REGULATORY FRAMEWORK FOR ADVERTISING OF MEDICINAL PRODUCTS IN THE REPUBLIC OF NORTH MACEDONIA AND THE EUROPEAN UNION

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Abstract: Pharmaceutical companies frequently engage in drug advertising to connect with potential buyers. In the competitive pharmaceutical market, where patients are highly sensitive to various forms of advertising, manufacturers aim to reach a broad audience. This rapid dissemination of information in the advertising of medicinal products leads to some details being unverified and inaccurate, which emphasizes the critical importance of establishing and enforcing legislation. This paper aims to evaluate the current legislation for advertising of medicinal products in Republic of North Macedonia, as well as the regulations in European Union member states, namely Germany, Slovenia and Spain. The basic legal act that regulates the advertising of medicinal products in the European Union is Directive 2001/83/EC of the European Parliament and of the Council of Europe of 6 November 2001 on the Community code relating to medicinal products for human use such as amended by Directive 2004/27/EC of 31 March 2004. By reviewing relevant literature and conducting a comparative analysis of regulations in the Republic of North Macedonia and European Union, it can be concluded that the European Directive serves as a foundational framework. Each country has transposed the European Directive in domestic laws and regulatory guidelines with local adaptations and all Member States have therefore adopted further specific measures concerning the advertising of medicinal products. Depending on the member state, pharmaceutical promotion can be monitored and controlled by the government, by a national competent authority or not, this approach is called “self-regulation.Upon examining the regulatory structures in each specific country, there are five key components that must be implemented: development and adoption of national laws and regulations; implementation of the regulation, codes and other standards; monitoring the pharmaceutical promotion to ensure compliance with legal regulations; enforcement of the law through suitable sanctions to prevent violations; and evaluation of regulatory efficiency. Drawing parallels between the practices of established European member states and the regulatory framework of the Republic of North Macedonia, it becomes evident that there is an opportunity for the Republic of North Macedonia to leverage positive experiences from the European countries. By incorporating successful elements of European member states' regulations, the Republic of North Macedonia could enhance its own pharmaceutical regulatory environment. Based on this evaluation of established practices and experiences in European countries, direction will be provided for harmonizing and improving the regulatory framework for advertising od medicinal products in the Republic of North Macedonia.
Keywords: advertising, medicinal products, regulation, European Union, pharmacy

1. INTRODUCTION

Advertising is the primary tool used by pharmaceutical companies to communicate with purchasers of medicinal products and patients. Article 86 of Directive 2001/83/EC defines any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products. The

Directive 2001/83/EC also includes specific provisions for medical products available only by prescription and those available without a prescription. Non-prescription medicines can be promoted to the general public, whereas prescription-only drugs can only be advertised to healthcare professionals, and strict legal regulations govern advertising activities related to the latter category. Therefore, the establishment of legal restrictions on the advertising prescription - only drugs within the European Union member states is solely directed towards healthcare professionals and persons authorized to prescribe them (Directive 2001/83/EC). Upon receiving marketing authorization approval, a prescription drug is accompanied by authorized information detailing indications, administration methods, dosage, precautions, warnings, contraindications, side effects, and interactions with other drugs and foods. The advertising of prescription drugs is directed towards healthcare professionals, aiming to provide accurate and scientifically substantiated information in alignment with the summary of product characteristics (SmPC) or the conditions governing its market placement. Promoting the drug to healthcare professionals must adhere strictly to the approved indications and usage methods (Directive 2001/83/EC, art. 91). Advertising prescription drugs for unapproved "off-label" uses is prohibited, although manufacturers can apply for approval for additional indications (Directive 2001/83/EC, art. 87). The objective of pharmaceutical advertising for prescription drugs is to dispense information on the rational use of these medications. While the primary purpose of drug prescription advertisements is to educate, their inherent complexity is further complicated by financial incentives, generating significant controversy. Advertising prescription drugs should not seek to encourage prescription, dispensing, or sales through promises or the provision of financial, material, or other incentives (Brandon K. So and Peggy Y. Kim, 2022). Conversely, the advertising of medications available without a doctor's prescription through public media, online platforms, public announcements, and various advertising channels targets the general public. Marketing authorization holders or manufacturers are permitted to engage in this form of advertising. However, such advertising is restricted only to medications available without a doctor's prescription, serving the purpose of informing the general public about the drug's characteristics (Directive 2001/83/EC, art. 88). Some European countries require prior approval from regulatory or industry bodies before advertising over-the-counter medicines, reducing the risk of legal actions for inappropriate advertising.

Additionally, in practice, advertising of medicinal products is often largely governed and enforced through the self-regulatory system and self-regulatory codes, such as the Code of Practice of the European Federation of Pharmaceutical Industries and Associations and its various national incarnations (EFPIA Code). To adhere to the principles of effective promotional practices, particularly in the context of self-regulation by the company, various guides and codes can serve as reliable tools. The "Ethical Criteria for Medicinal Drug Promotion," published by the World Health Organization (World Health Organization, 1988), laid the foundation for creating guides and measures to ensure ethical promotional practices . Furthermore, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) issues a Code of Practice, offering global guidance on pharmaceutical promotion (International Federation of Pharmaceutical Manufacturers and Associations [IFPMA],Code of Practice 2019), and also European Federation of Pharmaceutical Industries and Associations (EFPIA) regularly releases a Code of Practice, serving as a compilation of ethical rules for promoting medicinal products to Healthcare Professionals in the European Union (European Federation of Pharmaceutical Industries and Associations [EFPIA], Code of Practice 2019). The purpose of this article is to conduct a comparative analysis of the regulations governing the advertising of medicinal products in the European Union and the Republic of North Macedonia. The research aims to identify key similarities and differences between these regulatory frameworks. By examining these regulations, the article seeks to provide comprehensive guidelines and practical insights for ensuring compliance with established practices and rules in the advertising of medicinal products. The ultimate goal is to contribute to a better understanding of the regulatory landscape in these regions and offer valuable guidance for stakeholders involved in the promotion of medicinal products.

2. MATERIALS AND METHODS

We conducted a comprehensive literature review to identify and analyze existing studies, scholarly articles, and publications related to the regulations and codes of practice governing the advertising of medicinal products. Additionally, we systematically examined official documents and regulatory guidelines from the European Union including three member states (Germany, Slovenia and Spain) and the Republic of North Macedonia. This involved a detailed scrutiny of legal texts, directives, and official publications from relevant health and regulatory authorities. The focus was on extracting information regarding the specific rules and requirements governing the advertising of medicine products.

3. RESULTS

Every European member state has integrated the European Directive 2001/83/EC into its national laws and regulatory guidelines, customizing them to suit local contexts. As a result, each member state has introduced supplementary, country-specific measures regarding the advertising of medicinal products. In Germany, advertising of medicinal products is governed by the Law on Advertising in the Field of Healthcare and the Law against Unfair Competition (ICLG - Pharmaceutical Advertising Laws and Regulations, Germany 2023). With regard to advertising to healthcare professionals, a large part of the industry in Germany agreed to comply with the FSA-Code of Conduct on the Collaboration with Healthcare Professional (FSA Code of Conduct on the Interaction with Healthcare Professionals, 2020). The FSA-Code of Conduct Patient Organisations reflects the respective EFPIA rules governing relationships between the pharmaceutical industry and patient organisations, which now form part of the simplified EFPIA-Code of Practice (ICLG - Pharmaceutical Advertising Laws and Regulations, Germany 2023). The German regulation relies more on a self-assessment conducted by the company responsible for the advertisement of the medicinal product. Section 74a of the German Drug Act requires that any person who, as a pharmaceutical entrepreneur, places medicinal products on the market shall appoint an information officer who is responsible for ensuring that the labelling, the package leaflets, the expert information and advertisements correspond with the content of the marketing authorisation (Medicinal Products Act, 2023) Furthermore, in Germany, there is no requirement to submit advertising material to competent authorities, meaning that approval for advertising medicinal products is not mandatory, either in a general sense or under specific circumstances (ICLG - Pharmaceutical Advertising Laws and Regulations, Germany 2023). In accordance with both the Directive and the German regulations, the advertising of prescription drugs is restricted only to health professionals and advertising of over-the-counter drugs is allowed only to the general public. Advertising to healthcare professionals, including claims for use of a medicinal product, must contain the following mandatory information: the name or company and permanent address of the pharmaceutical company; the name of the medicinal product; the composition of the medicinal product; the therapeutic indication(s); contraindications; side effects; specific precautions for use insofar as these are required for the labelling of containers and outer packaging; and for medicinal products that can be obtained only on prescription, with the marking “prescription only” . Publications relating to unauthorised medicinal products or to indications or pharmaceutical forms that are not covered by the marketing authorisation must not be of a promotional nature. Comparisons with the medicinal products of competitors are only permissible with respect to advertisements to healthcare professionals; such comparative advertising is not allowed for the general public. (ICLG - Pharmaceutical Advertising Laws and Regulations, Germany 2023).

In contrast to the German regulation, Republic of Slovenia requires prior approval for advertising drugs (both prescription and over-the-countrer) from the Agency for Medicines and Medical Devices of the Republic of Slovenia (JAZMP). Marketing authorisation holders may advertise medicinal products in accordance with the Medicinal Products Act and regulations based on it, i.e. the Rules of advertising of medicinal products and with self-regulation codes such as The Slovene Code of Medical Ethics, The Code on Cooperation with Healthcare Professionals and Disclosure code and The Patient Organization Code. In 2019, these codes have been merged at a European level into the European Federation of Pharmaceutical Industries and Associations (“EFPIA”) Code. According Slovenian regulation, marketing authorization holders must, before starting to advertise medicines, notify the Agency about the medical representatives who will carry out the approval of medicines among healthcare professionals, and they must be registered in the JAZMP (JAZMP,2023). Based on the Medicinal Products Act and the Rules on Advertising of Medicines, only medicines available without prescription may be advertised to the general public. The law explicitly

prohibits advertising of prescription drugs to the general public, including advertising and publishing information about medicines containing psychotropic or narcotic substances. In addition, the law also prohibits the direct distribution of medicines for promotional purposes to end-users, medical professionals and health-care providers (Malči Grivec, 2015). Comparative advertising of medicines is allowed only for health workers and must be based on relevant, scientific and comparable aspects of the medicines (Rules of advertising of medicinal products, 2008).

Advertising of medicinal products in Spain is governed by a combination of laws, guidelines of the regulatory authorities, and codes of conduct adopted on a voluntary basis by the pharmaceutical industry. General rules on advertising are comprised in General Law 34/1988 on Advertising and Law 3/1991 on Unfair Competition. The overarching regulations on advertising are outlined in General Law 34/1988 on Advertising and Law 3/1991 on Unfair Competition. The fundamental principles outlined in Directive 2001/83/EC on the Community code relating to medicinal products for human use have been integrated into Spanish law through various regulations, including Royal Decree-Legislative 1/2015. Additionally, trade associations representing various sectors of the pharmaceutical industry in Spain have established their own codes of conduct for self-regulation, including the Code of Good Practices of the Pharmaceutical Industry of FARMAINDUSTRIA (the main Spanish trade association of the

innovative pharmaceutical industry), Code of Conduct on Interactions with the Health Community of AESEG (Spanish generic pharmaceutical industry trade association), Code of Ethics for the Marketing, Promotion and Advertising of Medicinal Products for Selfcare of ANEFP (Spanish trade association of the non-prescription medicinal products industry), (ICLG - Pharmaceutical Advertising Laws and Regulations, Spain 2023). In Spain, in addition to national legislation, each autonomous region adopts guidelines that pharmaceutical companies must adhere to, depending on their localization. Advertising of medicinal products to healthcare professionals does not require prior approval from a regulatory or industry authority, but pharmaceutical companies are obligated to forward a copy of the advertisement to the health authority in the Autonomous Region where the company is situated. Similarly, advertising targeted the general public does not require prior approval from regulatory authorities. However, it is essential to note that regulatory authorities and industry bodies retain the right to retrospectively scrutinize any advertising aimed at healthcare professionals or the general public. Only under specific circumstances, the Ministry of Health has the authority to require prior approval by regulatory authorities for the advertising of certain medicinal products (ICLG - Pharmaceutical Advertising Laws and Regulations, Spain 2023). Companies are prohibited from promoting the use of a medicinal product that is not authorised in Spain, even if the product is authorised in another country. Furthermore, they cannot promote the use of an authorised medicinal product for indications or conditions of use that are not those expressly provided for in its Summary of Product Characteristics (SmPC). According to Royal Decree 1416/1994, advertising targeted at healthcare proffesionals must contain specific information, including: the name of the product, the name and address of the marketing authorisation holder, the qualitative and quantitative composition of the product, essential data according to the SmPC, such as clinical data, indications, cautions and contraindications, different dosages and pharmaceutical forms available, the prescription and dispensation regime, the retail price, and the conditions under which the product is publicly financed, and the estimated cost of treatment (ICLG - Pharmaceutical Advertising Laws and Regulations, 2023). For non-prescription medicinal products, the National Association of Advertising Pharmaceuticals (ANEFP) published the "Spanish Code for the Promotion and Advertising of Non-Prescription Medicines." ANEFP, as a self-regulating body, promotes materials with a label named the " „sello ANEFP" to ensure compliance with the code (ANEFP, Code of deontological norms for marketing and advertising of OTC, 2020).

Advertising and promoting the medical products in the Republic of North Macedonia is regulated by the Law on Medicines and Medical Devices. In addition, the instruction on advertising medicines and medical devices is a by-law adopted in accordance with the Medicines Law, comprehensively regulates the way of advertising medical products. Additionally, the advertising of medical products should also comply with The Law on consumer protection, the Law on healthcare and The Code of professional ethical responsibilities and rights of health professionals. Apart from the above regulations in the European member states, in Republic of North Macedonia, there are no other legal regimes such as self-regulating codes of conduct which additionally regulate the way of advertising medical products. Similar to regulation in these European member states, the Republic of North Macedonia allows the advertising of medicinal products to the general public only for over-the-counter medicines.The national regulatory body, the Agency for Medicines and Medical Devices MALMED, must give prior approval for the advertising of medicines aimed to the general public (over-the-counter medicines) (Macedonian Agency for Medicines and Medical Devices [MALMED], 2023). In order to obtain approval for publishing the advertisement, the marketing authorization holder must submit a written request indicating all the data related to the drug, the type of media through which it will be implement the advertisement and the type of advertisement to be placed, as well as the proposed text of the advertisement. In addition to the application, the applicant should also submit the marketing authorization for the drug, the SmPC as well as the instructions for the patient (Law on Medicines and Medical Devices, 2007). Article 95 of the Law on Medicines and Medical Devices explicitly prohibits the advertising of medicinal products that do not have a marketing authorization in North Macedonia. An exception to this prohibition are medicines prescribed by a doctor to the general public, justified by the need to protect the public health or prevention of emergency situations (epidemics, natural disasters of a larger scope and etc.) (Law on Medicines and Medical Devices, 2007). When advertising medicines to health professionals through promotion, the marketing authorization holder must indicate the date of obtaining the marketing authorization approval, information about the method of dispensing the drug, updated indications, relevant data by specifying the relevant information source. In addition to this data on the promotion of the drug, the sale price of the drug can also be included. The advertising of medicines to the professional public is not subject to prior authorization (Law on Medicines and Medical Devices, 2007).

4. DISSCUSION

The comparative analysis of the literature highlights a noteworthy trend across European member states, including the Republic of North Macedonia, a candidate country for European Union membership. It becomes evident that

there is a general alignment of regulations with those of the European Union, showcasing a harmonized approach towards pharmaceutical advertising and promotion. The distinction between the promotion of prescription drugs, primarily targeting healthcare professionals, and over-the-counter drugs, which are accessible to the general public without a doctor's prescription, is a common thread among member states. The self-regulatory codes established by European member states, such as Germany, Slovenia, and Spain, reflecting the standards set by the European Federation of Pharmaceutical Industries and Associations (EFPIA), emerge as pivotal components in shaping the regulatory landscape. The ability of these codes to pre-approve advertisements not only ensures compliance with overarching standards but also streamlines the execution of promotional activities. This demonstrates a proactive and organized approach, fostering transparency and adherence to ethical practices within the pharmaceutical industry.

After conducting a comparative analysis of processed literary data, it can be inferred that each member state, including the Republic of North Macedonia as a candidate country for the European Union, has aligned its regulations with those of the European Union. Generally, the promotion of prescription drugs is restricted to healthcare professionals, whereas the advertising of over-the-counter drugs, which do not require a doctor's prescription, is directed toward the general public. European member states such as Germany, Slovenia and Spain have established their own self-regulatory codes that adhere to the European Federation of Pharmaceutical Industries and Associations (EFPIA) standards. These codes have the authority to pre-approve advertisements, contributing significantly to the streamlining of executive activities. The Republic of North Macedonia could benefit from incorporating positive experiences from European member states to enhance its pharmaceutical regulation. Drawing parallels between the practices of established European member states and the regulatory framework of the Republic of North Macedonia, it becomes evident that there is an opportunity for the Republic of North Macedonia to leverage positive experiences from its European countries. By incorporating successful elements of European member states' regulations, the Republic of North Macedonia could enhance its own pharmaceutical regulatory environment.

5. CONCLUSION

In conclusion, the comparative analysis of pharmaceutical regulations across European member states, including the Republic of North Macedonia, underscores a harmonized approach towards pharmaceutical advertising and promotion within the European Union. The comparative analysis underscores the potential benefits of cross-border collaboration and knowledge-sharing, emphasizing the importance of a harmonized regulatory environment for the advancement of the pharmaceutical sector. In summary, these insights shed light on the positive impact of adopting successful regulatory practices, paving the way for improved pharmaceutical governance and practices in the Republic of North Macedonia.

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