Macedonian Pharmaceutical Bulletin, 72 (Suppl 1) 203 - 204 (2026)
Online ISSN: 1857-8969
DOI: 10.33320/maced.pharm.bull.2026.72.03.097
Short communication

Bioequivalence studies: A regulatory overview of EMA and MALMED

Eljona Chilku[1,2*], Marija Trajchuleski[1,2], Katarina Smilkov[2], Darinka Gjorgieva Ackova[2]

[1]*Agency for Medicines and Medical Devices, Skopje 1000, Republic of North Macedonia*
[2]*Faculty of Medical Sciences, Goce Delčev University, Štip 2000, Republic of North Macedonia*

Introduction

A generic drug is more efficient, safe and low-cost alternative of the innovator medicinal product in the market (Sandeep, 2018). According to the Law on medicines and medical devices in North Macedonia, a generic medicinal product is a medicinal product that has the same qualitative and quantitative composition in active substance(s) and the same pharmaceutical form as the reference medicinal product (or a different immediate-release oral pharmaceutical form), and whose bioequivalence with the reference medicinal product has been demonstrated by an appropriate bioavailability study. Bioequivalence studies are essential for ensuring that the generic formulations meet the quality, safety and efficacy standards established by the reference medical products. They provide important data on absorption, distribution, metabolism and elimination characteristics of pharmaceutical formulations (Liana, 2025). In the case of generic drugs, clinical data on the safety and efficacy of the medicine is not required to be submitted, because it has been already provided for the reference product (Asif, 2010), therefor bioequivalence data is required for generic drug approval process, and are integral part of Module 2 (Summery of common technical documents) and Module 5 (Clinical report) (Amit, 2022). The two main characteristics of a generic medical product to be therapeutically equivalent to the innovator are to be pharmaceutically equivalent and bioequivalent as well. The innovator and generic medical product should be pharmaceutically equivalent, they should have the same dosage form, strength, and same route of administration. The products are bioequivalent when they have similar bioavailability when studied under same conditions. Bioequivalence is determined by evaluation of the AUC and the maximum concentration of the medicinal product (Cmax) (Sandeep, 2018).

Regulatory Framework and Guidelines

EMA follows robust regulatory requirements for the conduct of bioequivalence studies. The guidelines emphasize a comprehensive approach, including the design of clinical studies, statistical analysis plans, and the acceptable ranges for pharmacokinetic parameters.

Below are EMA's main guidelines for conducting bioequivalence studies:

- Guideline on The Investigation of Bioequivalence: This guideline defines the criteria for the design, conduct, and evaluation of bioequivalence for immediate-release dosage forms with systemic action;
- ICH M13A Guideline on Bioequivalence for Immediate-Release Solid Oral Dosage Forms: This

*ecilku@yahoo.com

guideline contains recommendations on conducting bioequivalence studies for orally administered immediate-release solid oral dosage forms, during both development and post approval phases;

• Product-Specific Bioequivalence Guidance: The EMA publishes product-specific guidance that provides relevant study design principles for demonstrating bioequivalence of particular products;

• Pharmacokinetic and Clinical Evaluation of Modified-Release Dosage Forms: This guideline specifies the studies required to investigate the efficacy, safety, and pharmacokinetic properties of modified-release formulations administered by different routes of administration (Liana, 2025).

Bioequivalence studies in North Macedonia are conducted according to the Law on medicines and medical devices. Below are MALMED's main documents for conducting bioequivalence studies:

• Rulebook on the conduct of clinical trials of medicinal products and the content of documentation: This rulebook establishes the requirements for the submission of applications to conduct bioequivalence studies and the documentation that should be provided in support of these applications; (MALMED, 2004)

• Guideline for the investigation of bioavailability and bioequivalence of medicinal products: This guideline defines the principles, requirements and procedures regulating the bioavailability and bioequivalence studies of medicinal products, including study design, conduct, documentation, statistical evaluation and reporting; (MALMED, 2009)

Although these documents are relatively old, it is important to emphasize that the guideline specify that, in specific instances, the applicable EMA guidelines in effect at the time should be followed.

The current Law on medicines and medical devices in North Macedonia was adopted in 2007. At the moment, MALMED is actively involved in preparation of a new law, which is expected to be further aligned with EU pharmaceutical legislation. The adoption of the new law will also require the revision and preparation of accompanying secondary legislation, including rulebooks and guidelines, while placing greater emphasis on compliance with the latest guidance documents published by EMA. This is expected to strengthen regulatory harmonization and facilitate the implementation of internationally recognised standards in the conduction and assessment of bioequivalence studies.

Conclusion

The Macedonian agency for medicines and medical devices like other regulatory bodies worldwide, follows comparable principles for the assessment of bioequivalence studies. Although study designs and acceptance criteria may vary slightly, the primary aim remains to ensure that generic medicinal products are therapeutically equivalent to the reference product.

References

Agency for Medicines and Medical Devices of the Republic of North Macedonia, 2004. Guideline for the investigation of bioavailability and bioequivalence of medicinal products. Agency for Medicines and Medical Devices of the Republic of North Macedonia, Skopje. https://malmed.gov.mk/wp-content/uploads/31-Instrukcija_za_biolekovi-Sl.Vesnik-br.68-2004.pdf

Agency for Medicines and Medical Devices of the Republic of North Macedonia, 2009. Rulebook on the conduct of clinical trials of medicinal products and the content of documentation. Agency for Medicines and Medical Devices of the Republic of North Macedonia, Skopje. https://malmed.gov.mk/wp-content/uploads/19-Pravilnik_za_klinicki_ispituvanja-Sl.Vesnik-br.29-2009.pdf

Patel, N. et al., 2022. Bioequivalence requirements of pharmaceutical products in US, Europe and Australia. Int. J. Drug Regul. Aff. 10, 56–61. https://doi.org/10.22270/ijdra.v10i2.524

Rafi, N. et al., 2018. Regulatory requirements and registration procedure for generic drugs in USA. Indian J. Pharm. Educ. Res. 52, 544–549. https://doi.org/10.5530/ijper.52.4.63

Susanto, L.W., 2025. A comprehensive review of bioequivalence studies: methodologies, regulatory considerations, and future directions. Medicinus 38, 29–40. https://doi.org/10.56951/80v3g940

Tamboli, A.M. et al., 2010. An overview on bioequivalence: regulatory consideration for generic drug products. J. Bioequiv. Availab. 2, 86–92. https://doi.org/10.4172/jbb.1000037