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Short communication

Regulatory requirements for the production of liquid non-sterile herbal products – compliance with GMP principles within the EU and the Republic of North Macedonia

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Introduction

Herbal medicinal products have a long-standing role in traditional and modern medicine. Liquid non-sterile herbal products such as solutions and drops, syrups, suspensions and tinctures, are particularly sensitive due to their composition and susceptibility to microbial contamination. Additionally, herbal raw materials are inherently variable due to environmental and processing factors, which can lead to batch-to-batch variability if not properly controlled. In this context, Good Manufacturing Practice (GMP) plays a critical role in ensuring consistent product quality throughout the entire lifecycle of the product (Barnes et al., 2007; WHO, 2007).

The aim of this study was to analyze regulatory requirements for the manufacturing of liquid non-sterile herbal products and to assess the level of harmonization between the European Union (EU) and the Republic of North Macedonia (RNM).

Regulatory Framework

The EU regulatory system for herbal medicinal products is primarily based on Directive 2001/83/EC and its amendment Directive 2004/24/EC, which introduce simplified registration procedures for traditional herbal medicines. GMP requirements are defined in EudraLex Volume 4, including specific provisions for herbal products (Annex 7) (European Commission, 2008; European Parliament and Council, 2004).

In RNM, the regulatory framework is established by the Law on Medicinal Products and Medical Devices and implemented through national GMP guidelines aligned with EU standards. The competent authority (MALMED) is responsible for authorization, inspection, and supervision (Law on Medicinal Products and Medical Devices, 2007).

Evaluation of GMP requirements

The assessment of GMP requirements highlights several critical areas that directly influence the quality of liquid non-sterile herbal products. These include the establishment of a robust pharmaceutical quality system, qualified personnel, controlled manufacturing environments, and comprehensive documentation practices. Particular emphasis is placed on raw material quality, where variability in phytochemical composition represents a fundamental challenge. Equally important are microbiological control, process validation, and stability testing, which must be specifically adapted

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to the nature of herbal preparations (EMA, 2022; WHO, 2007).

Results and discussion

The findings indicate a high degree of regulatory alignment between the EU and RNM, particularly in the adoption of GMP principles and the use of the European Pharmacopoeia as a reference standard. This alignment represents a significant advantage for domestic manufacturers aiming to access the EU market.

However, regulatory compliance alone does not guarantee consistent product quality. The most significant challenges arise at the level of practical implementation. The natural variability of herbal raw materials may result in significant batch-to-batch differences in active constituents.

This variability becomes particularly critical during extraction processes, where critical parameters such as “Drug to Extract Ratio”, solvent concentration, temperature, and extraction method must be tightly controlled and validated across multiple consecutive batches (European Commission, 2008).

Microbiological control remains another key concern. The composition of liquid herbal products provides a favorable environment for microbial growth, requiring a combination of preventive measures, validated cleaning procedures, and, where appropriate, the use of preservatives (WHO, 2007).

Additional challenges arise in the context of stability studies for oil-based herbal extracts or hydroalcoholic extracts, which are susceptible to oxidative instability, formation of degradation products, and physical non-homogeneity, requiring more complex testing protocols compared to conventional liquid pharmaceutical preparations.

Finally, traceability throughout the entire production chain-from raw material sourcing to final product release-emerges as a critical element of GMP compliance, requiring well-integrated quality systems and continuous oversight.

Conclusion

Quality of liquid non-sterile herbal medicinal products must be ensured throughout the entire product lifecycle rather than by final testing alone. The natural origin of herbal raw materials, their variability and the increased risk of microbiological contamination necessitate enhanced application of GMP principles, risk management, and continuous process validation.

The analysis shows that the national legislation of the Republic of North Macedonia is largely harmonized with European legislation, particularly in the area of basic GMP principles, registration of herbal medicines, and inspection oversight. What remains is translating formal harmonization into consistent, inspectable, market-ready practice. Closing the gap on Traditional Use Registration, investing in validated processes, and building robust quality systems are not optional upgrades, they are the price of entry into the European pharmaceutical market.

For manufacturers, regulators, and pharmacists alike, the message is the same: in herbal medicine, quality is not an outcome – “It is a process and it will never stop”.

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