Therapeutic substances qualified and marketed as medical devices: regulatory challenges in the EU

Umberto M. Musazzi, Sara Azari, Paola Minghetti
Università degli Studi di Milano, Dipartimento di Scienze Farmaceutiche

Substance-based medical devices (SBMDs) face classification challenges under Regulation (EU) 2017/745 (MDR). Unlike medicinal products (MPs), which act pharmacologically on specific biological targets (e.g., receptors, enzymes), their principal action is achieved non-pharmacologically, mainly—but not exclusively—via physical mechanisms (barrier formation, lubrication, osmotic modulation, organ/physiological support) or chemical means (pH adjustment, acid–base interactions, chelation) [1,2]. In general, SBMDs are classified under Rule 21 of the MDR. However, their precise qualification may be difficult, with risks of borderline situations among SBMDs, MPs, and supplements [1,2]. In this regard, this work examines the main regulatory classification challenges for SBMDs.

On review, SBMDs can be categorized into distinct functional groups. Antifoaming agents such as simethicone act locally in the GI tract by reducing the surface tension of gas bubbles through a physical mechanism. As it is neither absorbed nor metabolized, it is classified as Class IIb according to Rule 21 of the MDR. Osmotic and water-retaining agents—including fructooligosaccharides (FOS), glucomannan (KGM), and high-molecular-weight macrogols (PEG 3350/4000)— are Class IIb as well, since they are not absorbed and act primarily through physical mechanisms (e.g., bulking, water retention, and osmotic action) within the GI tract. Gel-forming and barrier-forming agents such as Na/Mg alginate act by forming hydrogels or mucoadhesive protective films on tissues or mucosal surfaces. Given the minimal absorption of Na/Mg alginate, it is classified as a Class III medical device. Borderline substances include cranberry-derived compounds and D-mannose [4], which inhibit bacterial adhesion in urinary tract infections after GI absorption. Their mechanism of action and systemic exposure have sparked regulatory debate on their classification over recent decades, and there is a judgment of the EU Court of Justice (May 2025) finding that they have pharmacological activity.

In conclusion, under the MDR, SBMDs with a principal physical mode of action (e.g., mechanical barriers, lubricants, bulking agents, or protective films) and not systemically absorbed represent the most predictable categories from a regulatory perspective, as they are clearly classifiable in Class IIb. By contrast, classifying Class III SBMDs is more challenging, particularly when distinguishing them from MPs based on the defined principal mode of action, especially when the mechanism of action is neither physical/mechanical nor pharmacological.

These borderline situations pose challenges for pharmacists, who must accurately identify the SBMD’s key features and differentiate it from other medicines or medical devices available on the market to ensure appropriate patient counselling on its proper use.

Literature:

[1] A.R. Bilia, et al., Planta Medica 2021, 87(12/13), 1110-1116.
[2] A. Mugelli and J. Tamargo, Frontiers in Drug Safety and Regulation 2023, 3, 1222790.
[3] E. Bianchini and C.C Mayer, Artery Research 2022, 28(2), 55-60.
[4] F. Scaglione et al., Front Pharmacol 2021, 2, 12:636377.