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Short communication

Pharmacovigilance challenges in generating real-world safety data for cannabidiol (CBD): Global vs North Macedonia

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Introduction

The global market for cannabidiol (CBD) products has expanded rapidly in the last decade, with increasing use of oral CBD oils, food supplements, wellness products, and authorized medicinal preparations (Brown & Winterstein, 2019; WHO, 2018). This growth has created regulatory and pharmacovigilance challenges because CBD products are classified differently across jurisdictions, affecting the generation of reliable real-world safety data (Manthey, 2019; Pavlovic et al., 2018). Authorized CBD-containing medicinal products are subject to established pharmacovigilance systems, including adverse drug reaction reporting, risk management plans, and periodic safety assessments (European Medicines Agency, 2025). In contrast, many commercially available oral CBD oils are regulated outside medicinal frameworks, limiting systematic safety monitoring and increasing the risk of fragmented adverse event reporting (European Commission, 2025; European Food Safety Authority, 2022). In the EU, oral CBD is generally considered a Novel Food requiring pre-market authorization under Regulation (EU) 2015/2283 (Regulation (EU) 2015/2283; European Commission, 2025). In North Macedonia, certain oral CBD oils are classified by MALMED as borderline products, positioned between medicines and consumer products. This review examines how these regulatory differences affect pharmacovigilance obligations and real-world evidence for CBD globally and in North Macedonia.

Materials and methods

A narrative review was conducted of scientific literature and regulatory documents from PubMed, EMA, EFSA, European Commission, WHO, and MALMED. The focus was on oral CBD oils classified as medicines, food supplements, Novel Foods, or borderline products. EU and selected European regulatory approaches were compared regarding classification, pharmacovigilance duties, adverse event reporting, and post-marketing surveillance, with attention to how classification impacts the quality and availability of real-world safety data.

Results and discussion

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Pharmacovigilance requirements for CBD depend strongly on product classification, with substantial differences across jurisdictions. In the EU, oral CBD is mostly regulated as a Novel Food; full pharmacovigilance applies only to authorized medicinal CBD products, with no harmonized system for non-medicinal CBD. In the UK, CBD is a Novel Food unless therapeutic claims trigger medicinal classification; pharmacovigilance then applies only to authorized medicines, with limited surveillance for food products. In the US, only Epidiolex is FDA-approved as a CBD medicine; many other CBD products are sold without FDA approval. Authorized medicinal CBD products (e.g., Epidyolex®) are subject to comprehensive pharmacovigilance under EU pharmaceutical law, including adverse reaction reporting and periodic safety updates (European Medicines Agency, 2025; Directive 2001/83/EC). Most oral CBD oils sold as supplements or wellness products are not medicines and thus lack mandatory pharmacovigilance (Regulation(EU) 2015/2283; European Commission, 2025).This limits systematic adverse event collection and likely causes underreporting (Manthey, 2019; European Food Safety Authority, 2022). Reported CBD associated adverse effects include hepatotoxicity, gastrointestinal issues, somnolence, fatigue, decreased appetite, and drug–drug interactions (Chesney et al., 2020; Huestis et al., 2019). EFSA notes key uncertainties about CBD's effects on the liver, GI tract, endocrine and nervous systems, and mental health, calling for more safety data (European Food Safety Authority, 2022). In North Macedonia, classifying some oral CBD oils as borderline products gives MALMED control over marketing and placement but does not impose full medicinal-product pharmacovigilance (MALMED, 2025). This gap may hinder generation of reliable real-world safety data for CBD use by Macedonian population.

Conclusion

The generation of real-world safety data for cannabidiol products remains significantly challenged by heterogeneous regulatory frameworks worldwide. While medicinal CBD products are covered by established pharmacovigilance systems, most oral CBD oils marketed as Novel Foods, dietary supplements, or borderline products are not North Macedonia's borderline framework shares the limitations seen across Europe in systematic adverse event collection and safety signal detection Structured post-marketing surveillance and greater international regulatory harmonization could improve CBD pharmacovigilance and strengthen the evidence base for CBD safety assessment.

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