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Research Article

Pharmacovigilance: procedures for uniform assessment of periodic safety update reports and their implementation in national settings. Focus on analgesics

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Abstract

Pharmacovigilance activities are of vital importance for ensuring effective and safe medicinal products. In order to clarify to which extent marketing authorisation holders (MAHs) meet the requirements of the Law and the Directives related to this activities, we conducted a systematic search among the procedures submitted to the Bulgarian Drug Agency (BDA) related to the implementation of the decisions of the Pharmacovigilance Committee and the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for a period of 6 years. The results of the study showed significant discrepancies between regulatory requirements and the behavior of the MAH at the national level. This could be a serious problem, as inadequate or late implementations of the PRAC (Pharmacovigilance Risk Assessment Committee)/CMDh/EC recommendations can lead to untimely informing of healthcare professionals and patients about potential safety concerns and risks related to the use of medicinal products.

Keywords

NSAIDs, opioids, regulatory requirements discrepancies

Introduction

Pharmacovigilance issues increasingly require serious monitoring and standardized standard procedures for assessing patients‘ risk levels. There are accumulating evidence that in many cases the treatment of adverse drug reactions is extremely detrimental to patients and health care budgets and could have serious consequences. The data presented here clearly show that analgesics and some antidepressants are widely used in society, which often has serious consequences. The development and implementation of modern unified standards for safety assessment, as well as their timely implementation in EU countries, is of great importance.

According to the current European pharmaceutical legislation, all periodic safety update reports (PSUR) are subject to a centralized assessment, the so-called Periodic Safety Update Report Single Assessment (PSUSA). PSURs are submitted in accordance with the timetable described in the Guidelines for Good Pharmacovigilance Practice (2011) (GVP), Module VII, effective July 2, 2012, and replaced Volume 9A.

Table 1. Deadlines (May 2020) for generic medicinal products or those not directly affected by the PSUR procedure.

Products that are included in the procedure	Yes	No
Need to submit an application for a variation of MA, type of the variation	Yes • IA $_{IN}$ C.1.3.a (harmonised national texts are available) • IB C.1.3.z (need for adaptation) • II (submission of new data, classification is a subject to proposed change)	Yes • IA $_{IN}$ C.1.3.a (harmonised national texts are available) • IB C.1.3.z (need for adaptation) • II (submission of new data, classification is a subject to proposed change)
Deadlines for submitting the variation application	• For CMDh position adopted by consensus: according to the date indicated in the table, i.e. 105 calendar days after its adoption. • In the case of CMDh's position adopted by a majority: 10 days after the publication of the EC decision on the EC website. • Position of the CHMP: 10 days after its publication on the website of the European Commission.	• For CMDh position adopted by consensus: according to the date indicated in the table, i.e. 105 calendar days after its adoption. • In the case of CMDh's position adopted by a majority: 60 days after the publication of the EC decision on the EC website. • Position of the CHMP: 60 days after its publication on the website of the European Commission.

According to the Official Journal of the European Union (2010), the generic medicinal products as well as homeopathic medicinal products, and herbal products of traditional use do not fall within the scope of these requirements and no PSUR submission is required unless a specific requirement is included in the marketing authorisation or the Product is included in the so-called European Union reference dates (EURD) list. This list is updated by the European Medicines Agency and is available on the EMA's website.

The procedures for a single assessment of periodic safety update reports shall be performed by EMA and affect all medicinal products containing the same active substance or combination of substances, even if they are subject to various authorisations or authorised by different countries. A Pharmacovigilance Risk Assessment Committee (2012) (PRAC) has been set up for this purpose. The assessment shall be carried out by the members of the PRAC or a Member State, following a nomination by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), and usually ends with a single assessment report, which is circulated to all marketing authorisation holders (MAH) whose products are included in that assessment. It should be noted that MAH is fully responsible for the quality of the documentation submitted and is essential for the overall assessment. The Pharmacovigilance Committee evaluates the safety data for centrally authorised medicinal products, PSURs on a group of products, some of which are centrally authorised and those that have received marketing authorisation (MA) under purely national procedures (including decentralized or mutual recognition), as well as for products that are authorised in one Member State (MS) only. The assessment of the periodic safety update reports is a national responsibility in case of certain specific medicinal products that are of national interest or contain active substances that are not included in the EURD list.

Following the publication of the PRAC recommendations, the European Commission (EC) issues a decision that is sent to all Member States and should be implemented by the national competent authorities within 30 days of notification of medicinal products under a national procedure. The concerned medicinal products are usually described in an annex to the EC decision. By analogy with the referral procedures, the variations in the marketing authorisations must be submitted to the Bulgarian Drug Agency (BDA) within 10 days after the publication of the EC decision. CMDh' s position includes a timetable for submission of Variation Applications, which is applicable to all affected products, including those not described in the Annex to the EC Decision. Changes in the product information after PSUSA procedures can be implemented using a Type IA with immediate notification variation, category C.I.3.a, provided they are available harmonized national translations and there is no need for additional assessment. If proposed by the Committee, resp. Commission text needs to be further adapted to the specific product information, a change may be submitted as a type IB, C.I.3.z. (Q 3.3 of CMDh/CMDv /132/2009, Rev.55, February 2020). Generic medicinal products, or those not directly affected by the PSUR procedure, have to comply with the deadlines (May 2020) showed in Table 1.

According to Art. 23 (3) Directive 2001/83 / EC, marketing authorisation holders must take the necessary action to actualize the product information – Summary of Product Characteristic (SPC) and Patient Leaflet, in accordance with current scientific knowledge, including the conclusions following an assessment by national and European regulatory authorities and the recommendations published on the website of the European Medicines Agency.

The Guideline on the classification of variations to the marketing authorisation specifies that if the variation does not meet any of the conditions for type IA/IA $_{IN}$ and/or no documentation is available, the same variation may be submitted as type IB.

The purpose of the current analysis is to establish how marketing authorisation holders comply with European legislation in the field of pharmaceutical regulation at national level and to identify potential regulatory gaps. And on this basis to find answers to some key questions such as:

- What are the regulatory activities related to pharmacovigilance recommended by the Pharmacovigilance Committee for active substances belonging to the group of Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics?
- What are the recommended deadlines for implementing the new safety data in the product information and how the PRAC recommendations are implemented?

Table 2. PAUSAs concerning NSAIDs and opioid analgesics (for the 2015–2019-year period) which completed with a PRAC recommendation for a change and the recommended date for submitting the change.

Active substance	Procedure number	Recommended date for submitting the change
Ibuprofen	PSUSA / 00010345/201702	02/21/2018
Tramadol	PSUSA / 00003002/201705	11/05/2018
Morphine, Morphine/ Cyclizine	PSUSA / 00010549/201710	10/10/2018
Meloxicam	PSUSA / 00010474/201607	05/07/2017
Tenoxicam	PSUSA / 00002893/201502	03/03/2016
Diclofenac for systemic use	PSUSA / 00001048/201509	09/07/2016
Naproxen	PSUSA / 00002125/201708	08/08/2018
Tapentadol	PSUSA / 00002849/201711	11/07/2018
Diclofenac for systemic use	PSUSA / 00001048/201 8 09	11/09/2019

Materials and methods

The materials are related to variation documentation for concerned medicinal products submitted at national level. It is regulated by the Law on Medicinal Products in Human Medicine Act and related regulations. A systematic review was carried out using the scientific conclusions published on the EMA website after each PSUSA, the data available in the register of authorised medicinal products and the published summary of product characteristics.

In the present research, we included a study of the submitted to the BDA and approved changes in the marketing authorisations of the cited groups of products, the terms in which they were submitted, and the types of changes used by the MAH.

The methodological approach that was chosen includes five successive stages:

1. Identification of PSUSA procedures that have resulted in recommendations for changes in the marketing authorisations for the indicated groups of active substances.
2. Clarification of the registration status of medicinal products.
3. Monitoring of the regulatory activities for each separate, authorised for use LP in Bulgaria, compliance of the applications for change received by the BDA with the recommendations of PRAC, resp. CMD (h) or EC.
4. Deadline for submission of applications and type of change, according to the classifier of changes.
5. Analysis of the results.

Results and discussion

In connection with the above, data analysis was performed for all medicinal products containing NSAIDs and opioid analgesics and regulatory activity in connection with the completed PSUSA procedures over the past five years (2015–2019).

For the period 2015–2019 year out of all PSUSA concerning NSAIDs and opioid analgesics, nine completed with a recommendation by the PRAC changes in marketing authorisations (of which two of diclofenac for systemic use). For the others, the Committee did not identify any changes in the safety profile of the active substances and did not recommend any changes to the product information.

Ibuprofen (PSUSA/00010345/201702)

For systemic use only and those found to have significant systemic resorption when applied topically. The procedure does not affect products for the treatment of ductus arteriosus. The products for local administration included in the review are included by the EMA in the list of products subject to change.

In the evaluation of safety data, a causal relationship was found between the use of ibuprofen and the occurrence of drug reaction with eosinophilia and systemic symptoms (Drug rash with eosinophilia and systemic symptoms syndrome – DRESS syndrome), which were of unknown frequency. Additionally, the development of metabolic acidosis has been observed with ibuprofen overdose. The PRAC recommendation was to include this information in the summary of product characteristics.

At the time of the study, 61 ibuprofen-containing medicinal products for systemic use (oral or parenteral) had been authorised in Bulgaria. Of these, 18 did not implement the PRAC recommendations, 17 were implemented in a timely manner, according to the recommendations of the CMDh using a type IA variation procedure with immediate notification. For the other products, the information was updated through a type IB change, which implies the presence of additional editorial changes in the text, late implementation or ignorance of the regulation by the MAH.

Tramadol (PSUSA/00003002/201705)

The evaluation of the safety data included in the PSURs established new pharmacokinetic interactions based on CYP2D6 and that about 7% of the Caucasian race is deficient in this enzyme. As a consequence, manifestations of general opioid toxicity may develop.

17 medicinal products had been authorised under national and mutual recognition procedure. The changes were implemented in a timely manner, leaving unclear the reason for the use of a type IB variation for part (5) of the products that received the RO under the mutual recognition procedure. The changes were submitted within the respective deadline and the availability of approved translations does not require additional assessment.

Morphine, Morphine/Cyclizine (PSUSA/00010549/201710)

Several changes were recommended – to add warnings for the occurrence of an acute thoracic syndrome in patients with sickle cell anemia, adrenal insufficiency, hypogonadism, as well as with prolonged use (which leads to a reduction in analgesic effects) is hyperalgesia, observed

mainly at high doses. In addition, the available data support the inclusion of anaphylactoid reactions, anxiety and dysphoria, hyperhidrosis, dry mouth, dependence, withdrawal syndrome, as well as allodynia and hyperalgesia as adverse reactions. It is recommended to include information on the risk of a neonatal withdrawal syndrome in neonates from mothers treated with opioid analgesics.

For all medicinal products (9 in total) containing morphine as an active substance, the marketing authorisation holders have complied with the instructions of the PRAC and the applicable regulatory requirements, the safety data have been implemented fully, adequately and without undue delay.

Meloxicam (PSUSA/00010474/201607)

It is recommended to add a new adverse reaction in section 4.8 of the SPC and the relevant section of the package leaflet.

15 medicinal products with valid marketing authorisation were identified. For 3 of the products, the MAH did not take the necessary actions to include the warnings in the product information (national change), for 4 of the products national procedures for type IB change were initiated, and for 1 incorrect classification was established. 12 marketing authorisations have been updated in full, accurately and in a timely manner in accordance with regulatory requirements.

Tenoxicam (PSUSA/00002893/201502)

During the period while tracking ADRs a risk of serious reactions in the elderly has been identified which include eye disorders, nervous system disorders, psychiatric disorders and pancreatitis. There is only one medicinal product in the country with a valid marketing authorisation. The variation application was submitted within the deadline recommended by the PRAC, but was implemented in practice with a 6-month delay.

Diclofenac for system administration (PSUSA/00001048/201509) and (PSUSA/00001048/201809)

Of the 27 valid marketing authorisations for medicinal products containing diclofenac for systemic use, all but one of the MAHs have implemented the decisions of the Pharmacovigilance Committee.

A detailed review of the submitted applications for variation of the marketing authorisations revealed that 15% of them were incorrectly classified by the MAH. Respectively they were validated by BDA experts or marketing authorisation holders took the opportunity to submit the variation applications as grouped, which allowed them to postpone their actual implementation in the product information. Other procedures were justified by the late submission of the application and /or need for revision of the text, regardless of available official translations.

Naproxen (PSUSA/00002125/201708)

Interaction with ASK; 4 products with a valid MA, the changes have been implemented, and only in one case the change has been introduced according to the recommended term and procedure.

Tapentadol (PSUSA/00002849/201711)

Tapentadol was firstly authorised in the United States in 2008 and is approved in 59 countries worldwide. Currently, there are no generic products in the EU. It is indicated for the relief of moderate to severe acute pain and for the treatment of severe chronic pain in adults that has been adequately treated with opioid analgesics. It is marketed as immediate-release film-coated tablets, prolonged-release tablets and oral solution.

The total number of cases/reports of serotonin syndrome was found to be too high during the assessment period (191), with most cases involving the combined use of tapentadol with other analgesics. The Pharmacovigilance Committee confirmed that the risk of serotonin syndrome with tapentadol was reflected in the product information, but considered that the existing warnings could mislead healthcare professionals and should be changed. Therefore, the introduction of additional warnings and information on potential drug-drug interactions is recommended.

In Bulgaria, 11 different concentrations and/or pharmaceutical forms of a single medicinal product containing this active substance were authorised during the period of this study. At the date of aggregation of the information, all products with this active substance have been suspended due to an explicit wish of the MAH.

The marketing authorisation holder of the above products has complied with the deadline for informing the Agencies and has applied for a variation under the Community procedure (by mutual recognition), IA with immediate notification. However, the variation has not been implemented in Bulgaria due to the withdrawal of the existing marketing authorisation by the MAH.

Conclusion

The systematic review of the marketing authorisations described above and their history during their life cycle identified significant inconsistencies with the established regulatory framework.

The most common discrepancies are:

- Submission of applications for type IB variation, in the presence of unified and approved national texts, which does not require an additional assessment.
- Incorrect classification of the variations, which implies different conditions and documentation.
- Failure to comply with the specified deadlines for implementation of the change.

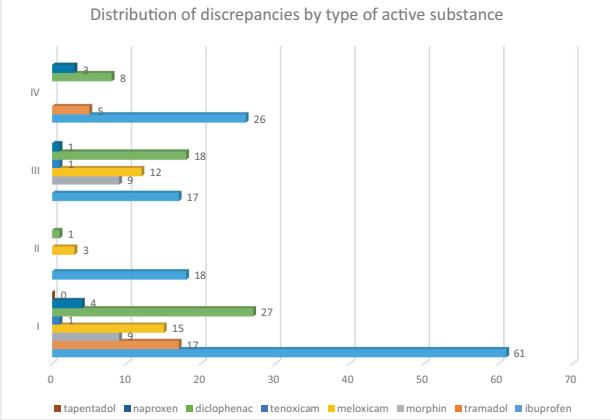

Figure 1. Distribution of discrepancies by type of active substance for all active substances/products affected by the PSUR evaluation procedures. Legend: I: Total number of products by active substances; II: The change has not been implemented; III: The change is implemented by an appropriate procedure; IV: The change is implemented outside the specified deadlines.

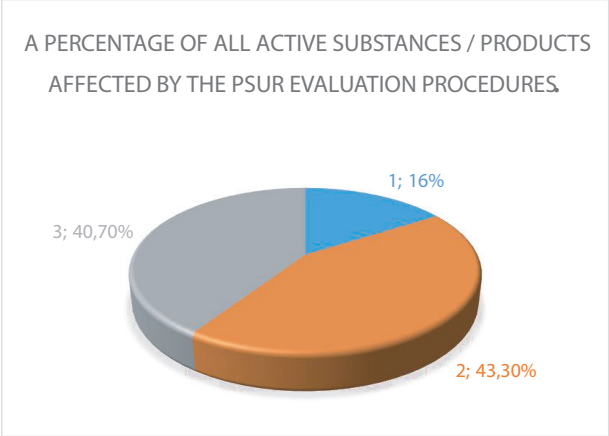

Figure 2. A percentage of all active substances/products affected by the PSUR evaluation procedures. Legend: 1: The change is not implemented; 2: The change is implemented with an appropriate procedure; 3: The change is implemented outside the specified deadlines.

- Failure to submit variation applications and, accordingly, lack of relevant safety information in the summary of product characteristics and/or package leaflet

Fig. 1 and Fig. 2 show the distribution of discrepancies by type of active substance, as well as a percentage of all active substances/products affected by the PSUR evaluation procedures.

Lack of understanding of modern pharmaceutical regulation or attempts to circumvent it is a possible reason for the identified discrepancies. In the practice of BDA, we often meet with ignorance of certain details of the procedures for variation of the MAs, such as the fact that the type IA and IA_{IN} variations are retrospect and are presumed to have already been implemented by the marketing authorisation holders before notifying the Agency thereof. Numerous meetings, training, and seminars were held to explain both the registration principles and those of drug safety.

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