Summaries of Product Characteristics

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The Summary of Product Characteristics (SmPC) is a legal document, is one of the obligatory elements of the registration dossier of a medication, and is necessary to issue a marketing authorization for a medicinal product. The obligation to draw up a Summary of Product Characteristics is laid down in several European Parliament laws. The first documents were Directive 2001/83/EC of the European Parliament and the Council relating to medicinal products for human use, and Regulation 726/2004. The document was amended several times and finally replaced in 2004 by Directive 2004/27/EC.

SmPC medicinal product patient safety

1. Introduction

The Summary of Product Characteristics (SmPC) is the main document containing details of a particular medicine. The document submitted by the marketing authorization holder shall contain key information for healthcare professionals on the safety and efficacy of the medicinal product. A Guideline on Summary of Product Characteristics issued in September 2009 by the European Commission provides detailed guidance on what should be included in specific sections [1]. Despite the structured form of this document, healthcare professionals (doctors, nurses, and pharmacists) repeatedly stressed that the development of the document requires a fresh approach, with the use of other provisions that are more comprehensible to professionals and whose interpretations will not be divergent or questionable. This problem was particularly highlighted when biosimilar medicinal products began to appear in large numbers on the pharmaceutical market.

2. Understanding of the Information Contained in the SmPC

One of the primary roles of the SmPC is to provide information to healthcare professionals. For this to be achieved, it is necessary to meet the basic conditions for effective data communication (the understanding of how different recipients perceive the message, as well as the key factors in changing patient and clinician behavior). The European Commission has included in its guides a laconic statement that SmPCs should be written in clear and concise language [1]. Furthermore, the legislation and the EU guidelines that are based on it only set standards for the readability of a package leaflet addressed to patients, but not the SmPC dedicated to healthcare professionals.

The EU directives, Polish pharmaceutical law, and other regulations do not oblige marketing authorization holders to test the SmPC for readability and comprehensibility before registration. To date, research on SmPCs has focused on the accuracy and completeness of content [2][3][4][5][6]. However, very little is known about how SmPCs

are used by healthcare professionals, or if they meet the needs of health professionals as a trusted source of information.

3. Differences in the Content of SmPCs for Medicinal Products with the Same Active Substances

Another problem with SmPCs is discrepancies in the registration dossiers of preparations with the same qualitative and quantitative composition of active substances. One of the analyses carried out covered 31 medicinal products and showed that more than 60% of them contained significant (critical) differences between original and generic products [7]. Fourteen of the thirty-one selected medicines had discrepancies in the content of the contraindication section. Of these, 71.5% of the medicines were assessed as demonstrating critical differences and 28.5% as demonstrating very minor differences. Moreover, registration dossiers differed from country to country [8], probably due to different legislation. An assessment of the consistency in the information contained in the SmPCs of generic antimicrobial medicines led to similar conclusions [9]. The omission of clinically relevant information related to pharmacokinetic properties was noted.

Disparities in the SmPCs of generic and original medicines are unfortunately a reality. According to the EMEA guidelines, all relevant aspects of the content of generic SmPCs should be consistent with the SmPCs of the reference medicinal products—the so-called ‘branded’ medicines [10]. This is because inconsistent information on medicines containing the same active substance contributes to confusion and poor prescribing decisions. Although similar regulatory requirements apply to generic medicines in the US, inconsistency has been noted among bioequivalent medicines, both there and in other countries for the same medicine authorized by the same regulatory agency. These discrepancies are particularly striking as they put specific subpopulations such as young children or patients with comorbidities at risk. Discrepancies in the SmPC could potentially be life-threatening or even fatal to the patient, which raises serious concerns. One such possibly deadly discrepancy concerned adrenaline: one generic product’s SmPC lacked contraindications for patients with ventricular fibrillation, cardiac dilatation, or coronary insufficiency. This discrepancy may lead to ventricular arrhythmias and/or coronary ischemia in such patients. The second potentially fatal discrepancy concerned promethazine: generic product labels lacked a contraindication for patients up to 2 years of age, leading to a risk of respiratory depression in this subpopulation. These discrepancies represent extremely important omissions from patient safety labels [7][11].

This suggests that if responsible parties do not continuously compare labels with their competitors (generic or originator companies), publicly available scientific information will not be updated to include new side effects. Moreover, this key information will not be available to patients and doctors. This fact may lead to a lack of awareness among patients and physicians about potentially important safety information for a specific medicinal substance.

This fact may result in inconsistent information being communicated to healthcare professionals and patients regarding the same active ingredient. It also raises questions about the duty to provide information and liability for medical malpractice. This is also problematic from the point of view of the pharmacist, who has the right to issue a

substitute to the patient. Under the current legislation, a ‘medicinal product having the same qualitative and quantitative composition in active substances, the same pharmaceutical form as the reference medicinal product and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies’ [12], is considered a substitute. Pharmaceutical law does not mention differences in the registration dossier for a medicinal product. The problem also relates to other aspects of the safety of medicinal products, such as side effects and risk assessment by the doctor.

4. Incomplete Information in SmPCs

Despite guidelines on the drafting of SmPCs, there are still some in widespread circulation that contain gaps in specific sections, for example, information on dosages in patient subpopulations. Knowledge of dose adjustments and contraindications for drugs in patients with, for example, hepatic impairment, is often based on the results of endpoint studies conducted by pharmaceutical companies. In recognizing that information was not always generated to the same extent for different drugs, the European Medicines Agency (EMEA) published a guideline on the assessment of endpoints in patients with hepatic impairment in 2005 (European Medicines Agency, 2005). Those guidelines provide recommendations for the design and reporting of test results in patients with hepatic impairment. The results of those studies needed to be included in the study report and discussed in the EPAR, and then included in the SmPC. However, of the 51 medicinal products registered in 2015- 2017, as many as 15 did not have the required dosage information for patients with hepatic impairment [13]. On average, 7 out of 9 pieces of information requested by the EMEA were available in these SmPCs. Safety information or dosage recommendations for patients with severe hepatic impairment were unavailable for almost 60% of the drugs evaluated and/or were ambiguously worded. Basic information on the type of liver disease of the patient included in the required studies was missing for 35 of the 36 drugs. For 21 drugs, this information could be found in the unpublished part [13]. Vague statements such as ‘not recommended’ or ‘use with caution’ leave open the interpretation of whether the drug is absolutely contraindicated and what the possible effects of its use would be. Ambiguous wording was also observed in studies analyzing SmPC recommendations in other clinical areas, such as renal impairment [13].

References

1. European Commission. A Guideline on Summary of Product Characteristics (SmPC). 2009. Available online: http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf. (accessed on 21 March 2021).
2. Savill, N.; Bushe, C. A systematic review of the safety information contained within the summaries of product characteristics of medications licensed in the United Kingdom for attention deficit hyperactivity disorder: How does the safety prescribing advice compare with national guidance? Child. Adolesc. Psychiatry Ment. Health 2012, 6, 2.

3. Arguello, B.; Fernandez-Llimos, F. Clinical pharmacology information in summaries of product characteristics and package inserts. Clin. Pharmacol. Ther. 2007, 82, 566–571.
4. Bergk, V.; Haefeli, W.E.; Gasse, C.; Brenner, H.; Martin-Facklam, M. Information deficits in the summary of product characteristics preclude an optimal management of drug interactions: A comparison with evidence from the literature. Eur. J. Clin. Pharmacol. 2005, 61, 327–335.
5. Wall, A.; Bateman, D.N.; Waring, W.S. Variability in the quality of overdose advicein Summary of Product Characteristics (SPC) documents: Gut decontamination recommendations for CNS drugs. Br. J. Clin. Pharmacol. 2008, 67, 83–87.
6. San Miguel, M.; Alfredo Martinez, J.; Vargas, E. Food-drug interactions in the summary of product characteristics of proprietary medicinal products. Eur. J. Clin. Pharmacol. 2005, 61, 77–83.
7. Thoenes, A.; Cariolato, L.; Spierings, J.; Pinçon, A. Discrepancies Between the Labels of Originator and Generic Pharmaceutical Products: Implications for Patient Safety. Drugs Real World Outcomes 2020, 7, 131–139.
8. Alshammari, T.M.; Devadasu, V.R.; Rathnam, R.P. Comparison of the safety information on drug labels in three developed countries: The USA, UK and Canada. Saudi Pharm. J. 2017, 25, 1103–1107.
9. Shimazawa, R.; Kano, Y.; Ikeda, M. Natural language processing-based assessment of consistency in summaries of product characteristics of generic antimicrobials. Pharmacol. Res. Perspect. 2018, 11, e00435.
10. European Medicines Agency. QRD General Principles Regarding the SmPC Information for a Generic/Hybrid/Biosimilar Product. 2018. Available online: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/quality-review-documents-general-principles-regarding-summary-product-characteristics-information/hybrid/biosimilar-product_en.pdf (accessed on 24 March 2021).
11. Gahr, M.; Freudenmann, R.W.; Connemann, B.J.; Schönfeldt-Lecuona, C.; Muche, R.; Hiemke, C.; Sillmann, Y.M. Unterschiedliche Anzahl von Kontraindikationen zwischen Fachinformationen wirkstoffgleicher Arzneimittel—eine Analyse von Daten aus Fachinformationen von neuropsychiatrischen Arzneimitteln . Fortschr. Neurol. Psychiatr. 2020, 88, 152–169.
12. Act of 6 September 2001 Pharmaceutical Law (Journal of Laws 2020.944, i.e.). Available online: https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20011261381/U/D20011381Lj.pdf (accessed on 31 January 2022).
13. Weersink, R.A.; Timmermans, L.; Monster-Simons, M.H.; Mol, P.G.M.; Metselaar, H.J.; Borgsteede, S.D.; Taxis, K. Evaluation of Information in Summaries of Product Characteristics (SmPCs) on the Use of a Medicine in Patients with Hepatic Impairment. Front. Pharmacol. 2019, 10, 1031.