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REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

on the national and European Medicines Agency experience regarding the list of medicines for human use subject to additional monitoring

1. INTRODUCTION

In the EU medicinal products for human use are subject to strict testing and assessment of their quality, efficacy and safety before being authorised either at national or EU level. Once placed on the market the safety of medicines continues to be monitored through a system of pharmacovigilance. This means that anything that affects a medicine's safety profile can be swiftly detected, assessed, and understood. Appropriate measures can be taken to manage the issue and assure public and patients' health.

Regulation (EC) No 726/2004[1] and Directive 2001/83/EC[2] provide the EU legal framework for pharmacovigilance for medicinal products for human use. The provisions on pharmacovigilance were amended in 2010[3] and 2012[4]. As a result of the changes the tasks and responsibilities for all parties were outlined within a proactive and proportionate risk management system. The link between safety assessments and regulatory action, along with transparency, communication and patient involvement were strengthened. This report concerns the experience gained regarding 'additional monitoring', a specific aspect of pharmacovigilance activities which was introduced through the revision of the legislation[5].

For some medicines there are limitations in the clinical trials, for example because the number of patients are restricted and the available evidence has limitations. The experience of use in the real life setting can complement the evidence form the clinical trials. Additional monitoring aims to enhance adverse drug reaction (ADR) reporting for medicines for which the clinical evidence base is less well developed. The main goals are to collect information as early as possible to further inform the safe and effective use of these medicines and their benefit-risk profile when used in everyday medical practice.

The 2010 revision[6] introduced additional monitoring for certain medicines and a mandatory scope of new biological medicines or those containing a new active substance. The medicines which are subject to additional monitoring are identified by the inclusion of a 'black symbol'[7] (a black inverted triangle) in the product information.

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1 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

2 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

3 Regulation (EU) No 1235/2010 (OJ L 348, 31.12.2010. p 1), Directive 2010/84/EU (OJ L 348, 31.12.2010. p 74).

4 Regulation (EU) No 1027/2012 (OJ L 316, 14.11.2012. p 38), Directive 2012/26/EU (OJ L 299, 27.10.2012. p 1).

5 The concept and scope of additional monitoring was introduced in Article 23 of Regulation (EC) No 726/2004 through Regulation (EU) No 1235/2010 and amended by Regulation (EU) No 1027/2012.

6 Article 1(11) of Regulation (EU) No 1235/2010 amendment of Article 23 of Regulation (EC) No 726/2004.

7 The 'black symbol' is defined by Article 23 of Regulation (EC) No 726/2004 and Article 11 of Directive 2001/83/EC. It was designated as a black inverted triangle through Commission Implementing Regulation (EU) No 198/2013 of 7 March 2013 on the selection of a symbol for the purpose of identifying medicinal products for human use that are subject to additional monitoring (OJ L 65, 8.3.2013, p. 17).

In 2012[8] the mandatory scope was extended to include medicines with certain post authorisation obligations. At the time, some Member States expressed reservations about the extension of the mandatory scope. Therefore, the Commission was asked to report to the European Parliament and the Council on the use of the additional monitoring list[9].

The Member States and the European Medicines Agency (EMA) collected information on the experience of the implementation of the additional monitoring of medicines through:

a. A survey to estimate patient and healthcare professional (HCP) awareness of the black symbol and the additional monitoring concept.
b. EMA's experience with the use of the additional monitoring list and a study on whether the inclusion of products on the list had an effect on reporting of their ADRs.
c. A survey to understand Member States' experience with additional monitoring.

A joint report of the Heads of Medicines Agencies (HMA) and EMA based on the above surveys and analysis forms the main basis of this report[10].

2. BACKGROUND

The safety of medicines is monitored throughout their lifecycle, including the collection of information on suspected ADRs (side effects). EMA is responsible for developing and maintaining EudraVigilance, an IT system for managing and analysing information on suspected ADRs to medicines authorised in the European Economic Area (EEA)[11].

As part of the implementation of the new pharmacovigilance provisions the new system to label medicines that are being monitored particularly closely, generally because there is less information available about them was applied in 2013. These medicines are described as being under 'additional monitoring'.

Medicines subject to additional monitoring include an inverted black triangle (referred to as the black symbol in the legislation) and an explanatory statement in the product information[12]. For example, the following is included in the package leaflet:

> ▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

A list of medicines under additional monitoring is published by EMA and updated monthly to add new medicines and any changes in monitoring status of those medicines on the list[13].

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8 Article 1(4) of Regulation (EU) No 1027/2012 amendment of Article 23 of Regulation (EC) No 726/2004.

9 Article 23(4a) of Regulation (EC) No 726/2004.

10 European Medicines Agency and Member States joint report to the European Commission on the experience with the list of products subject to additional monitoring, EMA/153015/2018, 8 March 2018.

11 Data from EudraVigilance is published in the European database of suspected adverse drug reaction reports http://www.adrreports.eu/.

12 Leaflet on the black triangle https://ec.europa.eu/health/sites/health/files/files/pharmacovigilance/2013-10_blacksymbol/bs2013_10_en.pdf.

To support the Member States implementation of the new pharmacovigilance provisions the Commission funded a Joint Action on Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE)[14]. SCOPE gathered information and expertise on how regulators in Member States run their national pharmacovigilance systems and developed a variety of tools to support best practice[15].

The *Guideline on good pharmacovigilance practices (GVP): Module X – Additional monitoring* drafted by EMA explains the general principles for assigning additional monitoring status to medicines, the communication and transparency aspects, and a description of the operation of the EU network regarding the supervision of additional monitoring[16].

2.1 Which medicines are subject to additional monitoring?

The mandatory scope of additional monitoring obligation included in the 2010 revision of the legislation was the names and active substances of:

- medicinal products authorised in the Union that contain a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the Union;
- any biological medicinal product that was authorised after 1 January 2011.

During the 2012 revision of the legislation, the mandatory scope of the additional monitoring list was extended to certain medicines with specific post-authorisation obligations, namely:

- products for which a post authorisation safety study (PASS) was requested at the time of marketing authorisation or following the granting of an authorisation;
- products which were granted a conditional marketing authorisation (CMA);
- products authorised under exceptional circumstances;
- products authorised with obligations for stricter recording/monitoring of suspected ADRs.

The legislation also provides the possibility to include medicines subject to other conditions falling under the so-called 'optional scope' of additional monitoring[17]. This can be done at the request of the Commission or a national competent authority (NCA) following consultation with the Pharmacovigilance Risk Assessment Committee (PRAC). This option had not been used during the period of the reported experience.

In principle, the additional monitoring status is time limited. This is 5 years for those included solely on the basis of being a new biological medicine or containing a new active substance.

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13 https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medicines-under-additional-monitoring/list-medicines-under-additional-monitoring

14 http://www.scopejointaction.eu/

15 Radecka A. Loughlin, L., Foy, M. et al., Enhancing Pharmacovigilance Capabilities in the EU Regulatory Network: The SCOPE Joint Action, Drug Safety, (2018) 41: 1285. https://doi.org/10.1007/s40264-018-0708-5

16 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-x-additional-monitoring_en.pdf

17 Article 23(1a) of Regulation (EC) No 726/2004.

In other cases it is after all the conditions for the inclusion in the additional monitoring list have been fulfilled. When medicines are no longer subject to additional monitoring the black symbol is removed from the product information.

Only those medicines specifically named in the list are subject to additional monitoring. This means that medicines not specifically named are not subject to additional monitoring, even if they have the same active substance and indication as medicines in the list.

The first version of the list was published in April 2013 and included 105 medicines. In December 2016[18] the list included in total 2099 medicines (see section 4.1 for details).

3. PUBLIC AWARENESS OF THE CONCEPT OF ADDITIONAL MONITORING

In 2017 EMA conducted a public survey to understand awareness of reporting adverse drug reactions, including for medicines under additional monitoring[19].

In total 2862 responses were received from EEA countries and 56 responses from non-EEA countries (2918 in total). Healthcare professionals were 53% of the respondents and 47% were non-HCP (i.e. patients or members of the public).

Within the HCP group 85% had observed at least one ADR, of whom 76% had reported at least one ADR. In the non-HCP group, 67% had experienced at least one ADR, of whom 73% had reported at least one ADR.

Overall, 88% of the respondents indicated they would definitely or probably report an ADR for a medicine identified with black triangle (i.e. subject to additional monitoring). From the reported experience of ADR reporting, of the 227 responders who had reported an ADR for a product identified with a black triangle 37% indicated that the black triangle was an influencing factor. Reasons given for not reporting an ADR were: it was already listed (28%); it was not serious (15%); unsure if ADR was related to the medicine (13%); practical/technical/other reasons (18%).

Of all the respondents, 51% indicated that they had seen the black triangle and accompanying statement. The highest awareness was among pharmacists (83%), with the lowest awareness among patients (30%). The majority (83%) indicated that they understood the meaning of the black triangle/accompanying statement. Although in response to a question exploring what the black triangle and the accompanying statement meant, it was judged by EMA that 53% had acceptable understanding and 17% had misunderstood the concept[20]. Among the responses assessed as 'misunderstanding', the most frequently mentioned themes for the inclusion of the black triangle were safety concerns or lack of safety data.

Among all respondents to the survey, 36% showed an acceptable understanding. The level of understanding was different among various groups of responders. The best was among

[18] The cut-off date for the reporting of the EMA experience.

[19] The survey was available to the general public on the EUSurvey platform for 5 weeks between September and October 2017. Information about the survey was disseminated by EMA, NCAs, HCPs and patient organisations.

[20] The remaining replies were assessed as insufficient information, no understanding or not responded.

pharmacists (45%) and lowest among nurses (23%). Nearly half of responders (48%) who had previously seen the black triangle had 'acceptable' understanding, compared to 24% of those who had not seen it before.

The HMA/EMA report mentioned a 2016 survey conducted by European Organisation for Rare Diseases (EURORDIS) on the meaning of the new pharmacovigilance system to patients[21]. According to the EURORDIS survey, 61% of patients experienced an ADR, of whom 84% reported the ADR. Within the survey 20% of the patients reported that they had seen a black triangle.

A survey[22] of the awareness of HCP of pharmacovigilance for biological medicines took place in Ireland [23]. The majority of HCP surveyed were aware of the concept of additional monitoring (82%). Among pharmacists 94% were aware compared to 73% of doctors and nurses. Among those who were aware of the concept of additional monitoring, the awareness of the black triangle was 88% of pharmacists and 30% of doctors and nurses.

4. IMPACT ON MONITORING OF SIDE EFFECTS

4.1 The additional monitoring list

Based on experience between April 2013 to December 2016, EMA analysed whether the inclusion of a medicine in the additional monitoring list had an effect on the reporting of ADRs.

The first version of the additional monitoring list was published in April 2013 and included 105 medicines (101 centrally authorised medicines (CAPs) and 4 non-CAPs). The reasons for inclusion in the list were: new active substance (NAS)[24] 70%; new biological medicine 2%; an imposed PASS 8%; marketing authorisation granted under exceptional circumstances or CMA 21%.

In December 2016, the list included a total of 2099 medicines (273 CAPs and 1826 non-CAPs) separated into a main list of 301 medicines and 13 annexes with 1798 medicines. Each annex included medicines with the same active substance for which a PASS had been imposed as an outcome of an EU review of the safety of the active substances concerned. The reasons for inclusion in the list were: NAS 9%; new biological medicine 2%; imposed PASS 88%; marketing authorisation granted under exceptional circumstances or CMA 1%. However, if each of the annexes is considered as one entry in the main list (making a total of 314 products) the reasons for inclusion would be: NAS 63%; new biological medicine 15%; imposed PASS 18%; marketing authorisation granted under exceptional circumstances or

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21 Presentation by François Houÿez "What does the new PhV [*pharmacovigilance*] system mean for patients in real life?" Available at: https://www.eurordis.org/sites/default/files/Eurordis_patients_and_pharmacovigilance.pdf.

22 The research was supported by the Health Products Regulatory Authority, Regulatory Science Ireland and University College Cork.

23 J. O'Callaghan *et al*, BioDrugs (2018) 32:267-280.

24 The figures where NAS is the reason for inclusion in the additional monitoring list include all products which contained a new active substance.

CMA 5%. The majority (87%) of the products in the December 2016 list were non-CAPs due to the high number of nationally authorised products subject to an imposed PASS.

4.2 Reporting of side effects (ADRs) for medicines under additional monitoring

The primary aim of additional monitoring is to enhance side effects (ADR) reporting. EMA investigated whether ADR reports to the EudraVigilance database (EV) changed after inclusion of the medicine in the additional monitoring list.

EMA used the December 2015 additional monitoring list to identify medicines for analysis as this allowed at least 12 months follow-up for ADR reporting whilst under additional monitoring. The final analysis was restricted to medicines for which at least 10 ADR reports from within the EEA had been received per month. EMA analysed the ADR reporting for 11 medicines for 12 months prior to and 12 months after their inclusion in the additional monitoring list.

EMA reported that the ways in which ADR reporting changed after addition to the list were heterogeneous. Of the five medicines containing a NAS, two demonstrated a statistically significant increase in the slope of ADR reporting after inclusion in the list, the others did not show significant changes. Among the six products included due to a PASS, no changes in reporting were identified for three products, whilst three products showed a significant decrease in the slope of ADR reporting.

EMA noted that the study had several limitations, for example due to the limited data set (11 medicines), the length of the observation period (up to 24 months). Time-dependent confounders could not be accounted for in the analysis and the assumptions for the calculations could affect the results. The power to detect a difference in reporting was restricted.

In summary, EMA indicated that there was some evidence that reporting may be increased for some medicines containing a NAS. There was no evidence that additional monitoring increases reporting of ADRs for products subject to a PASS. EMA noted that the analysis was restricted to a small subset of products and was possibly underpowered, so the results need to be interpreted with caution. In addition, EMA noted that ADR reporting may also have increased due to factors other than inclusion in the additional monitoring list.

The EMA/HMA report concludes '*If the analyses had shown marked and consistent increases in ADR reporting then it would be reasonable to conclude that AM [additional monitoring] was increasing the reporting for these products. However, the inconsistent and marginal results, combined with the known, disparate external influences on ADR reporting, suggest that even with a larger sample size and longer follow up the potential to definitively demonstrate a causal link between AM and increased reporting, is unlikely.*'

4.3 Impact of additional monitoring status on safety signals for medicines

A safety signal is information on a new or known adverse event that may be caused by a medicine and requires further investigation[25]. EMA looked at whether inclusion of a medicine

[25] 'Signal' is defined in Article 19 of Commission Implementing Regulation (EU) No 520/2012.

in the additional monitoring list affected the detection and management of safety signals related to it. Between April 2013 and December 2016, 269 signals were assessed by PRAC, of which 58 concerned only active substances in medicines subject to additional monitoring while 26 signals involved several medicines some of which were on additional monitoring list.

Of the 58 signals (21%) which concerned active substances only in medicines subject to additional monitoring, 78% related to medicines with a NAS, 19% had an imposed PASS and 3% had marketing authorisation granted under exceptional circumstances or CMA.

A safety review (referral)[26] was initiated in four cases (7%) of signals concerning medicines on the additional monitoring list compared to 2 cases (1%) of those not on the list. Circulation of a direct healthcare professional communication (DHPC) was recommended in 7% of assessed signals related to medicines on the additional monitoring list, compared to 5% for medicines not on the list. However, EMA noted that any differences must be evaluated with caution. With an update of the product information the outcome for 38% of the assessments for medicines on the list compared to 49% of those not on the list. It was concluded by EMA that signal outcomes were similar for the products subject to additional monitoring or not and that it could not be concluded that the additional monitoring status has an impact on signal outcomes.

5. NATIONAL EXPERIENCE WITH ADDITIONAL MONITORING

5.1 Experience of Member States

The SCOPE Joint Action investigated the Member States' experience of ADR collection, including additional monitoring[27]. It reports that 60% of the Member States do not specifically identify ADR reports for medicines subject to additional monitoring.

In a separate survey in 2017, EMA asked Member States about their experience with additional monitoring. Twenty-six NCAs responded to the survey and all had undertaken at least one activity to promote the additional monitoring concept. Twenty five NCAs had such initiatives in 2013, around the time that the black triangle and accompanying statement was included in the product information. Between 2014-2017, on average eight NCAs per year reported doing new communication activities.

Twenty NCAs reported that there had been an increase in the workload associated with the introduction of the additional monitoring symbol. Where estimates of the additional time were given, the estimated range was from around 0.02 to 1 full-time equivalent[28], although no information was available on the initial baseline of resources. The main reasons mentioned for

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[26] Referral procedures are used to address concerns over the safety or benefit-risk balance of a medicine. Safety reviews of signals are on the basis of Articles 31 or 107i of Directive 2001/83/EC and Article 20 of Regulation 726/2004.

[27] Work package 4 - Identification, management and raising awareness of ADR reports for drugs subject to additional monitoring - http://www.scopejointaction.eu/_assets/files/WP4-DEL3-Additional-Monitoring.pdf.

[28] Three NCAs mentioned a low additional workload, whilst four NCAs mentioned 0.5 day per month, 1 full time equivalent (FTE), 0.1 FTE, and 150 hours per year respectively.

the increase in workload were administrative and regulatory tasks such as: signal detection activities; ADR management; increase in ADR reporting; website updates; dealing with queries; other regulatory tasks (e.g. variations of the marketing authorisation, review of educational materials).

In the survey additional comments were made by three NCAs. One noted that there were indications that some patients may refrain from using products subject to additional monitoring. One reported that they had noted awareness among HCPs about the black symbol and that the HCPs specifically report ADRs for the medicines subject to additional monitoring. Two NCAs expressed reservations about the usefulness of the scheme, especially for products with an imposed PASS.

5.2 Views of the Pharmacovigilance Risk Assessment Committee

PRAC was consulted on the draft EMA/HMA report on the experience of additional monitoring. During this consultation some members raised concerns regarding an imposed PASS being a mandatory trigger for inclusion of a medicine in the list. The committee noted that additional pharmacovigilance activities, such as a PASS, would be imposed if routine activities, such as spontaneous reporting, do not sufficiently address the safety issue. PRAC also noted that there could be cases where a PASS might be imposed for one product whilst other similar products do not have a PASS imposed. In such cases, only the medicine with a PASS would be included in the additional monitoring list. It was mentioned that some NCAs have experienced that patients may question the lack of consistency, such that among the same-substance medicines some are perceived as 'safer' because they do not have the black triangle. PRAC considered that such inconsistency can undermine confidence in the pharmacovigilance system in general and in additional monitoring specifically.

PRAC suggested that additional monitoring status imposed at an active substance level, rather than individual medicinal product level, would prevent situations where several products containing the same active substance have different additional monitoring status. They also indicated that if substance level additional monitoring were considered to lead to other challenges, then many of the difficulties could be resolved by removing the additional monitoring status of products with an imposed study.

5.3 Overall conclusions presented in the HMA/EMA report

The overall conclusions presented in the HMA/EMA report of the experience of additional monitoring were that, the results suggest:

- *Both more time and more communication are needed to raise the awareness of AM [additional monitoring], as well as the need for ADR reporting in general. The EMA survey results suggest that knowledge of AM is higher in some groups than others and that these data could be used to target the messaging and intensity of communications;*
- *The EudraVigilance analysis investigating the effect of additional monitoring status on reporting of ADRs was not conclusive and the known disparate influences on ADR reporting raise doubts as to whether a longer period and larger product sample would*

enable the detection of an impact of AM on ADR reporting and signal detection, if such an effects exists;

- *The inclusion of imposed PASS as a mandatory trigger for additional monitoring leads to large numbers of established products being included in the list and is of limited value.*
- *Additional monitoring status being at product level combined with the inclusion of imposed PASS as a mandatory trigger for additional monitoring were highlighted as major issues with the additional monitoring concept. This is because of the resulting misunderstanding among patients and HCPs, due to situations when several products containing the same active substance have different AM status. Most examples of this inconsistency could be resolved by removing imposed PASS as a mandatory trigger of additional monitoring status;*
- *PRAC would support reconsideration of the scope of additional monitoring, particularly the mandatory inclusion of products subject to imposed PASS.*

6. CONCLUSIONS AND RECOMMENDATIONS

The report presented by the HMA/EMA on the experience of the Member States and EMA on additional monitoring gives an overview of the experience in the three years after the introduction of the black triangle in 2013.

At the time of inclusion of the black triangle in the information about the concerned medicines there were activities organised by the national competent authorities to promote the concept of additional monitoring and the importance of reporting ADRs in general.

Regarding the **awareness** about additional monitoring, the reported experience of additional monitoring indicates that the groups surveyed, including patients and healthcare professional, had knowledge of the concept of additional monitoring, although the level of understanding varied. The survey of patient and healthcare professionals indicated that there is a misunderstanding about the reasons for a medicine being subject to additional monitoring. It is suggested in the HMA/EMA report that more time and more communication activities are needed to raise awareness of the additional monitoring and the reasons for inclusion of a medicine in the list.

The Commission supported the activities of the SCOPE Joint Action. Through this project various materials have been developed that can support raising awareness of how to report adverse events associated with use of medicines[29].

Recommendation 1 – Member States and EMA are encouraged to continue promoting ADR reporting and sharing their experience to further develop best practices.

Regarding the **impact** of the inclusion of a medicine on the additional monitoring list, the EV analysis investigating the effect of inclusion in the additional monitoring list on reporting of ADRs was not conclusive. It was also not possible to conclude on whether additional

[29] SCOPE ADR Awareness toolkit - http://www.scopejointaction.eu/outputsandresults/adr-collection/awareness-levels/.

monitoring status has an impact on the number of signals validated and assessed by the PRAC or on signal outcome.

For the HMA/EMA report a survey of Member States was completed in which it was mentioned by some respondents that the inclusion of medicines with an imposed PASS in the additional monitoring list leads to a large number of medicines which have been on the market for many years being subject to additional monitoring. Some Member States questioned the added value in these cases and the possibility for misunderstanding the reason for inclusion of the black triangle in the product information. It was also mentioned that confusion can be created when products with the same active substance are not always subject to additional monitoring. The issue of whether there is any confusion regarding products with the same active substance was not part of the surveys mentioned in the report.

Recommendation 2 – the evidence does not allow a conclusion on the impact of additional monitoring on the reporting or detection of adverse events. It is recommended to continue to monitor the impact to strengthen the evidence base for future review of the scheme.

Regarding the **scope** of the additional monitoring list, PRAC indicated its support for the reconsideration of the scope of the additional monitoring obligations, in particular the mandatory inclusion of products subject to imposed PASS.

The Commission notes that there have been observations and concerns from some Member States about the reasons for inclusion in the additional monitoring list, in particular those that have an imposed PASS, and that PRAC supports reconsideration of the mandatory scope for additional monitoring.

The Commission does not consider that these concerns require an immediate review of the legislation but evidence on the implementation and impact of additional monitoring can be considered as appropriate in any future review of the legislation.

Recommendation 3 – competent authorities are invited to continue to collect data regarding the implementation of additional monitoring to allow at a later stage further assessment of the understanding of additional monitoring and its impact with respect to medicines with the same active substance, as well as experience concerning medicines with an imposed PASS.