating mechanistic pharmaceutical principles
- Regional bioequivalence research addressing variations in drug absorption patterns
- Standardized documentation practices and validation criteria
- Validated software platforms suitable for pharmaceutical applications

4. Conclusion

The integration of computational methods, IVIVC, and RWE presents a promising approach to enhance bioequivalence assessment, particularly for transitional markets implementing new BE requirements for previously marketed generic products. This framework addresses specific challenges faced in these regulatory environments and could potentially reduce unnecessary clinical testing while maintaining scientific rigor.

The approach offers value for transitional markets such as Morocco, where generic products have established clinical use histories but now face stricter regulatory standards during marketing authorization renewals. In these contexts, the framework leverages existing clinical experience, potentially preventing unnecessary disruptions to medication access while supporting appropriate regulatory advancement.

As pharmaceutical regulation becomes more globally harmonized, frameworks that address the specific needs of transition markets are becoming increasingly important to ensure that strengthened regulatory standards improve, rather than hinder, patient access to quality-assured generic medicines. The proposed approach represents a pathway toward this goal, although considerable validation work is still required before widespread implementation.

Compliance with ethical standards

Disclosure of conflict of interest

This perspective was developed independently and does not represent the views, opinions, or interests of Alcon or any of its subsidiaries or affiliated companies. This work was conducted in the author's personal capacity without institutional resources, funding, or support from Alcon.

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