8 March 2018
EMA/385597/2019
Inspections, Human Medicines Pharmacovigilance & Committees Division

European Medicines Agency and Member States joint report to the European Commission on the experience with the list of products subject to additional monitoring

Draft finalised by the Agency	16 February 2018
Released for PRAC/MS consultation	19 February 2018
End of consultation (deadline for comments)	2 March 2018
Revised draft finalised by the Agency in collaboration with Member States	8 March 2018
Revised draft adopted by HMA	20 June 2018
Final Report sent to the EC	26 June 2018

1. Purpose of the report

This report summarises experience to date with the list of medicines under additional monitoring (AM) and on the additional monitoring concept in general that has been gained by the EU medicines regulatory network since 2013.

It has been developed by the European Medicines Agency (EMA) and the medicines regulators of the EU Member States to form the basis for a report from the European Commission (EC) in line with Article 23(4a) of Regulation (EC) No 726/2004 as amended (REG)[1]:

> the European Commission (EC) shall present by 5th June 2018 to the European Parliament and the Council a report on the use of the list of products subject to additional monitoring list, hereafter referred to as the AM list. If considered appropriate, the Commission shall, on the basis of that report, and after consultation with the Member States (MSs) and other appropriate stakeholders, present a proposal in order to adjust the provisions relating to the AM list referred to in REG 23.

This obligation was introduced following the views expressed by some Member States during the revision of the legislation in 2012, which extended the scope of the mandatory application of additional monitoring to products that have a conditional marketing authorisation or a MA for exceptional circumstances, or have additional measures imposed such as post-authorisation safety studies.

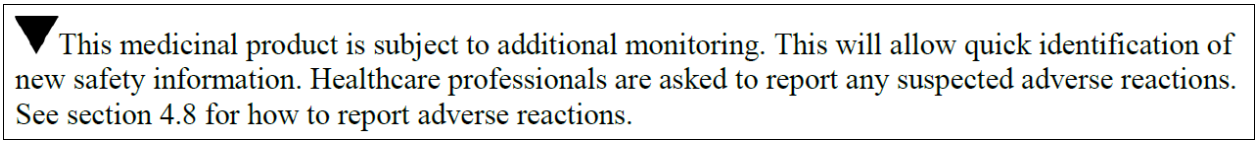
2. Background

The concept of additional monitoring introduced by the 2010 pharmacovigilance legislation, which came into effect in July 2012, originates primarily from the aim of enhancing adverse drug reaction (ADR) reporting for certain types of medicinal products for which the clinical evidence base is less well developed. The main goals are to collect additional information as early as possible to further inform on the safe and effective use of these products and ultimately inform on their benefit-risk profile when used in everyday medical practice [2].

REG Article 23 provides that the Agency shall, in collaboration with the Member States, set up, maintain and make public a list of medicinal products that are subject to additional monitoring. REG Article 23(4) and Article 11 of Directive 2001/83/EC (DIR) [4] provide that these products shall include the statement 'This medicinal product is subject to additional monitoring' preceded by black symbol and followed by an appropriate standardised explanatory statement. The Commission Implementing Regulation (EU) No 198/2013 [3] identified that the black symbol should be an inverted equilateral black triangle. The explanatory statements in the summary of product characteristics (SmPC) and package leaflet (PIL) which should encourage healthcare professionals and patients to report all suspected adverse reactions.

The identifying black triangle symbol and statement are shown in Figure 1.

Figure 1.



Scope of additional monitoring

The following medicinal products fall under the mandatory scope of the AM list (REG 23(1)):

- medicinal products authorised in the EU that contain a *new active substance* which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- any *biological medicinal product* not covered by the previous category and authorised after 1 January 2011;
- *products for which a PASS was requested* at the time of marketing authorisation or following the grant of marketing authorisation;
- products which were granted a *conditional marketing authorisation*;
- products authorised under *exceptional circumstances*;
- products authorised with *obligations for stricter recording/monitoring of suspected ADRs*.

The additional monitoring status can be assigned to a medicinal product at the time of granting a marketing authorisation or at later stages of the product life cycle for a medicinal product for which a particular new safety concern has been identified.

As set out in REG Article 23(1a) it is also possible to include medicinal products subject to other conditions falling under the so-called additional monitoring "optional scope". This can be done at the request of the EC or a national competent authority, as appropriate, following consultation with the Pharmacovigilance Risk Assessment Committee (PRAC).

As defined in Article 107c(5) of Directive 2001/83/EC (DIR)[4], products containing a new active substance or a new biological shall be removed from the AM list 5 years after the Union reference date. Other products shall be removed once all the conditions for the inclusion in the additional monitoring list have been fulfilled.

The up-to-date list of medicines under additional monitoring is available on EMA's website (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000366.jsp&mid=WC0b01ac058067c852) and is also published by the national medicines regulatory authorities in the EU Member States. The list is reviewed every month by the PRAC.

Existing evidence

Several investigations have already been made of the impact of additional monitoring at national level. One of them is the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action project, including:

- Work Package 6 on *Risk Communications* included a survey of patients and consumers which asked about various areas of risk communication including the black triangle symbol [5]. Responses were received from eleven patient/consumer organisations across the EU. Results showed that the awareness of the additional monitoring scheme was very limited, and that more work was needed to enhance recognition and understanding of the symbol in these groups.
- Work Package 4 on *ADR collection* undertook a survey addressed to Member States in order to ascertain (among other things) how they manage ADR reports associated with medicinal products on the AM list compared to those which are not on the list [6]. Almost 60% (15/26) of the MSs indicated that their databases do not identify ADR reports for products under AM in an automated manner (e.g. through database flag combined with reference data/drug dictionary level) but do so manually instead (11/26). Only a few MSs implemented technical solutions for automatically tracking ADRs of products subject to additional monitoring.

In 2016, the European Organisation for Rare Diseases (EURORDIS) conducted a survey on what the new pharmacovigilance system meant for patients in real life [7]. A few questions were related to ADR reporting and awareness of AM and black triangle. These are discussed in chapter 5 of this report.

The Irish NCA (the Healthcare Products Regulatory Agency, HPRA) has carried out a project exploring awareness, attitudes and practice behaviours of healthcare professionals in relation to adverse reaction reporting, which includes a number of questions relevant to additional monitoring. It is anticipated that the results from the project will be published as a paper in 2018.

What this report adds

A thorough analysis of AM has now been performed by the EMA and the MSs in line with REG Article 23(4a). The analysis is presented in this report, composed of 3 main parts summarising the 3 main work streams:

1. A survey to understand MSs' experience with AM.
2. The results of the Agency's experience with the use of the AM list and a study on whether the inclusion of products on the AM list had an effect on reporting of their ADRs.
3. A survey to estimate patient and health care professional (HCP) awareness of the black triangle and the AM concept.

3. Survey to Member States on their experience with AM (MS responses to the NUI)

During its meeting in May 2017, the PRAC agreed to survey the MSs on their experience with AM. The following questions prepared by the EC and the Human Pharmaceutical Committee were circulated to the EU Regulatory Network as a request for Non Urgent Information (NUI) on the 11th May 2017:

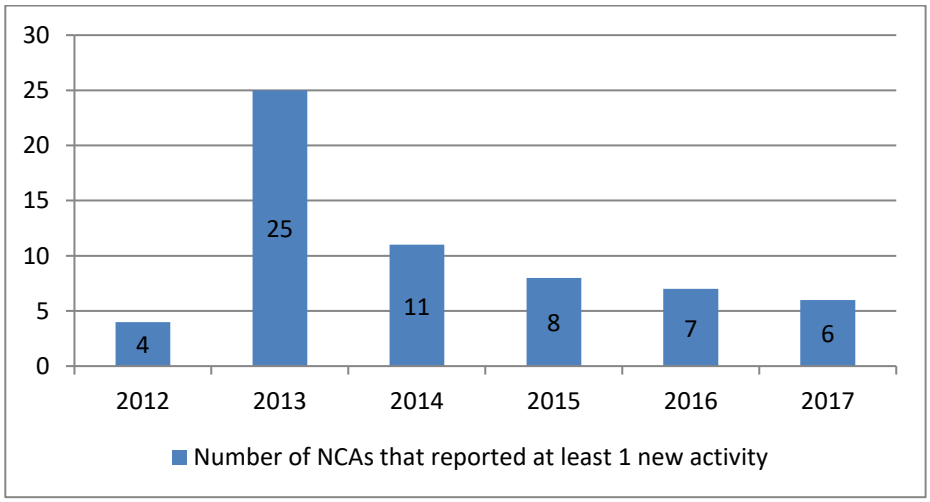
1. What initiatives have been done in your MS to inform HCPs and patients about additional monitoring/black triangle (awareness sessions, information on NCA website, etc.)? Please list these activities per year (2012 – 2016).
2. Are you aware of any data to estimate patients and HCPs awareness of the black triangle symbol and additional monitoring? If yes, please specify the date of any study/survey and briefly summarise the results.
3. What impact has additional monitoring had on the workload in your NCA?
4. Please provide any other comments you have.

Responses were received from 26 national competent authorities (NCAs) out of 30 across 25 MSs (2 NCAs based in Germany responded to the survey) and are presented in the sub-sections below.

3.1. Initiatives in MS to inform HCPs and patients about additional monitoring/black triangle

All NCA respondents said that they had undertaken at least one activity to promote the additional monitoring concept (26/26). In most NCAs the initiatives started in 2013 at the time when the additional monitoring legislation came into effect, while 4 NCAs mentioned educational activities in 2012, including the UK where a black triangle scheme was already in place. The number of initiatives peaked in 2013 and then gradually decreased. Figure 2 shows the number of new communication activities per year in all NCAs combined (routine NCA website updates were not considered as a new activity and therefore were not counted in this review).

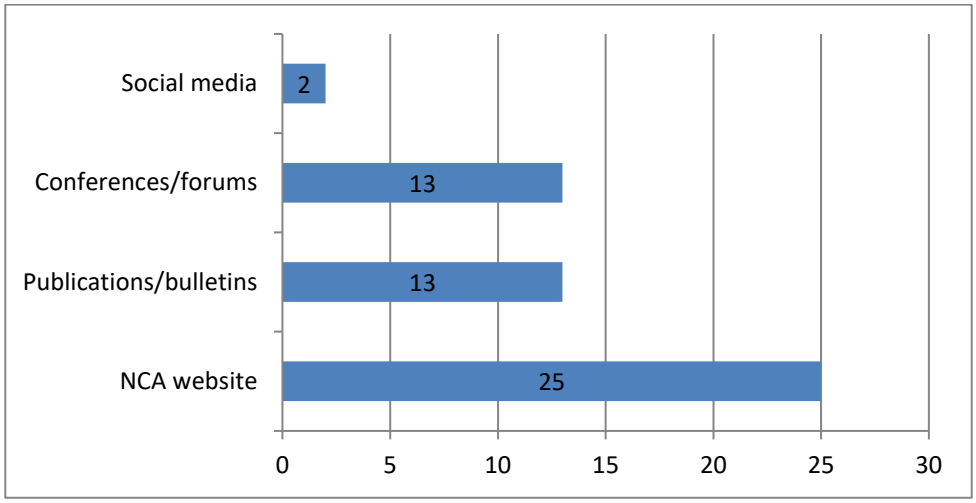
Figure 2: Number of NCAs that reported at least 1 initiative



The initiatives were classified as follows (Figure 3):

- Postings on NCA website;
- Publications/bulletins in medical journals, newsletters, educational materials, other web-sites (non–NCA websites);
- Conferences/forums: all face-to-face events, including educational events for HCPs;
- Social media: Facebook and Twitter.

Figure 3: Number of NCAs that reported the following initiatives at least once[1]



3.2. Data to estimate patient and HCP awareness of additional monitoring

Twenty-four NCAs out of 26 were not aware of any data to estimate patient/HCP awareness of the black triangle. Ireland has been carrying out a project exploring awareness and attitudes of HCPs in relation to ADR reporting, which includes a number of questions relevant to AM (publication expected in Q1/Q2 2018). Spain referred to SCOPE WP 6.

3.3. AM impact on the NCAs' workload

Twenty out of 25 NCAs responded that they experienced an increase in workload (3 NCAs mentioned low workload, 4 mentioned 0.5 day per month, 1 FTE, 0.1 FTE and 150 hours per year workload respectively). Twelve of these NCAs specified the main reasons for the increase including signal detection (4), ADR management (2), increase in ADR reporting (3), administrative tasks such as website updates and dealing with queries (7), and regulatory tasks (variations, educational material) (4).

3.4. Other comments from NCAs

Twenty two NCAs did not provide any additional comments. One NCA responded that according to their experience, there are indications that some patients may refrain from using products under AM. One NCA reported that they had noted awareness among HCPs about the black triangle/AM and that they specifically report ADR for medicinal product subject to AM. Two NCAs expressed reservations about the usefulness of the scheme, especially for products with an imposed PASS.

[1] In Figure 2 each type of activity was counted only once for each NCA, e.g. if a NCA had 3 publications and organised 2 conferences, it was counted 1 for 'publications' and 1 for 'conferences'.

During PRAC consultation concerns were raised regarding an imposed PASS being a mandatory trigger for inclusion in the AM list and the consequences for the understanding of the concept by patients. Specifically:

- PRAC would normally ask for additional pharmacovigilance activities (such as a PASS) if routine activities such as spontaneous reporting do not sufficiently address the safety issue. An imposed PASS triggers the inclusion of the product in the AM list and AM status is supposed to stimulate spontaneous reporting. Therefore, for a product with an imposed PASS a decision has been made that an additional type of data is needed, rather than a need to increase spontaneous reports.
- PASS as a mandatory trigger for AM status, in combination with product specific application of the AM status, often leads to disparity with some products having a black triangle and some not. For example this can happen when new generics are authorised after a referral where the referral resulted in imposition of a PASS for the products included. This is confusing for patients and HCPs. NCAs have experienced that patients may question this lack of consistency, such that among same-substance products some are perceived as 'safer' because they don't have the black triangle. The PRAC considered that such inconsistency can undermine confidence in the system in general and in AM more specifically.
- It is not only PASSs imposed as an outcome of a referral that are causing issues in this context. PASS imposed for an individual product generates similar confusion as generics of the product will not have AM status, leading to the same disparity.

AM status at a substance level would prevent situations when several products containing the same active substance have different AM status. However, if substance level AM status were considered to lead to other challenges, then many of the difficulties could be resolved simply by removing the mandatory AM status of products with an imposed study.

3.5 Conclusions

- Most activities to promote the additional monitoring concept were started by MSs in 2013, at the time the additional monitoring legislation entered into force and the AM list was first published, mostly through publications on their websites.
- The majority of NCAs experienced an increase in workload, mainly because of administrative and regulatory tasks; 3 NCAs mentioned a "small" workload increase, 4 mentioned 0.5 day per month, 1 FTE, 0.1 FTE and 150 hours per year respectively.
- Imposed PASS as a mandatory trigger for inclusion in the AM list resulting in inconsistent application of AM status for interchangeable products was highlighted as the key issue as this leads to misunderstanding among patients and HCPs about the relative safety of products and about the purpose and meaning of AM. Many of the difficulties could be resolved simply by removing the mandatory AM status of products with an imposed study.

4. Results of EMA's experience with the AM list

This section of the report describes the European Medicines Agency's experience with the AM list from its creation in 2013 until December 2016, and to investigate whether the inclusion of products had an effect on reporting of ADRs.

The objectives of this analysis were to:

> 4.1. Describe the numbers of products that have been subject to additional monitoring and included on the list over time: the products have been classified according to their marketing authorisation type and the reason for adding them to or removing them from the list.
>
> 4.2. Describe whether reporting of ADRs for products increases after their addition to the AM list as compared to the period before addition.
>
> 4.3. Describe the numbers and outcomes of safety signals validated and confirmed during the period from April 2013 to December 2016 for products with and without the AM status. This will include the numbers of signals for which communication to healthcare professionals via a Direct Healthcare Professional Communication (DHPC) has been issued during the period from April 2013 to December 2016 between AM products and non-AM products.

The analysis focuses on products that have been subject to additional monitoring under the mandatory scope, as no product was included on the AM list under the optional scope during the analysis period.

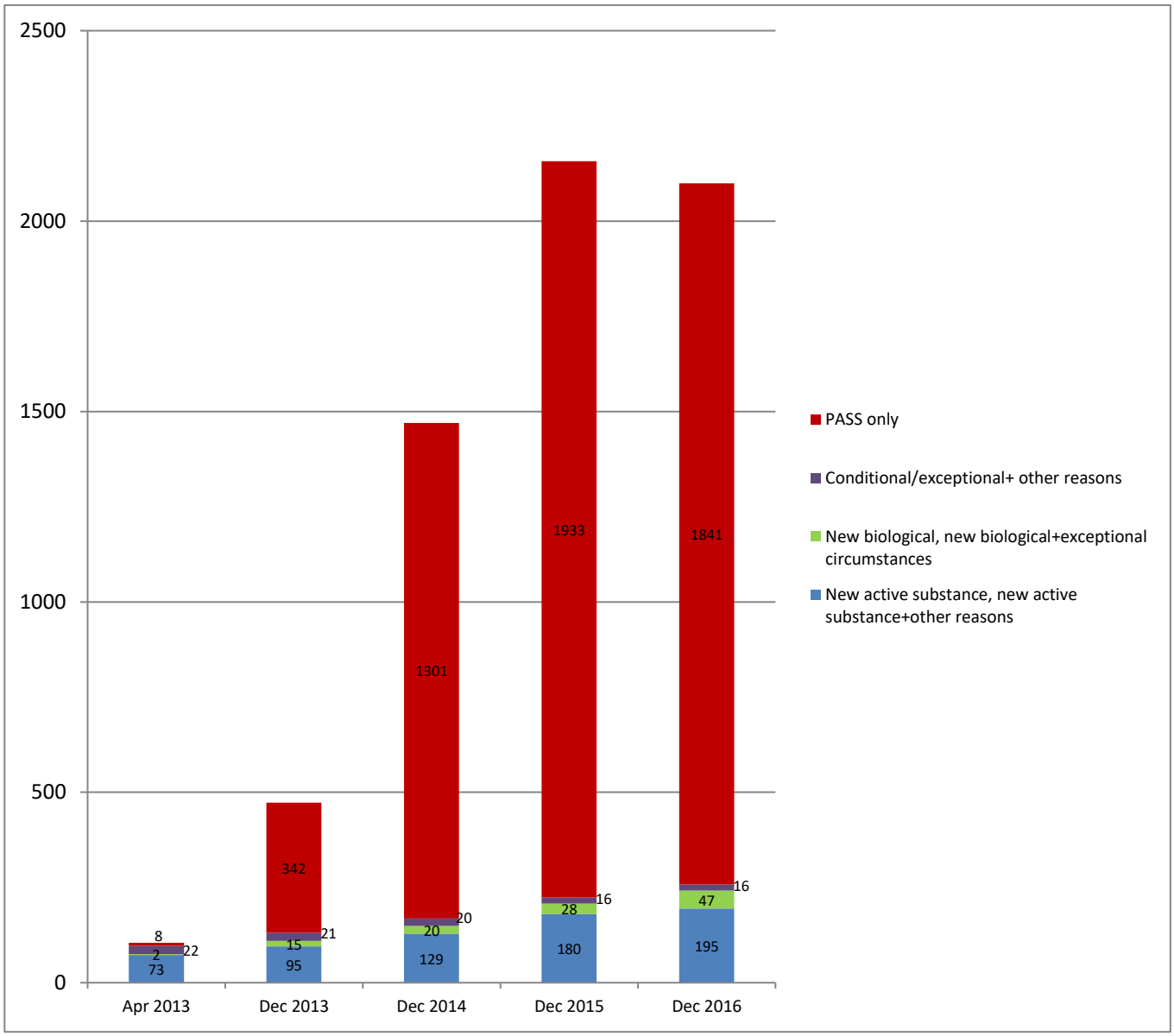
4.1. Numbers of products that have been subject to additional monitoring and included on the list over time (results for objective 3.1)

The first version of the AM list was published in April 2013 and contained 105 products (101 CAPs and 4 non-CAPs). In December 2016, the list contained 301 products and 13 annexes (2099 products in total). Each of these annexes have been created to list all the products containing the same active substance subject to a PASS imposed during a referral procedure and which are therefore subject to AM (REG 23(1)). As the number of products concerned can be rather high, it was agreed to create these separate annexes for presentation purposes.

Inclusion of product on the AM list (mandatory scope only):

On the December 2016 list, 88% of products on the AM list were included due to an imposed PASS, 7% due to a new active substance alone and 9% due to a new active substance in combination with other criteria, and 2% due to "new biological" status. In contrast, the first version of the AM list dated April 2013 included 21% of products due to an imposed PASS, and 70% due to a new active substance, alone in 48% and in combination with other criteria for the remainder.

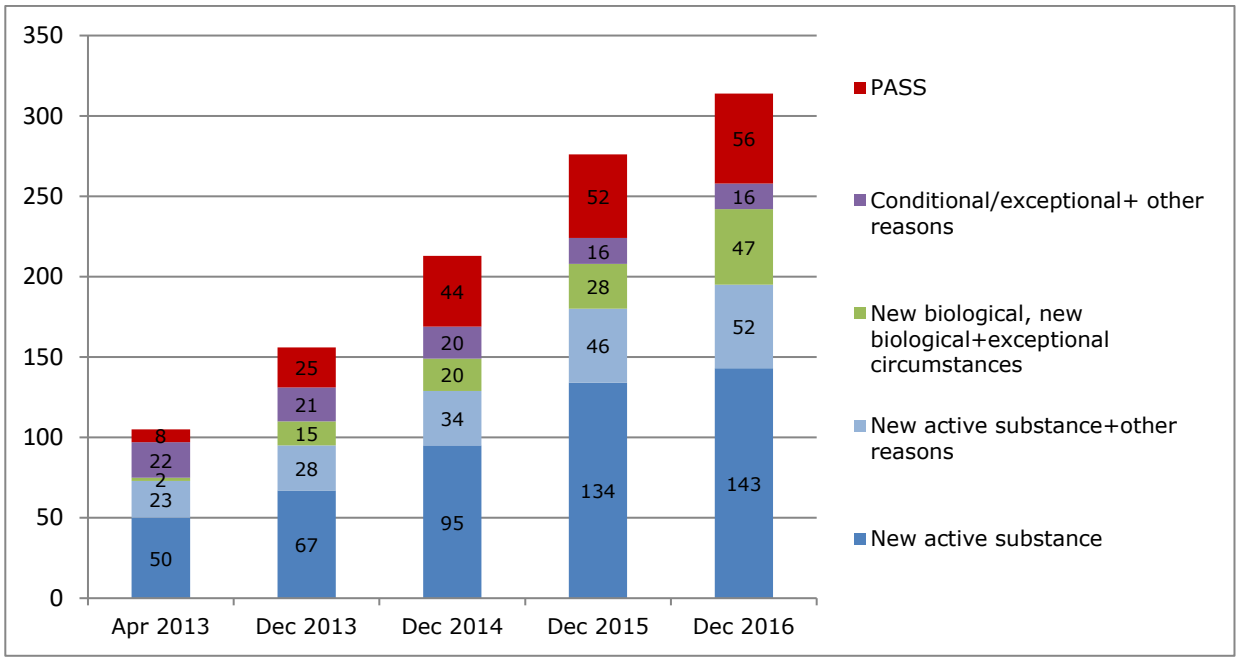
Figure 4: Number of products in the additional monitoring list over time



The large increase in the number of products in December 2013 and after occurred after the first two PASSs were imposed during referral procedures in 2013. Referral procedures are usually based on the active substance level (for which many products might be available on the market) and hence all products containing that active substance authorised at the time of the start of the referral will qualify for AM.

If 1 annex is counted as 1 product (i.e. 1 row) on the main list, the AM list looks different: on the December 2016 version, 46% of products were included on the AM list due to a new active substance alone or 63% including those in combination with other criteria, and only 18% due to an imposed PASS and 15% due to "new biological" status (Figure 5).

Figure 5: Additional monitoring list over time (by reason for inclusion, one annex counted as 1 product)



The majority of products included on the cumulative AM list have been non-centrally authorised (non-CAP): 1826 out of 2099 as of December 2016 (87%). This is mainly because of high number of nationally authorised products (NAP) in the annexes. In the first list published in April 2013, 101 out of 105 (96%) were centrally authorised (CAPs).

Figure 6: Additional monitoring list over time (number of products in each annex is provided separately, in table 1 below).

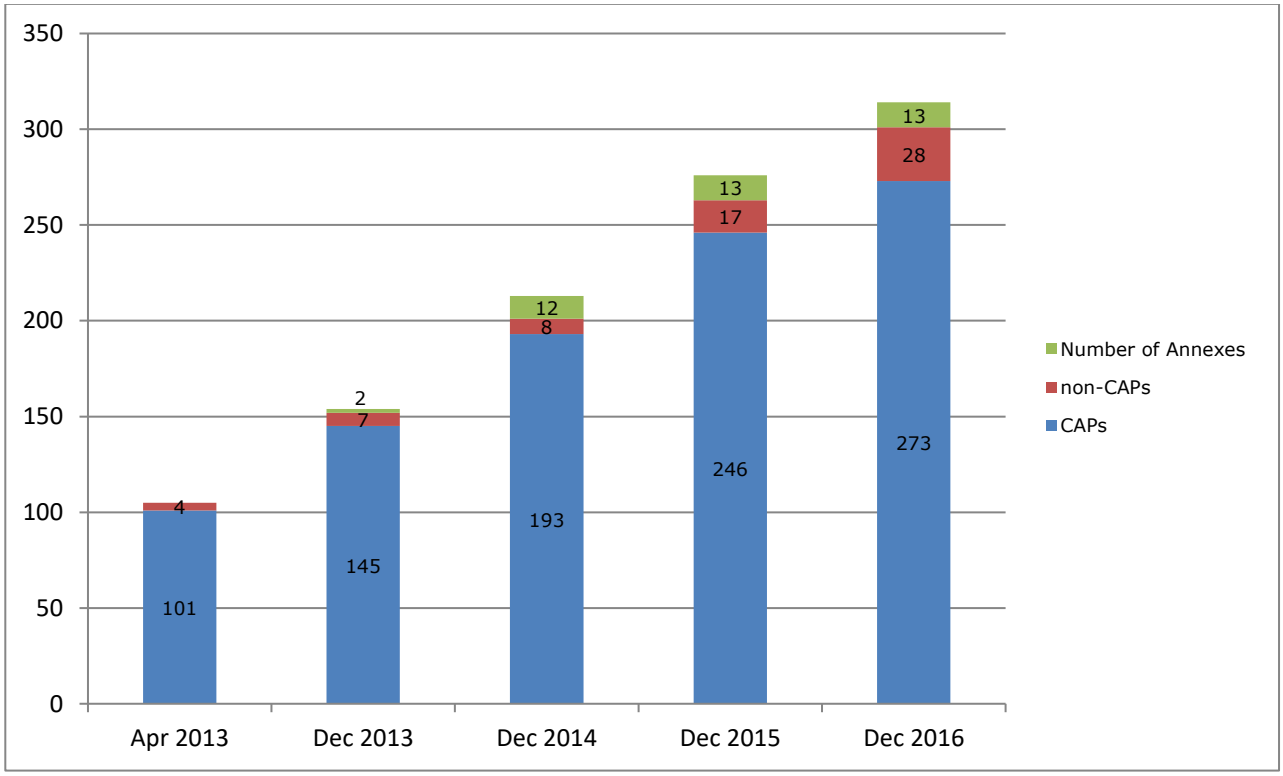


Table 1: Number of annexes and number of products in annexes over time

	2013	2014	2015	2016
Number of annexes created	2	10	1	0
Number of products in annexes (cumulative)	319	1269	1893	1798

The first 2 annexes were created in 2013 and contained 319 products. As of December 2016 there were 13 annexes containing 1798 products, see Table 1 for more details. The list of products in annexes as per December 2016 version is provided in Appendix 8.1.

Removal of products from the AM list:

Products containing a new active substance or a new biological are removed from the AM list 5 years after the Union reference date. Other products are removed once all the conditions have been fulfilled (REG Article 23(3)).

The number of removals in 2016 increased more than 2-fold, mostly due to completed PASSs (Annex II – trimetazidine containing products was removed as the imposed PASS was completed) and the elapse of five years for various new active substances (Figure 7).

Figure 7: Products removed from the AM list over time.

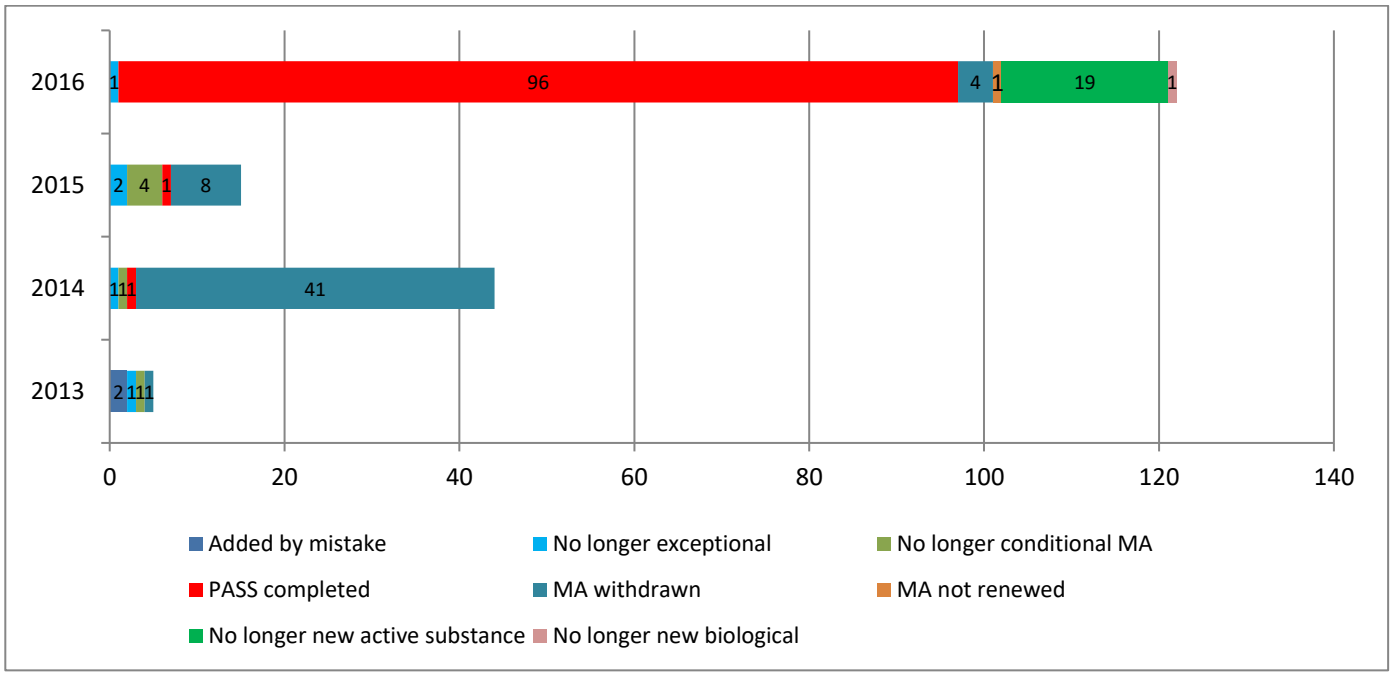
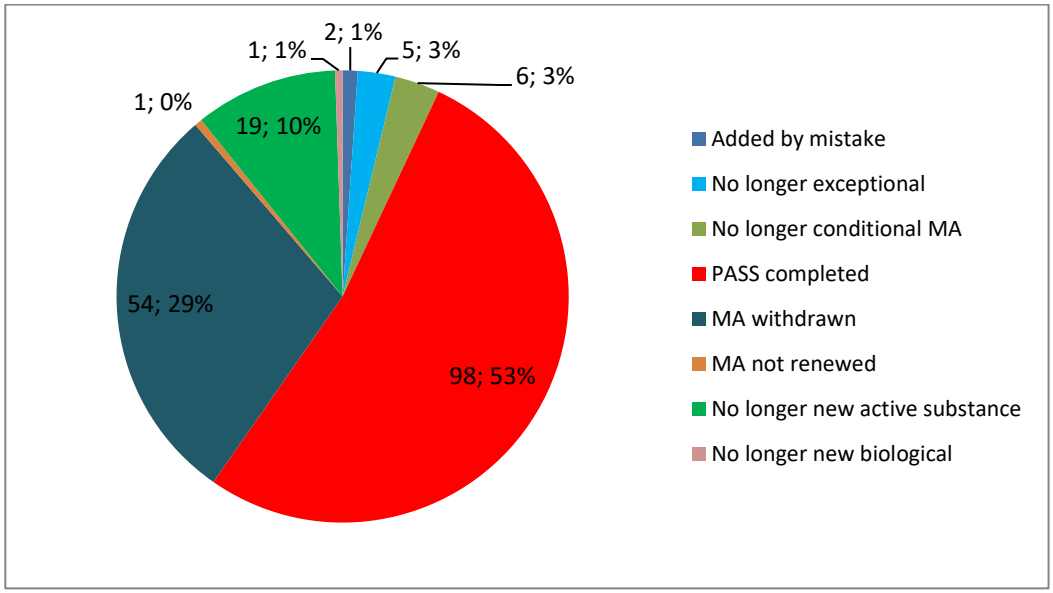


Figure 8: Cumulative reason for removal from the list (April 2013 – December 2016).



Conclusions:

- The number of products subject to AM increased 20-fold between April 2013 and December 2016.
- The majority of products have been included on the AM list due to PASSs being imposed as a term of the marketing authorisations (88% of products in December 2016 version).
- Counting at substance level 46% of products on the AM list were included due to a new active substance alone or 63% also counting those in combination with other criteria
- The majority of products (87%) on the list are non-CAPs due to the high number of nationally authorised products subject to imposed PASS.

4.2 Reporting of ADRs for AM products

The concept of AM originates primarily from the aim of enhancing ADR reporting; therefore one of the objectives of EMA's analysis is to investigate whether ADR reporting to the EudraVigilance database (EV) changed at the time of the inclusion of the products in the AM list. To examine such changes it was necessary to identify products that had reporting data available both before and after their inclusion in the list and that met additional eligibility criteria for analysis.

4.2.1. Selection criteria of the AM products and data collection

We used the December 2015 list to identify medicinal products for analysis as this allows at least 12 months follow-up for ADR reporting whilst under additional monitoring. We identified 82 products authorised for at least 12 months before their inclusion in the AM list, corresponding to 79 active substances. Considering the total period of 24 months included in the analysis, we restricted the analysis to products for which at least 10 EEA reports were received per month, this led to a set of 12 substances. We further excluded one substance because of the large number of products available on the market, only one of which was subject to additional monitoring and had less than 10 reports per month, leading to a final set of 11 substances.

For one substance (denosumab) we identified two products with different indications (Xgeva and Prolia) which differ in their AM status (Xgeva subject to AM and Prolia not subject to AM). The analysis of these products was performed at product level with the non-AM product used as control.

The numbers of EEA case reports for each of the selected products (at the level of active substance) were extracted from the EV post-marketing module for the period from 12 months before to 12 months after its addition to the AM list. Case numbers excluded backlog cases, PSUR ICSRs and duplicate masters.

To standardize the reported case numbers for analysis, estimates of the numbers of patients treated were obtained from the PSURs for CAPs (data for Europe or EEA) by dividing the person-years reported by the number of years covered by the PSUR. This was considered reasonable as all the treatments analysed are for long-term use. The stepwise functions obtained were then smoothed over time using a piecewise linear form that matched the stepped functions exactly at the mid-points of intervals and took the mean value at each step. Secondly, where PSUR data were not available, estimates of exposure data (mostly as DDDs) were obtained from publicly available nationwide drug consumption databases (DK, SE, NO, UK, NL, FR)[2].

We used Poisson regression with the above exposure data as an offset, and increased the standard error to account for over-dispersion. The model was seasonally adjusted using Fourier terms with two pairs of sine/cosine functions. A step change in reporting at the time of addition to AM list was selected as an *a priori* impact model. Additionally, we also tested for slope change. We undertook further time series analysis using Joinpoint Regression Program 4.5.0.1 as sensitivity analysis, using the Grid search method and Permutation testing for model selection.

4.2.2. Data analysis and results

After applying the above mentioned criteria, 11 products were eligible for the analysis 5 of which were included in the AM list because of new active substance status and 6 because of an imposed PASS. The list of selected products is presented separately in Table 2 and Table 3 below. As the imposition of a PASS frequently follows a referral to the PRAC with consequent media attention, inclusion in the AM list of products subject to PASS may result in confounded analyses of trend due to other regulatory actions

[2] These 6 countries represent approximately 30% of EEA population.

and possibly media attention which can influence reporting, while new active substances should be free of such confounding unless there are significant regulatory changes during this time frame.

Table 2: Products selected for further analysis (new substances)

Active substance	Product name	Reason for inclusion in the AM list	Product authorisation date	Date of inclusion in the AM list	Results
Boceprevir	Victrelis	New active substance	18/07/2011	April 2013	**Increase in slope** RR 1.10 (95% CI 1.03-1.18)
Telaprevir[3]	Incivo[4]	New active substance	19/09/2011	April 2013	No significant change detected in step or slope
Vemurafenib	Zelboraf	New active substance	17/02/2012	April 2013	No significant change detected in step or slope
Fingolimod	Gilenya	New active substance, PASS	17/03/2011	April 2013	No significant change detected in step or slope
Denosumab	Xgeva	New biological	13/07/2011	April 2013	**Increase in slope** RR 1.13 (1.04-1.22)
	Prolia	Not in the AM list (control for Xgeva)	26/05/2010	n/a	No significant change detected in step or slope

Table 3: Products selected for further analysis (included in AM list due to PASS)

Active substance	Product name	Reason for inclusion in the AM list	Product authorisation date	Date of inclusion in the AM list	Results
Imatinib[5]	Glivec	PASS	07/11/2001	September 2014	No significant change detected in step or slope
Lenalidomide	Revlimid	PASS	14/06/2007	June 2014	No significant change detected in step or slope
Natalizumab	Tysabri	PASS	27/06/2006	April 2013	**Slope decrease RR 0.95 (0.90-0.99)**
Rivaroxaban[6]	Xarelto	PASS	30/09/2008	July 2013	Step increase* RR 1.65 (1.12-2.43) **Slope decrease RR 0.92 (0.88-0.96)**
Valproic acid[7]	Various	PASS	n/a	January 2015	No significant change detected in step or slope
Varenicline	Champix	PASS	26/09/2006	April 2013	**Slope decrease RR 0.84 (0.79-0.90)**

*step increase neither corroborated when analysing with extrapolated exposure data to allow for 12 months follow-up; nor by Joinpoint model.

Among the five new substances, we identified a significant increase in the slope of the trend line for ADR reporting after the addition to AM list for two products – boceprevir and denosumab-Xgeva; no significant change in step or slope was identified for the other three products (telaprevir, vemurafenib and fingolimod). For boceprevir the increase was in the order of about 10% per time point; and for denosumab-Xgeva, the increase was about 13% per time point. This is illustrated in figures 9A and 9C

[3] Only 7 months data available before addition to AM list (missing exposure data).
[4] Drug withdrawn in October 2016.
[5] 4 generics authorized in 2013, they all are non-AM. Analysis using exposure database data.
[6] Only 8 months follow-up data available (missing exposure data).
[7] Analysis using exposure database data.

below. A comparison was possible for denosumab due to another product with the same substance available (Prolia) which is not subject to AM, and we did not detect significant changes in reporting of ADRs for Prolia, as seen in figure 9B.

Among the six products included in the AM list due to PASS, for three products (imatinib, lenalidomide and valproate – seen in figure 9D), we did not identify a significant change in reporting of ADRs at the time of addition to the AM list. For three products we identified a slope decrease after addition to the list: natalizumab - of the order of 5% per time point, rivaroxaban – 8% per time point, and varenicline - in the order of 16% per time point. This is illustrated for natalizumab in figure 9E. Additionally, a step increase was identified for rivaroxaban, but this was not corroborated when analysing with 12 months follow-up, nor by Joinpoint analysis; this was followed by a significant slope decrease (figure 9F).

Additionally, we repeated the analyses using the Joinpoint Trend Analysis Software. The results were broadly comparable, with the exception of natalizumab for which Joinpoint did not identify any changes, and rivaroxaban where only a slope change was identified in Joinpoint.

4.2.3. Limitations

The final data set contains only 11 eligible products deemed suitable for analysis, potentially limiting the generalisability of the results. The expected response to regulatory and policy decisions such as AM may vary. A step change, i.e. an immediate sustained rise in reporting, might be anticipated or alternatively a slope change (slower or faster increase in reporting over time) may be more likely as reporters gradually became aware of the change in AM status Variation in the timing of any slope change is also possible. Effects may also be temporary rather than sustained, and a longer observation period is ideally needed in future analyses to ascertain this, such as assessing the impact when products are removed from the AM list. Additionally, we used the date of addition to AM list as the expected time of changes in ADR reporting. There may be a delay in the availability of the product information marked with the black triangle and thus an effect at this later stage; this was not investigated. The response may also differ according to the reason for inclusion of the product on the list, and due to the type of therapeutic product. We only investigated an overall EEA change in reporting, and cannot exclude changes in individual countries.

Some products undergo changes in the authorised indications (extensions, restrictions) that may change the nature of the exposed population (e.g. including only lower-risk patients at first and higher-risk patients later, leading to higher occurrence and reporting of ADRs later). Similarly, regulatory activity such as DHPCs or media publicity associated with safety concerns may affect reporting activity (indeed, for four substances, there was a DHPC during the period; additionally, there was a DHPC for another substance just before the study period). In particular, for products with AM introduced in response to safety concerns which received media attention, there is a possibility of stimulation of ADR reporting due to media attention rather than the inclusion in the AM list itself.

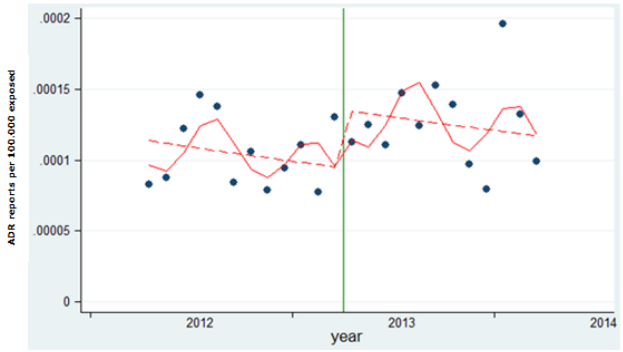
Time-dependent confounders could not be accounted for in our analysis, due to absence of data, and therefore the apparent increases seen for some products may be due to factors other than inclusion in the AM list. Further, our estimates of exposure are subject to assumptions in their calculations and therefore subject to measurement error and this could affect the results by e.g. overestimating the number of patients treated, especially if this was unequal in the comparison periods.

Low numbers of cases reported per month, often counted only in the order of tens and usually being lower at the beginning of the observation period, may influence power for our analysis. Our total observation period of 24 time points (months) was also limited, and this coupled with unequal variability in the number of reports restricted the power to detect a difference in reporting, and the utility of seasonality adjustment; the results need to be interpreted in this light.

Figure 9: Examples of reporting of ADRs from the EEA before and after addition to AM list.

New products:

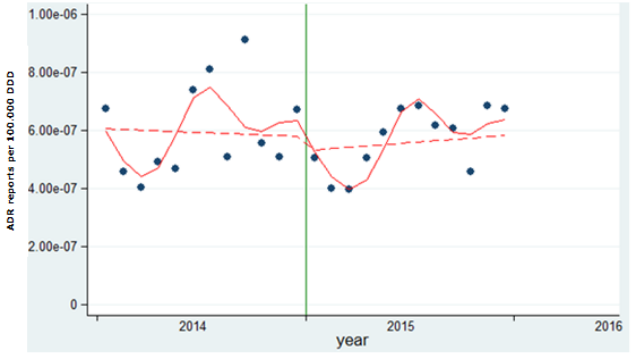
A. Xgeva (denosumab) reporting of post-marketing ADRs from the EEA. Green line – addition to AM list in April 2013. Red line: predicted reporting from seasonality-adjusted model. Dashed line – de-seasonalised trend.



B. Prolia (denosumab product not subject to AM) reporting of post-marketing ADRs from the EEA. Green line – addition of Xgeva to AM list in April 2013. Red line: predicted reporting from seasonality-adjusted model. Dashed line – de-seasonalised trend. The postulated step change was not statistically significant (RR 1.43, 95% CI 0.62-3.27), nor was there evidence of slope change, p=0.903. Note the difference in y-axis scale compared to Xgeva in figure **A**.

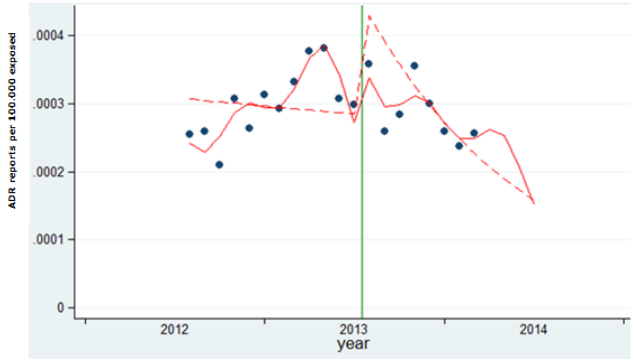
C. Victrelis (boceprevir) reporting of post-marketing ADRs from the EEA. Green line – addition to AM list in April 2013. Red line: predicted reporting from seasonality-adjusted model. Dashed line – de-seasonalised trend.

Products subject to PASS:



D. Valproate reporting of post-marketing ADRs from the EEA. Green line – addition to AM list in Jan 2015. Red line: predicted reporting from seasonality-adjusted model. Dashed line – de-seasonalised trend.

E. Tysabri (natalizumab) reporting of post-marketing ADRs from the EEA. Green line – addition to AM list in April 2013. Red line: predicted reporting from seasonality-adjusted model. Dashed line – de-seasonalised trend.



F. Xarelto (rivaroxaban) reporting of post-marketing ADRs from the EEA. Green line – addition to AM list in July 2013. Red line: predicted reporting from seasonality-adjusted model. Dashed line – de-seasonalised trend. NB Only 8 months follow-up data available (missing exposure data).

4.2.4. Conclusions

The ways in which ADR reporting changed after addition to the AM list were heterogeneous. Of the five products with new active substances included in the analysis, two demonstrated a statistically significant increase in the slope of ADR reporting after addition to the AM list, while three did not show significant changes. Among the six products included due to a PASS, we did not identify any changes for three products, while three products showed a significant slope decrease.

In summary, we found no evidence that AM increases reporting of ADRs for products subject to PASS, and some evidence that reporting may be increased for some new products. Our analysis was restricted to a small subset of AM products and possibly underpowered, so the results need to be interpreted with caution. Reporting may also have increased due to factors other than addition to the AM list.

If the analyses had shown marked and consistent increases in ADR reporting then it would be reasonable to conclude that AM 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 Safety signals for products with and without the AM status (results for objective 3.3)

The third objective of the analysis was to look at whether inclusion of a product on the AM list affected the detection and management of safety signals for that product, i.e. whether it influenced the number of signal reports or their outcome.

4.3.1. Background on signal management

A safety signal is defined as information on a new or known adverse event that may be caused by a medicine and requires further investigation. The EMA, together with the medicines regulatory authorities in the MS and the marketing authorisation holders (MAH) are responsible for detecting and managing safety signals.

EMA takes the lead on EudraVigilance data monitoring, signal detection and signal validation for substances contained in at least one CAP authorised in accordance with Regulation (EC) 726/2004. For non-CAPs, a lead MS monitors data in EudraVigilance and validates and confirms signals on behalf of the other MSs. This applies to active substances contained in medicinal products authorised nationally in more than one MS. For substances with no lead Member State, all Member States have joint responsibility for monitoring those medicines they have authorised. Nevertheless, the entire network collaborates in signal detection, regardless of the product authorisation process.

The PRAC is responsible for assessing all aspects of the risk management of medicines for human use including the **prioritisation and assessment of signals** in order to issue recommendations on the safe and effective use of both nationally and centrally authorised medicines.

At the end of the assessment, the PRAC may recommend:

- The need for regulatory actions including the variation, suspension or revocation of the marketing authorisation of the products concerned;
- The need for additional information from the MAH in order to allow for an informed scientific conclusion or the trigger of a community procedure;
- No actions needed other than the continuation of routine pharmacovigilance activities.

More information on the signal management process can be found in Good Pharmacovigilance Practice (GVP) IX [8].

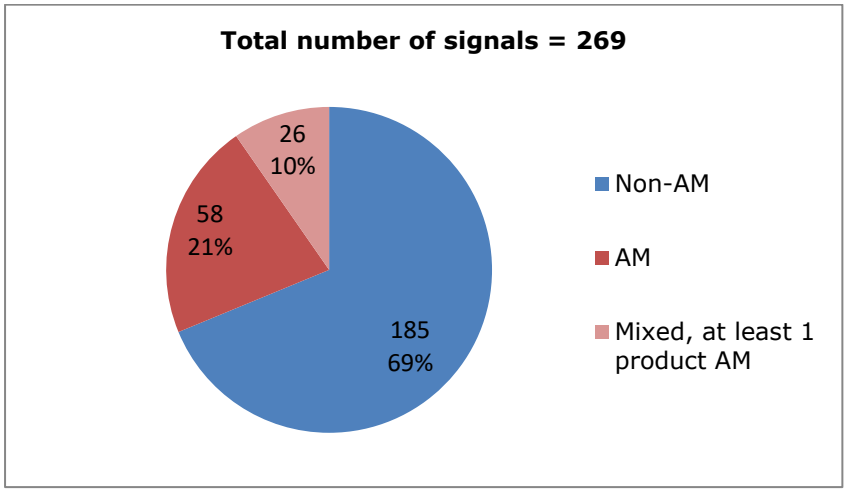
One of the main sources used by the EMA and the MSs in order to monitor medicinal products is Eudravigilance. In GVP IX it is recommended to monitor EudraVigilance data at least every 6 months. A more frequent monitoring is recommended for active substances contained in medicinal products included in the additional monitoring list unless the sole reason for inclusion on the list is the request of a post-authorisation safety study (PASS).

For products subject to AM, the frequency applied by the EMA for reviewing the statistical outputs is every 2 weeks until the end of additional monitoring. A 2-week frequency for reviewing the statistical outputs may also be applied for any other product taking into account the various safety/risk specific criteria.

4.3.2. Number of signals

From April 2013 to December 2016 inclusive, 269 signals were validated and confirmed for PRAC prioritisation and assessment. Fifty eight signals (21%) concerned only active substance(s)[8] subject to AM (hereafter referred as "AM products") while 26 (10%) of signals involved several products only some of which were under AM (shown as "mixed signals" in the figure below). The remainder (69% of all signals) concerned only active substance(s) not under AM. Figure 10 shows whether the products concerned were under AM or not at the time of the signal validation.

Figure 10: Number of signals with AM and non-AM products.



Of the 58 AM signals, 78% of the products concerned were listed as new active substances with or without other AM criteria, 19% had an imposed PASS and 3% had conditional or exceptional marketing authorisations.

4.3.3. Signal outcomes

The outcomes of the signals are presented in Figure 11 below. Signal outcomes in the figure below were classified as following:

- Ongoing – signal was ongoing at the time of data collection, no outcome available yet;
- PASS – PRAC recommended to conduct a PASS;
- Routine PhV - no actions needed other than the continuation of routine PhV activities;
- PI update – all outcomes resulting in SmPC and PI updates (included PI and RMP updates);
- Referral – PRAC recommended to trigger a community procedure;
- DHPC- one of the outcomes of the signals concerned was a DHPC.

[8] As signals are validated and confirmed at the level of the active substance, the numbers of CAP and non-CAP products represent the number of active substances and not the numbers of products. One signal could be related to more than one active substance.

Figure 11: Signal outcomes for AM/non-AM products

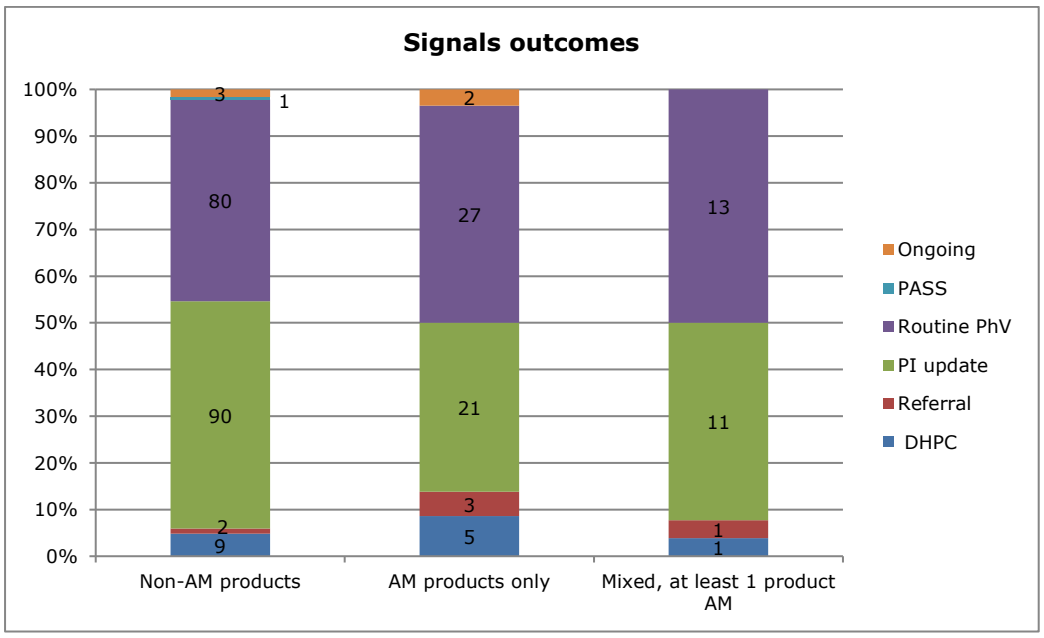


Table 4 below provides information on the number of DHPCs recommended as a part of the signals outcomes.

Table 4: Number of DHPCs recommended as a part of signal outcome

Status	Number of DHPCs	Total number of signals	%
Non-AM products	9	185	5%
AM products	5	58	9%
Mixed, but at least 1 AM)	1	26	4%
Total:	**15**	**269**	6%

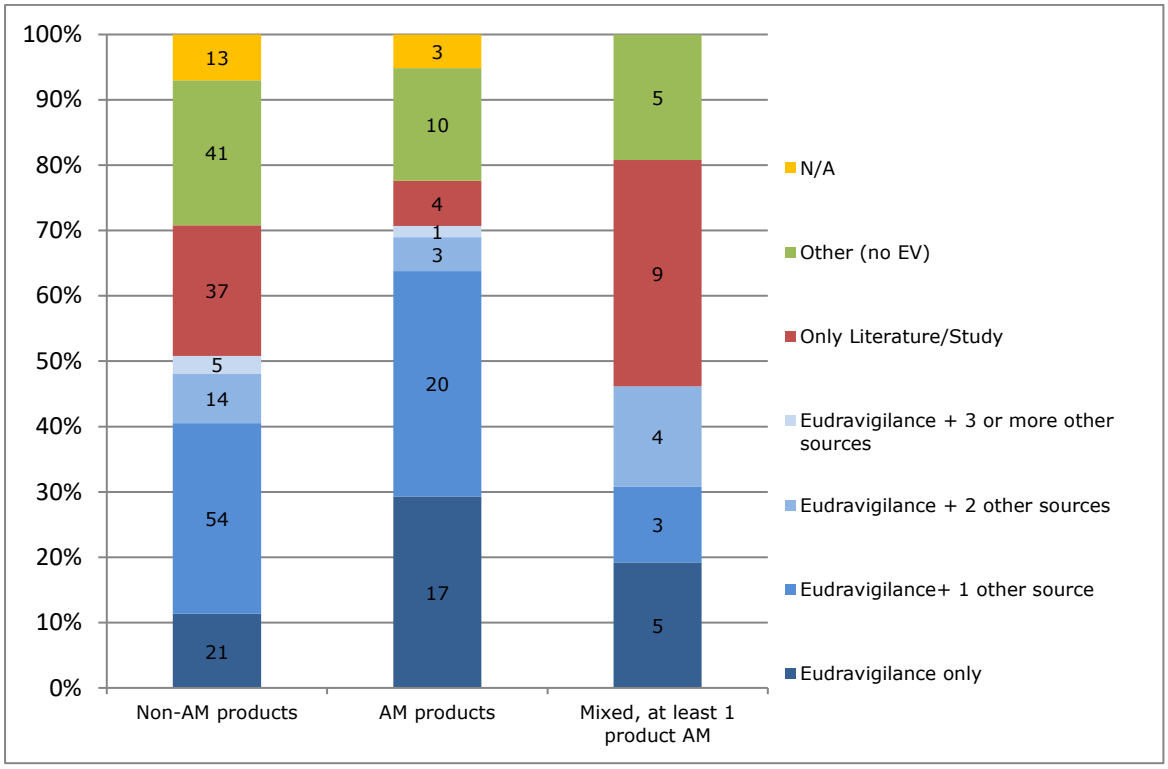
The proportion of signals resulting in important new warnings and information provided to prescribers via a DHPC is higher for AM signals.

4.3.4. Signal sources

Safety signals can be detected from a wide range of sources, such as spontaneous reports, clinical studies and scientific literature. The EudraVigilance database is an important source of information on suspected adverse reactions and signals. As described above, signals could be validated by NCAs or by the Agency. The Agency is responsible for monitoring CAPs (which constitute the majority of the AM list) and NCAs assist the Agency in monitoring EV data for CAPs as well as participate in signal work-sharing for monitoring non-CAPs.

Signal sources are presented below.

Figure 12: Data sources for signals (based on their description).



EudraVigilance was used in 51% of signals with non-AM products and in 71% of signals with AM products.[9]

4.3.5. Conclusions

- 1/5 of the signals reviewed by PRAC concern AM products, involving mostly new active substances;
- The proportion of DHPCs was slightly higher for AM than non-AM-related signals (7% versus 5%), but any differences must be evaluated with caution (as PRAC recommendations are issued depending on the seriousness of event, need for risk minimisation and communication).
- Signal outcomes were similar in AM and non-AM groups. We cannot conclude that the AM status has an impact on signal outcomes.

[9] This field was not always mandatory; therefore there are 16 signals with no sources selected.

5. Awareness of the concept of additional monitoring

The final component of the review was to look at the extent of awareness of the additional monitoring concept among healthcare professionals and patients, and to try to identify any important areas of misunderstanding.

5.1. Background information

In September 2017, the Agency conducted a survey to better understand patients' and healthcare professionals' awareness of reporting adverse drug reactions, including for medicinal products under additional monitoring. The questions on AM were included within this broader survey and neutral introduction statements on additional monitoring were made to avoid biasing the responses.

The survey collected four socio-demographic questions (country, gender, age and type of responder). Questions on actual ADR reporting and attitudes to ADR reporting (Q5-6) have been followed by questions related to additional monitoring, starting with awareness of AM (Q7), understanding of AM (Q7.1 and 8), attitude about reporting ADRs (Q9), actual reporting behaviour (Q10) and lastly whether actual reporting was affected by the black triangle/AM status (Q10.1).

The questions were drafted by EMA, pre-tested internally and agreed with PRAC Rapporteurs (topic leaders of PRAC Work Plan for 2017), and the Patient & Consumer and Healthcare Professional Working Parties. The survey was translated into all official EU languages using Translation Centre for the Bodies of the EU and the quality of the translation was checked internally by native speakers. Before publishing, the survey was tested internally by 34 responders (half of them were non-HCP). The survey was hosted on the EU survey tool and was published on the Agency's website. NCAs, HCPs and patients organisations helped to disseminate this survey. The survey was open for responses for five weeks until 9th October 2017.

A copy of the survey is provided in Appendix 8.2.

5.2. General information and demographic questions

In total 2918 responses were received covering all EEA countries (range 4 to 569), including 56 responses from non-EEA countries - India (11), Switzerland (8), Brasil (5), USA (4), Israel (4) and others (24).

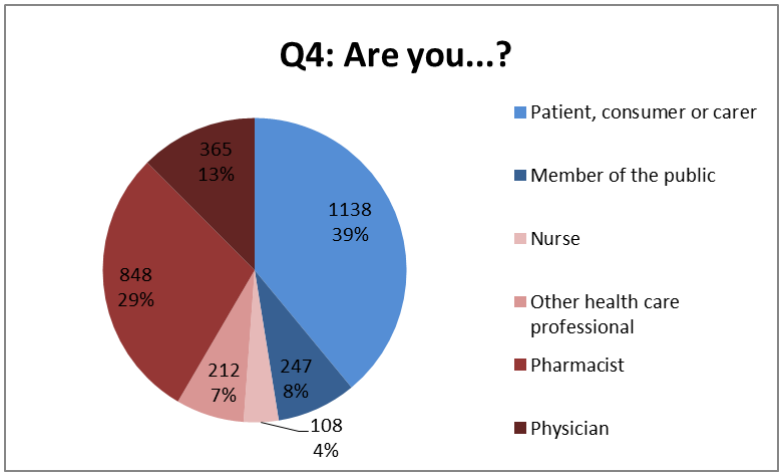
shows the number of responses received per country split by responder type (patients (includes patients, consumers or carers) and or members of the public (hereafter referred as public) versus HCPs (includes nurses, pharmacists, physicians or other HCPs)).

Table 5: Number of questionnaire responses per EEA country (highest to lowest)

Country	Responses from public/patients	Responses from HCPs	Total
Portugal	183	386	569
Germany	205	264	469
Italy	83	304	387
United Kingdom	235	44	279
Austria	112	48	160
Romania	63	43	106
Finland	54	37	91
Croatia	42	43	85
Spain	46	38	84
Netherlands	51	21	72
Belgium	51	20	71
Denmark	42	22	64
Other country	22	34	56
Greece	24	27	51
Iceland	10	34	44
Ireland	19	23	42
France	23	15	38
Bulgaria	23	11	34
Latvia	26	4	30
Estonia	4	23	27
Lithuania	2	21	23
Slovak Republic	12	11	23
Malta	4	15	19
Hungary	10	6	16
Sweden	8	8	16
Poland	7	6	13
Czech Republic	8	4	12
Slovenia	6	6	12
Liechtenstein	3	5	8
Cyprus	4	3	7
Norway	2	4	6
Luxembourg	1	3	4

Overall, 47% of respondents identified themselves as non HCPs (i.e. members of the public or patients), and 53% of respondents as various types of HCP. A significantly higher proportion of the respondents who provided this information were female (66% female and 30% males). The median age of non-HCPs was 45 years and 40 years for HCPs. The age distribution is presented in the appendix 8.2.

Figure13: Number and percentage of responses by type of respondent.



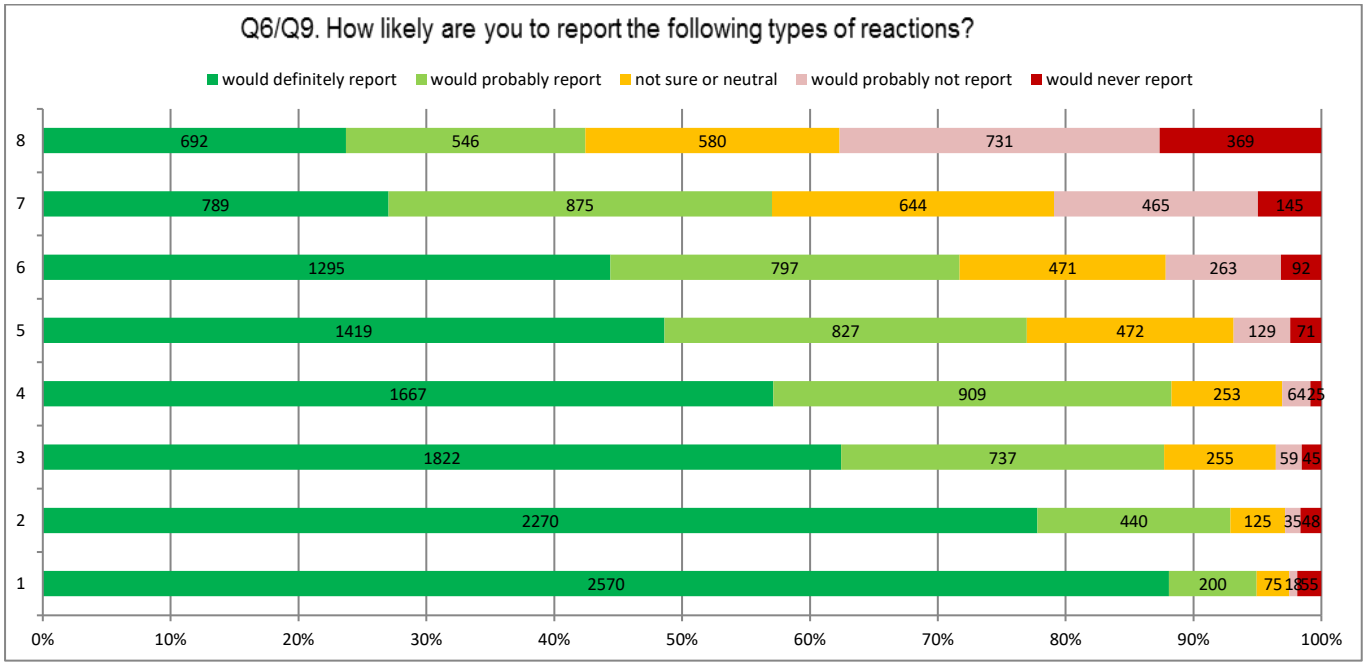
Patients and public, hereafter referred to as non-HCPs, were asked how many different medicines they had taken in the last month. The median number of medicines taken by the members of the public is 2 (mean 2.05) compared to 4 for patients (mean 5.35). More detailed results are presented in the appendix 8.2. Out of 1533 HCPs that responded to the survey, 807 (53 %) were working in primary or secondary care sectors and 726 (47 %) were working in industry, academia, pharmaceutical companies or other.

Some 85% of HCPs reported that they had observed at least one ADR, while 67% of non-HCPs (i.e. patients and members of the public) reported that they experienced at least 1 ADR (Appendix 8.2). This result for patients is in line with the EURORDIS survey, which showed that 61% of patients (not including off label use) experienced an ADR (any severity).

5.3. Adverse drug reaction-reporting attitude

Question 6 asked about the likelihood of reporting various types of ADRs in general (6 categories of ADRs were listed in a matrix table). Respondents were more likely to report serious ADRs (fatal and leading to hospitalisation) and ADRs associated with a new medicine. A total of 88% indicated that they would definitely or probably report an ADR for a medicine identified with black triangle which mirrors the answers to the question on new medicines (also 88%).

Figure 14: Attitudes towards reporting various types of ADRs, all respondents combined (where: 1 - The patient died as a result of the ADR; 2 - The ADR caused the patient to be hospitalised; 3 - The ADR followed use of a new medicine; 4 - Medicine identified by the black-triangle symbol; 5 - The ADR followed use of a biological product; 6 - The ADR followed vaccination; 7 - Any ADR; 8 - The ADR is included in the product information.)



Reporting attitudes were different ($p<0.001$) among different respondents' types. Physicians and pharmacists are less likely to report "any ADR" but more likely to report fatal and serious ADRs. More detailed figures are presented in appendix 8.2.

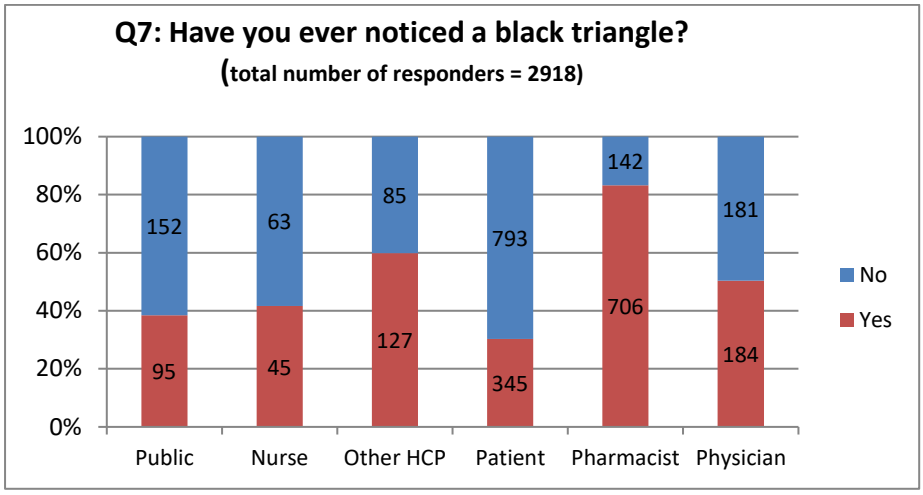
5.4 Awareness of additional monitoring

Only 51% of the 2918 responders indicated that they had seen the black triangle and the accompanying statement. Awareness varied between different respondents, as shown below in Figure 15. The lowest awareness of the black triangle was among patients (only 30% reported that they had seen it before) and the highest among pharmacists (83%).

The survey conducted by EURORDIS on the new pharmacovigilance system produced similar results with 20%[10] of respondents (patients) indicating that they had seen a black triangle (compared to 30% of patients from EMA's survey).

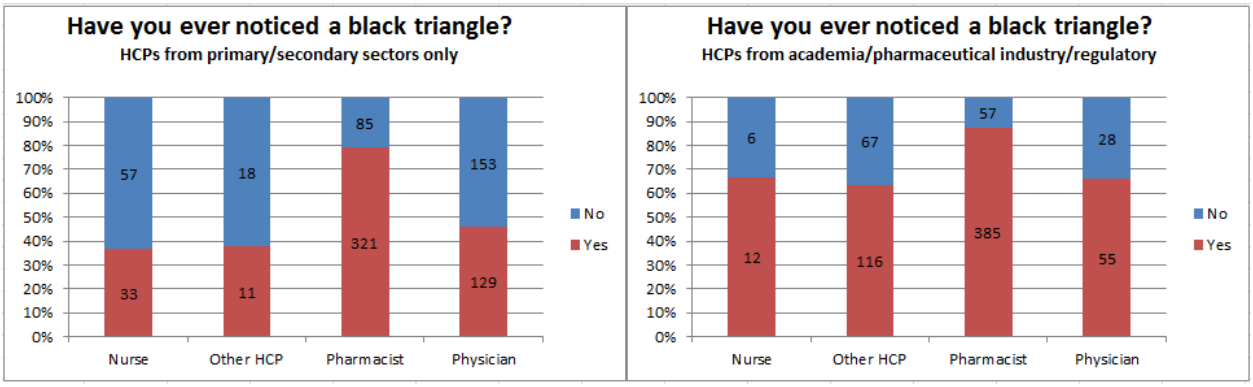
[10] This question of EURORDIS' survey asked patients to select one of their medicines and respond to survey's questions based on their experience/PL leaflet information of this medicine.

Figure 15: Number of responders indicating whether they have seen the black triangle before.



Awareness was also significantly lower among HCPs working in primary/secondary care settings compared to HCPs working in academia, pharmaceutical industry or regulatory authorities (OR 3.45, 95% CI 1.19 - 10.07, p=0.023).

Figure 16: Awareness of the black triangle among health care professionals (HCPs) in different sectors

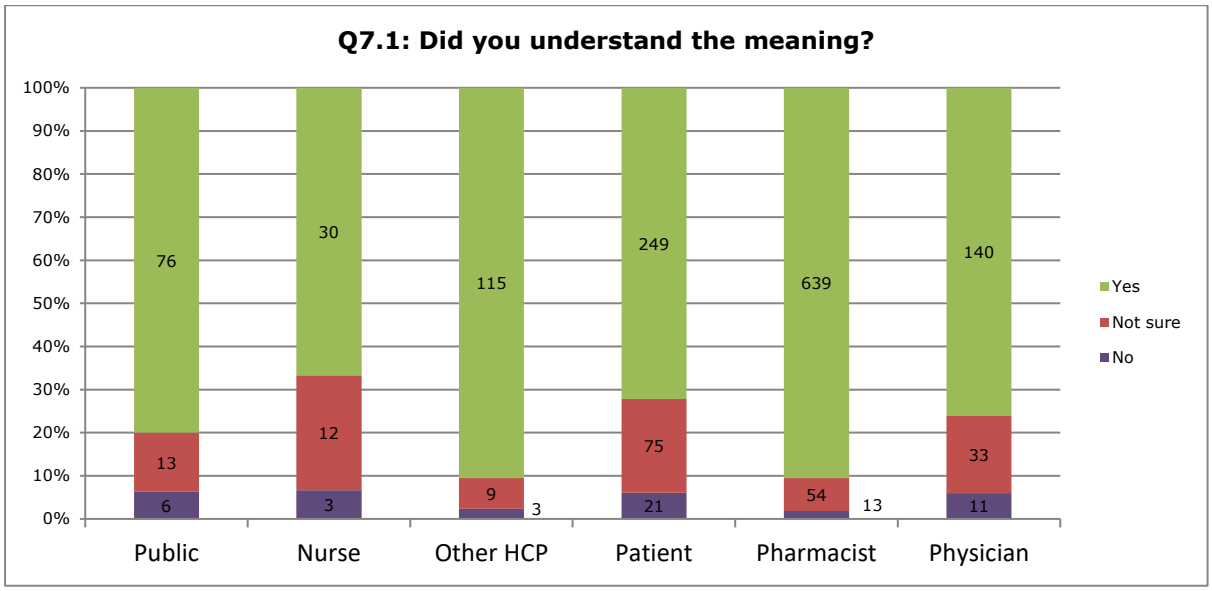


The most commonly mentioned source was SmPC or PL (indicated by 1204 respondents, 80% of those who have seen the black triangle before), other information sources such as drug information web-sites were indicated by 573 respondents (38%), educational/promotional materials were the third most common source and were mentioned by 509 respondents (34%). Publications such as formularies or bulletins were selected by 357 respondents (24%). The question about the source of information ("Where have you seen it?") was a multiple choice question and 657 responders (44%) selected more than one answer.

5.3 Understanding of the additional monitoring concept

The majority (83%) of those who responded that they had seen a black triangle indicated that they understood the meaning of the black triangle/accompanying statement.

Figure 17: Understanding of the additional monitoring concept



In the subsequent open field question, the responders were asked to describe, what in their opinion the black triangle and the accompanying statement means. The responses were evaluated as:

- "Acceptable understanding": if the responses contained at least one of the elements: ADRs reporting, novelty of the drug, need of post-marketing data, regulatory definition of the additional monitoring but did not have elements from "misunderstanding" section;

- "Misunderstanding": responses stating that the black triangle means more toxic drug, drug with no clinical trial data or other elements that are clearly not a definition of the black triangle.

- "Insufficient information": responses containing dots, commas or other symbols, untranslatable abbreviations and also simply the phrase "additional monitoring".

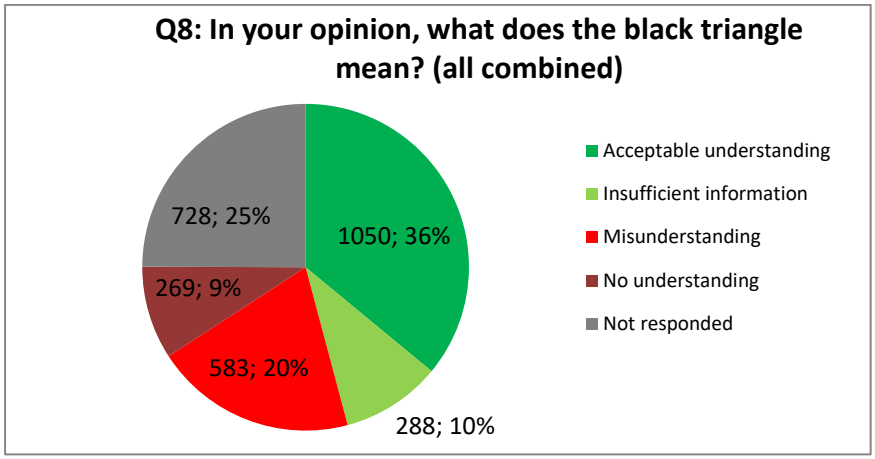
- "No understanding" – responses, stating "I do not know" or similar phrases.

- "Not responded" – field was left blank (the question was not mandatory).

In total, 36% (1050 of 2918 responders) of responses showed an acceptable understanding while 20% of the responses were assessed as misunderstanding; see Figure 18 for more details.

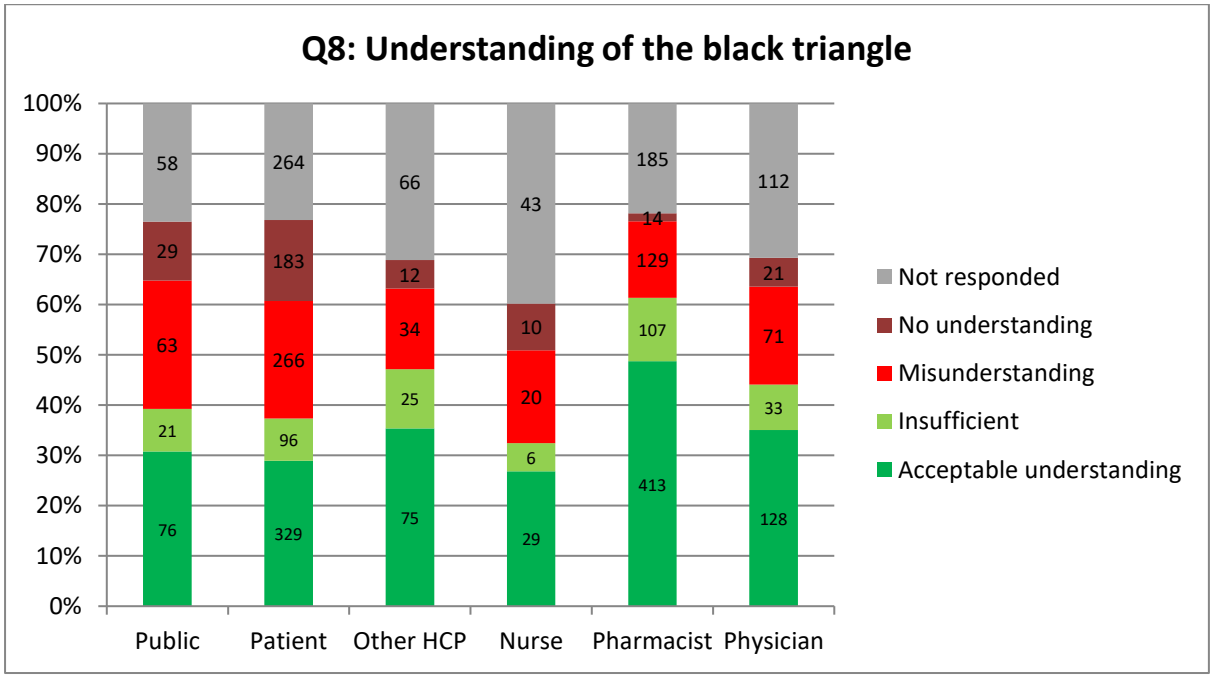
Of those who responded that they had understood the meaning of the black triangle (n=1249), 17% had actually misunderstood the concept and 53% had acceptable understanding as assessed according to the responses to question 8.

Figure 18: Understanding of black triangle and AM concept (all responders, n=2918)



The level of understanding was different among various types of responders, greatest among pharmacists (45%) and lowest among nurses (23%), shown in Figure 19 below. The highest misunderstanding of the AM concept was among members of the public (26%).

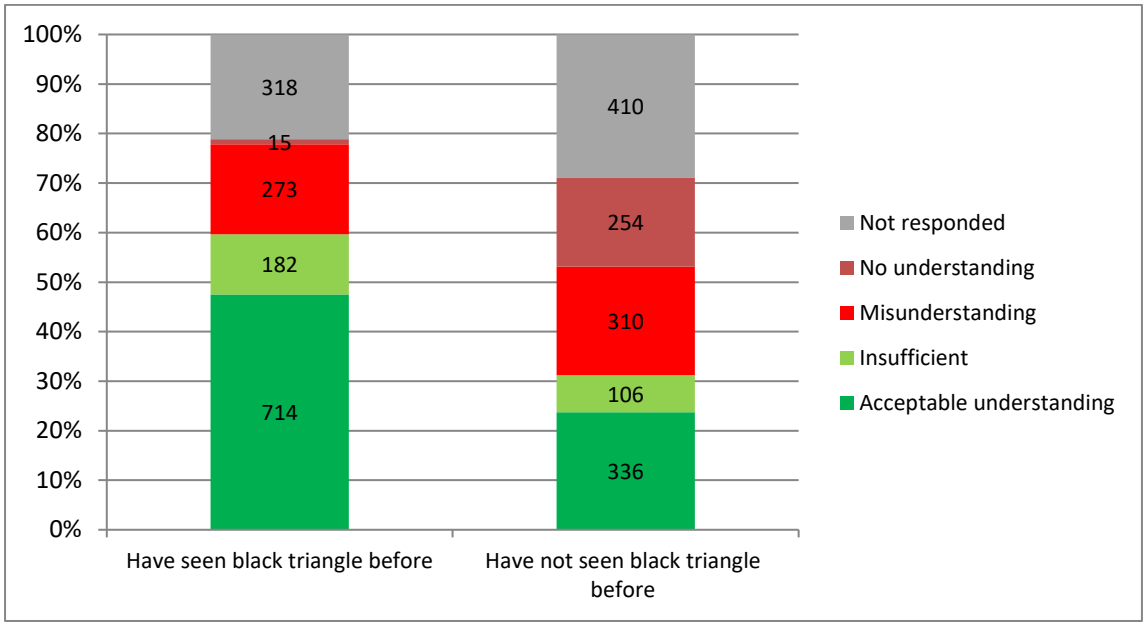
Figure 19: Understanding of black triangle and AM concept by different responders



For HCPs in primary/secondary sectors, "acceptable understanding" was lower than in HCPs from industry, regulatory authorities or academia.

The level of understanding varied significantly depending on previous awareness of the black triangle, assessed based on responses to Q7:"Have you ever noticed a black triangle?": 48% of responders who responded "yes" to this question, had "acceptable" understanding, compared to 24% of those who indicated that they have not seen the black triangle before, see Figure 20 below.

Figure 20: Understanding of black triangle and AM concept depending on previous awareness



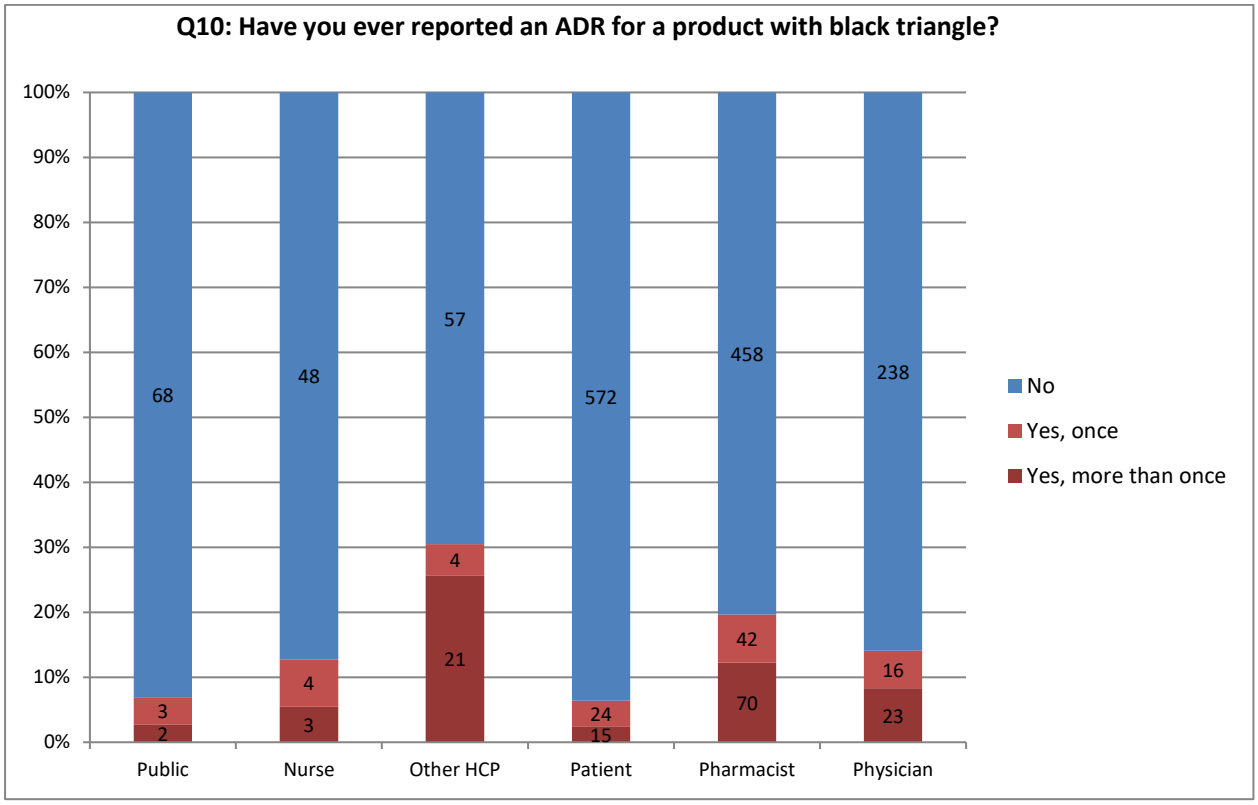
Among responses assessed as "acceptable understanding", most prevalent themes were: need for post-marketing safety data, need for ADR reporting and the novelty of the drug. The themes in the responses were similar between HCPs and non-HCPs.

Among responses assessed as "misunderstanding", the most prevalent themes were safety concerns (e.g. drug is toxic, drug causes more side effects than other drugs), lack of safety data (e.g. "trial drug", "drug marketed without clinical trial", "unknown safety profile") and combination of other themes ("narrow therapeutic index drug", "a need of patient monitoring", "keep out of reach of children", "careful driving", etc). The themes in the responses were also similar between HCPs and non-HCPs.

5.4 Impact of the black triangle on the motivation to report ADRs

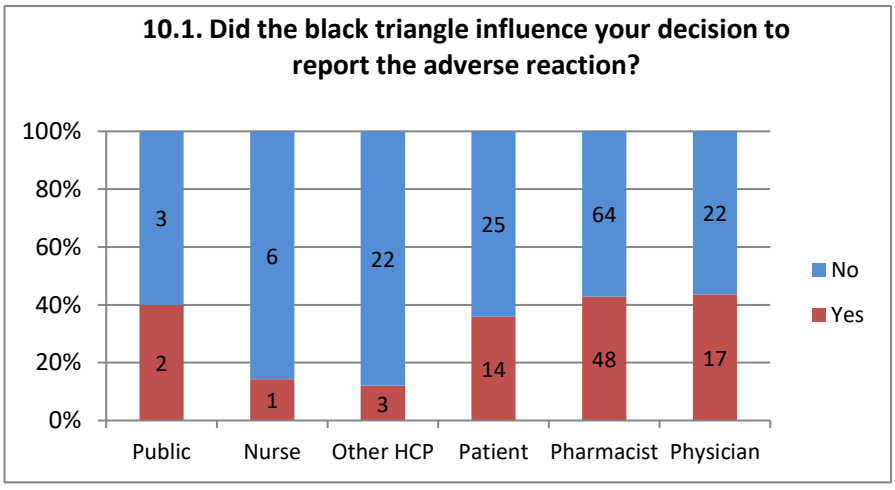
57% of all responders to the survey reported at least one ADR. Of reporters (n=1668), only 14% (n=227) reported an ADR for a product identified with a black triangle (this question was populated only if responder did not select "none" in the question on how many ADRs they had ever reported).

Figure 21: ADR reporting for a product with black triangle



Those who responded "yes, once" or "yes, more than once" to this question (n=227), were asked if the black triangle influenced their decision to report the ADR. Only 37% of this group indicated that the black triangle was an influencing factor. The responses varied between different categories of the responders, see Figure 22 below.

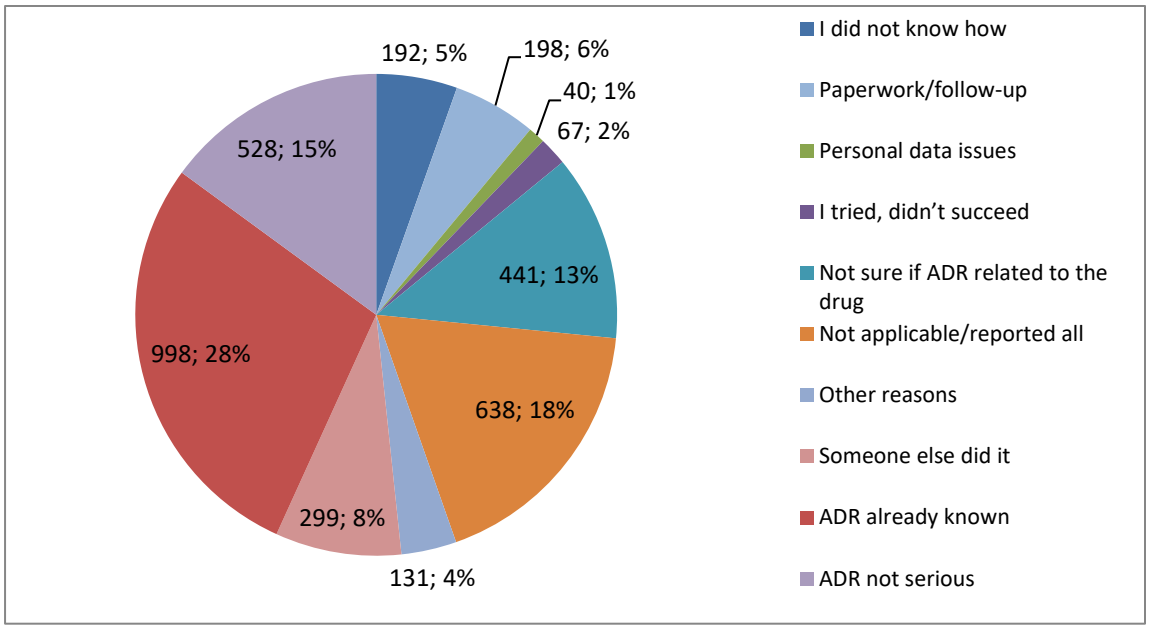
Figure 22: Black triangle as a motivating factor to report an ADR



To the question "Did the black triangle influence your decision to report the adverse reaction?" 88% of the respondents reported that they would definitely or probably report an ADR for a medicine identified with the black triangle, see Figure 14. This is slightly below the score for "serious ADR leading to death or hospitalisation" (95% and 93% respectively).

A question on ADR reporting (Q 5.2 "In case you have not reported all ADRs you observed/ experienced, what were the main reasons for this?") showed that 28% of respondents did not report an ADR because it was already listed and 15% because it was not serious. Most commonly reported reasons (58%) were ADR judgement-related (novelty or seriousness of an ADR or being unsure if ADR is related to the drug) and only 18% did not report because of practical/technical reasons (unwilling to deal with paperwork, personal data issues, lack of knowledge how to do that etc.).

Figure 23: Reasons for not reporting ADRs, based on question 5.2



The question on real experience/behaviour "Did the black triangle influence your decision to report the adverse reaction?" showed that the black triangle was a motivating factor to report an ADR for 37% of respondents, which demonstrates that other factors, such as the seriousness of the reaction encountered, were more important reasons for reporting an ADR.

The results of this survey are in line with a similar survey conducted by EURORDIS [7] in 2016 on the meaning of the new pharmacovigilance system to patients. EURORDIS's survey included a few questions on ADR reporting and awareness of the black triangle concept. According to the EURORDIS survey, 61% of patients experienced an ADR (not in off-label use), and of those, who did, 84% reported the ADR. In the EURORDIS survey, reporting was higher for serious ADRs. Only 20% of patients reported that they had seen a black triangle, which is slightly lower than the results of this survey, where 30% of patients and 38% of the public reported that they had seen it before.

A similar study exploring the knowledge of ADR reporting and the pharmacovigilance of biological medicines is being conducted by O'Callaghan *et al*. in Ireland (communication by the author). This survey was made available to HCPs online and included a number of questions relevant to AM. Overall awareness of AM among HCPs in Ireland was higher than seen in EMA survey responses. The greatest awareness was among pharmacists in both surveys: 97% of hospital pharmacists and 92% of community pharmacists in Ireland were aware of the AM concept while 83% of pharmacists in EMA's survey indicated that they have seen a black triangle before (EMA survey did not distinguish between hospital and community pharmacists).

5.4. Limitations

This survey was an open online survey published on EMA's website. NCAs, HCPs and patients organisations were asked to help disseminate this survey. The nature of dissemination and online-only availability of the survey will have favoured responders who were more knowledgeable on the topic and this also may have had a differential effect on patients versus HCPs.

The possibility of multiple responses from the respondent cannot be excluded despite the statement/request in the survey opening page not to do so. However less than 7% of the responses were submitted with the same IP addresses. It is possible that the decision to complete the survey would have been influenced by personal experience of ADRs.

5.5. Conclusions

- Responses were received from all EEA countries; however response rate varied among countries. 47% of responders identified themselves as non-HCPs and 53% of responders as HCPs.
- 85% of HCPs and 67% of non HCPs have observed/experienced at least one ADR. 76% of HCPs and 73% of non-HCPs who experienced/observed an ADR, reported at least once.
- Responders are more likely to report serious ADRs and ADRs associated with a new medicine: 88% of responders indicated that they would definitely or probably report an ADR for a medicine identified with a black triangle. However, only 37% of those who had ever reported an ADR for a product with black triangle indicated that the black triangle was the influencing factor.
- Only 51% of all responders indicated that they had seen the black triangle and the accompanying statement before. The awareness varied between different responders with greatest awareness among pharmacists (83%) and the lowest among patients (30%). As the black triangle only applies to a minority of products, it can be expected that a large proportion of patients or members of the public will not have yet seen it on the package leaflets of their medicines.
- 36% of total responders had an acceptable understanding of the AM concept, with need for post-marketing data, ADR reporting and novelty of the drug as main themes in the responses and 20% of all responses were assessed as misunderstanding, with safety concerns and lack of safety data among most prevailing themes. The level of understanding varied slightly among different responder groups, with highest proportion of acceptable understanding among pharmacists and lowest among nurses. HCPs not working in primary care or hospitals (employed in academia, pharmaceutical industry or regulatory authorities) had better understanding of AM. Responders who have seen a black triangle before also had better understanding, compared to those who indicated that they have not seen black triangle before (48% versus 24%). Of those who responded that they understood the meaning of the black triangle (n=1249), 17% had actually misunderstood the concept and only 53% had acceptable understanding.

6. Discussion and overall conclusions

Research has already been performed to investigate the impact of additional monitoring through SCOPE, the 2016 EURORDIS survey, and ongoing NCA projects (Ireland). The work coordinated by EMA and described in this document aimed to provide further information by investigating the experience of the EU regulatory network with the use of the AM list since its creation and the knowledge of patients and HCPs about the AM concept.

This report summarises the EMA's and MS's experience as follows:

1. A survey to understand MSs' experience with AM.
2. The results of the Agency's experience with the use of the AM list and analyses on whether the inclusion of the products on the AM list had an effect on reporting of ADRs and on the detection and outcome of signals. These focus on products subject to additional monitoring under the mandatory scope, as no product was included on the AM list under the optional scope during the analysis period.
3. A survey to estimate patients' and health care professionals' (HCP) awareness of the black triangle and the AM concept.

Most of the activities initiated by MSs to promote the additional monitoring concept took place in 2013 at the time the relevant legislation came into force, and mostly involved publications on their websites. Some NCAs also used additional means of communication including publications, conferences and forums. The majority of NCAs indicated an increase in workload (3 NCAs mentioned a small increase, 4 mentioned 0.5 day per month, 1 FTE, 0.1 FTE and 150 hours per year respectively). An imposed PASS as a mandatory trigger for inclusion in the AM list together with AM concept being at product level were highlighted as the major issues with AM causing misunderstanding among patients and HCPs due to several products containing the same active substance having different AM status. Many of the difficulties could be resolved simply by removing the mandatory AM status of products with an imposed study.

The number of products subject to AM increased over time, with a 20 fold increase between April 2013 and December 2016. The majority of products in the AM list are included due to an imposed PASS (88% of products in December 2016 version). The great increase in the proportion of products included for this reason (from an earlier majority included as new active substances) occurred after the first PASSs were imposed during referral procedures. The majority of products (87%) on the list are non-CAPs due to the high number of such products added because of an imposed PASS during a referral procedure.

EudraVigilance analysis investigating the effect of AM listing on reporting of ADRs was not conclusive.

The patterns of ADR reporting changes after addition to the AM list were heterogeneous. Out of the five new products included in the analysis, two products demonstrated a statistically significant increase in the slope of ADR reporting after addition to the AM list, while three did not show significant changes. Among the six products included due to PASS, we did not identify any changes for three products, while two products showed a significant slope decrease and one product showed a step increase followed by a slope decrease.

Our analysis was restricted to a small subset of the products and likely underpowered, so the results need to be interpreted with caution.

It is also not possible to conclude whether AM status has an impact on the number of signals validated and assessed by the PRAC or on signal outcomes. The proportion of DHPCs was slightly higher for AM than non-AM-related signals, but the reasons for these differences cannot clearly be attributed to AM status.

The survey to assess the awareness of the concept of additional monitoring showed that responses were received from all EEA countries and half of respondents identified themselves as HCPs and half as non-HCPs. Responders were likely more familiar with medicines regulation and pharmacovigilance due to the way in which the survey was conducted.

Half of all respondents indicated that they had seen the black triangle and the accompanying statement before the survey. The awareness varied between the type of respondents with the greatest awareness among pharmacists and the lowest among patients. Nearly 90% of respondents indicated that they would definitely or probably report an ADR for a medicine identified with a black triangle, however only 37% of those who reported an ADR for an AM product indicated that the black triangle was effectively the influencing factor.

About a third of the respondents had an acceptable understanding of the AM concept whilst a fifth of the responses indicated some misunderstanding of the reasons for AM listing, with safety issues and lack of safety data or adequate clinical trial data among the most prevalent misconceptions. Pharmacists had the highest awareness and understanding of the AM concept. Awareness and understanding was lowest among nurses. HCPs not working in primary and secondary care (i.e. HCPs from industry and academia) also had lower understanding. These findings suggest that further AM awareness campaigns could be targeted and may be beneficial in maximising the awareness among reporters.

The results suggest that:

- Both more time and more communication are needed to raise the awareness of AM, as well as the need for ADR reporting in general. The survey results suggest that knowledge of AM is higher in some groups than others and these data could be used to target the messaging and intensity of communications;
- The EudraVigilance analysis investigating the effect of AM 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 AM leads to large numbers of established products being included in the list and is of limited value.
- AM status being at product level combined with the inclusion of imposed PASS as a mandatory trigger for AM were highlighted as major issues with the AM 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 AM status;
- PRAC would support reconsideration of the scope of AM, particularly the mandatory inclusion of products subject to imposed PASS.

7. References

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2. Guideline on good pharmacovigilance practices Module X – Additional monitoring. Available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/04/WC500142282.pdf

3. 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. Available at:

http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2013_198/reg_2013_198_en.pdf

4. Directive 2001/83/EC on the Community code relating to medicinal products for human use; Official Journal L – 136, 30/04/2004, p. 34 – 57. Available at:

http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1520436949241&uri=CELEX:32001L0083

5. SCOPE Awareness Work Package 6: Survey Report. Patient and Consumer Consultation, 2016. Available at: http://www.scopejointaction.eu/_assets/files/WP6-Patient-Consumer-Consultation-Report(1).pdf

6. SCOPE Work Package 4: Survey Report. Available at: http://www.scopejointaction.eu/_assets/files/SCOPE-WP4-Topic-1,2,5-survey-report.pdf

7. Presentation by Francois Houÿez "What does the new PhV system mean for patients in real life?" Available at: https://www.eurordis.org/sites/default/files/Eurordis_patients_and_pharmacovigilance.pdf

8. Guideline on good pharmacovigilance practices Module IX – Signal management. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129138.pdf

9. List of substances and products subject to work-sharing for signal management (18/07/2016)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/10/news_detail_001624.jsp&mid=WC0b01ac058004d5c1

8. Appendixes

8.1. Products that have been subject to additional monitoring and included on the list over time (results for objective 3.1). Products in annexes as per December 2016 AM list.

Active Substance (s)	Reason (s) on list	Annex
Cilostazol	PASS	Annex VIII
Chlormadinone /Ethinylestradiol, Chlormadinone Acetate /Ethinylestradiol	PASS	Annex IX
Cyproterone acetate/Ethinylestradiol	PASS	Annex I
Dexamfetamine sulphate	PASS	Annex XII
Domperidone	PASS	Annex X
Flupirtine	PASS	Annex VI
Hydroxyethyl starch	PASS	Annex V
Ferric carboxymaltose, iron dextran, sodium ferric gluconate, iron isomaltoside, iron sucrose	PASS	Annex III
Teicoplanin	PASS	Annex VII
Thiocolchicoside	PASS	Annex IV
Trimetazidine	PASS	Annex II
Sodium valproate, valproic acid, valproate semisodium, valpromide	PASS	Annex XIII
Alanine, arginine, aspartic acid, calcium chloride, cysteine, glucose monohydrate, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, magnesium acetate, methionine, olive oil, ornithine hydrochloride, henylalanine, potassium acetate, proline, serine, sodium chloride, sodium glycerophosphate, soybean oil, taurine, threonine, tryptophan, tyrosine, valine	PASS	Annex XI

8.2. Survey to assess the awareness of the concept of additional monitoring

Survey's questionnaire:

EMA-survey-on-repo
rting-adverse-drug-re

Figure 1. Distribution by age

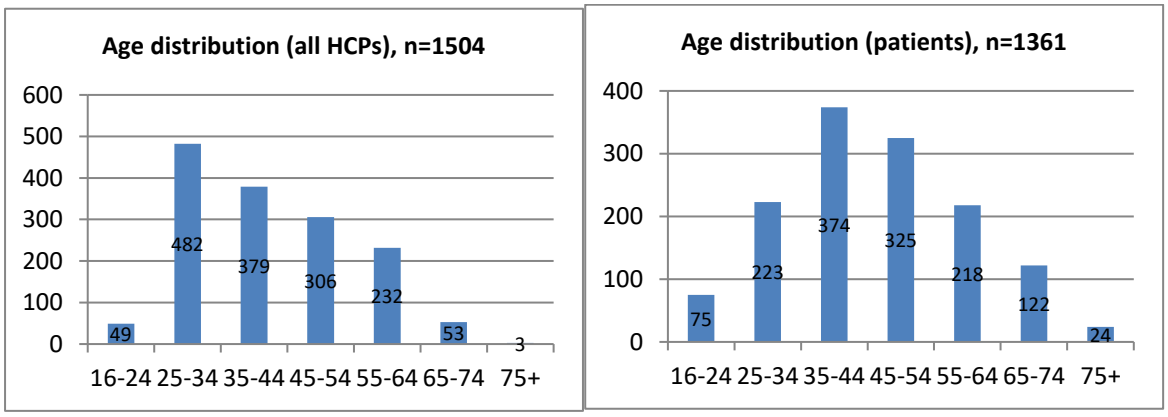
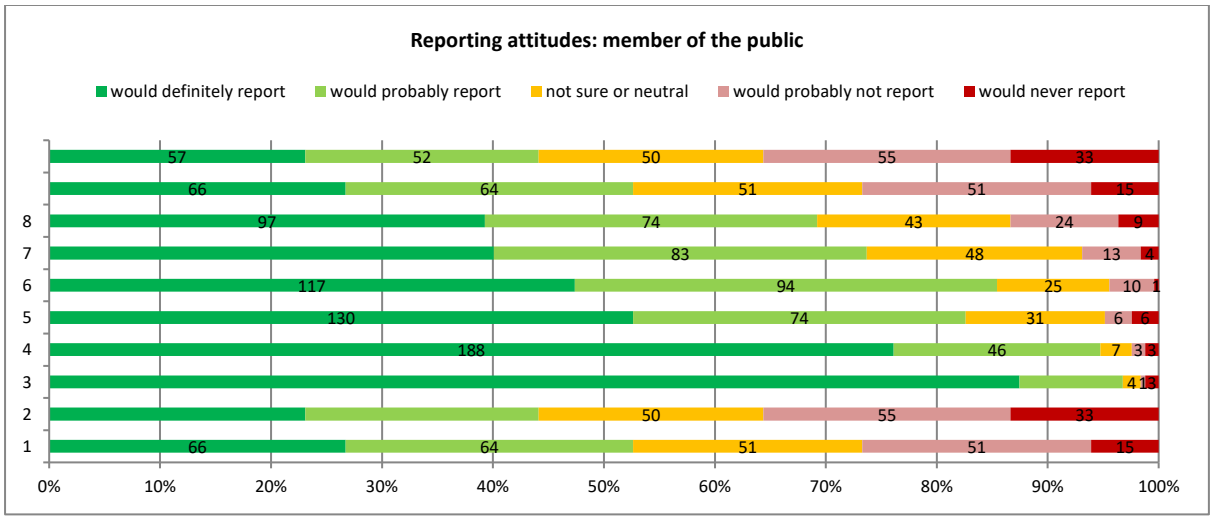
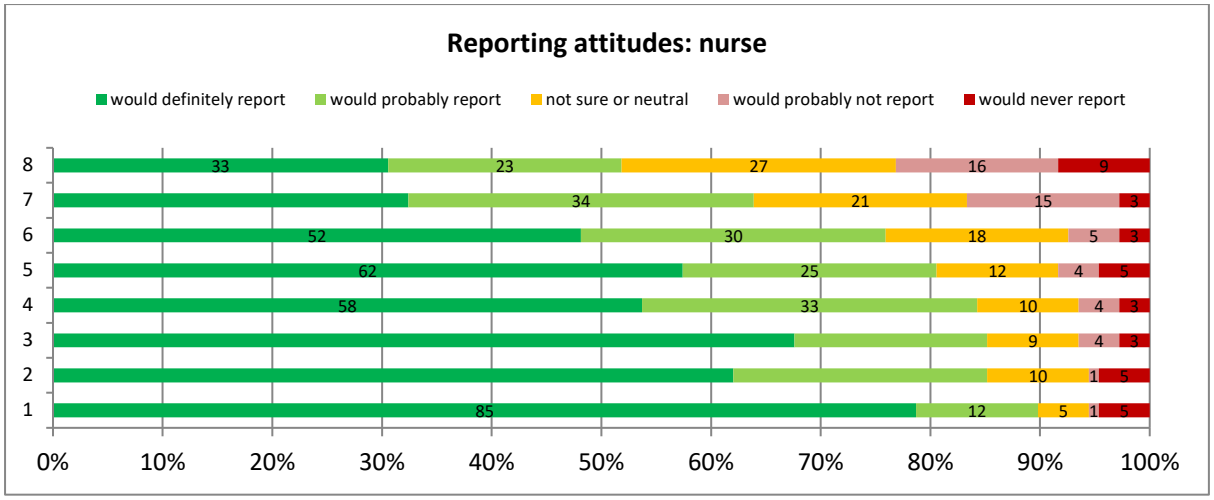
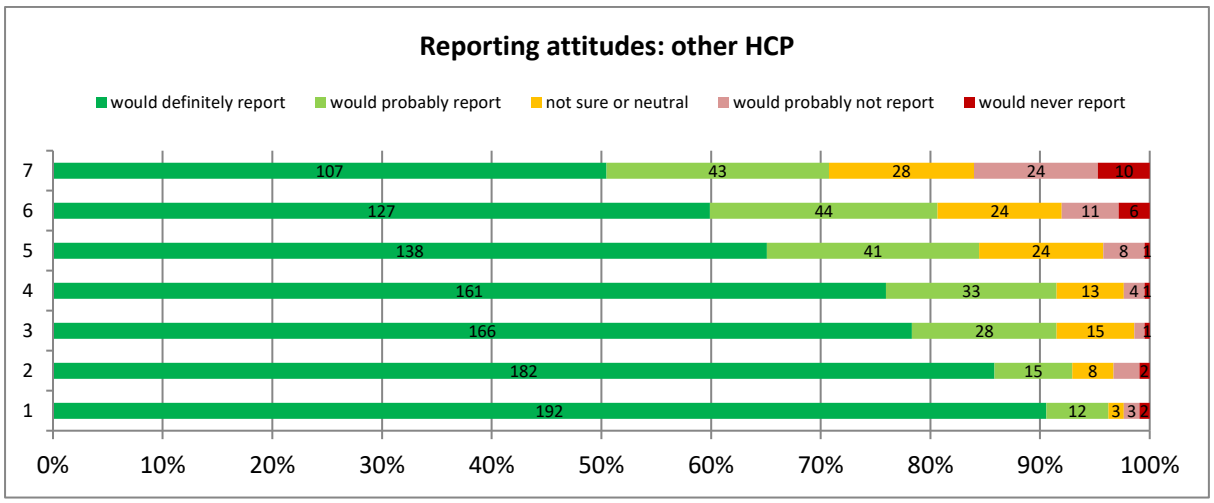
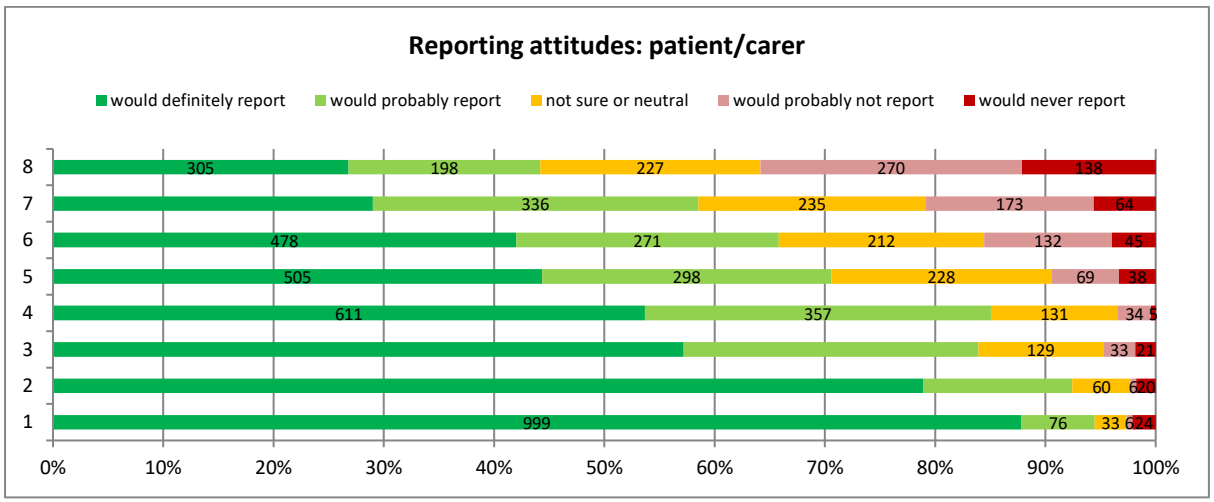


Figure 4. Attitudes towards reporting various types of ADRs, per responder type (where: 1 - The patient died as a result of the ADR; 2 - The ADR caused the patient to be hospitalised; 3 - The ADR followed use of a new medicine; 4 - Medicine identified by the black-triangle symbol; 5 - The ADR followed use of a biological product; 6 - The ADR followed vaccination; 7 - Any ADR; 8 - The ADR is included in the product information.)




Reporting attitudes: nurse
would definitely report
would probably report
not sure or neutral
would probably not report
would never report
8
7
6
5
4
3
2
1
33 23 27 16 9
34 21 15 3
52 30 18 5 3
62 25 12 4 5
58 33 10 4 3
9 4 3
10 1 5
85 12 5 1 5
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%


Reporting attitudes: other HCP
would definitely report
would probably report
not sure or neutral
would probably not report
would never report
7
6
5
4
3
2
1
107 43 28 24 10
127 44 24 11 6
138 41 24 8 1
161 33 13 4 1
166 28 15 1
182 15 8 2
192 12 3 3 2
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%


Reporting attitudes: patient/carer
would definitely report
would probably report
not sure or neutral
would probably not report
would never report
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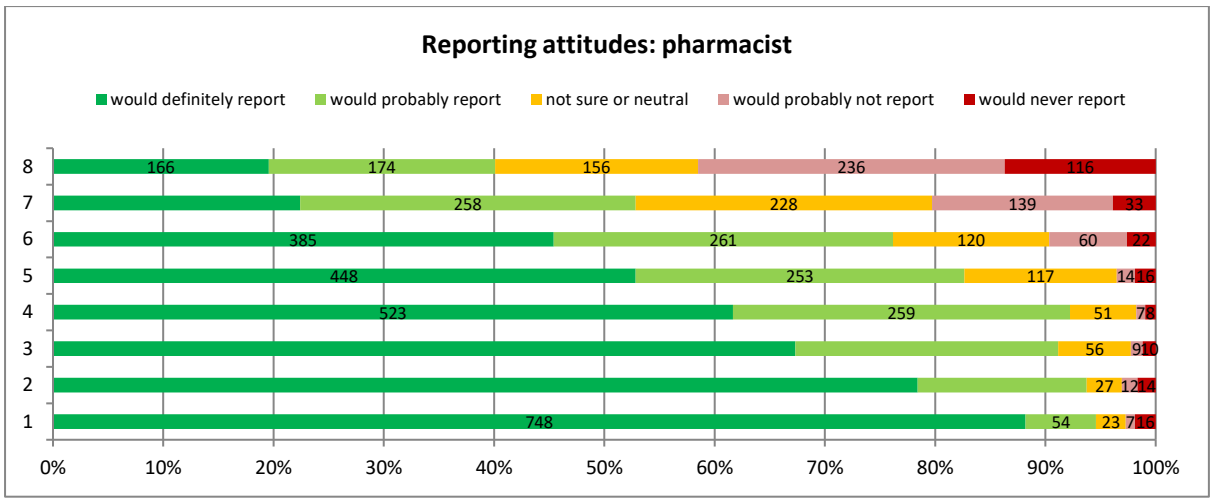
305 198 227 270 138
336 235 173 64
478 271 212 132 45
505 298 228 69 38
611 357 131 34 5
129 33 21
60 6 20
999 76 33 6 24
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%


Reporting attitudes: pharmacist
would definitely report
would probably report
not sure or neutral
would probably not report
would never report
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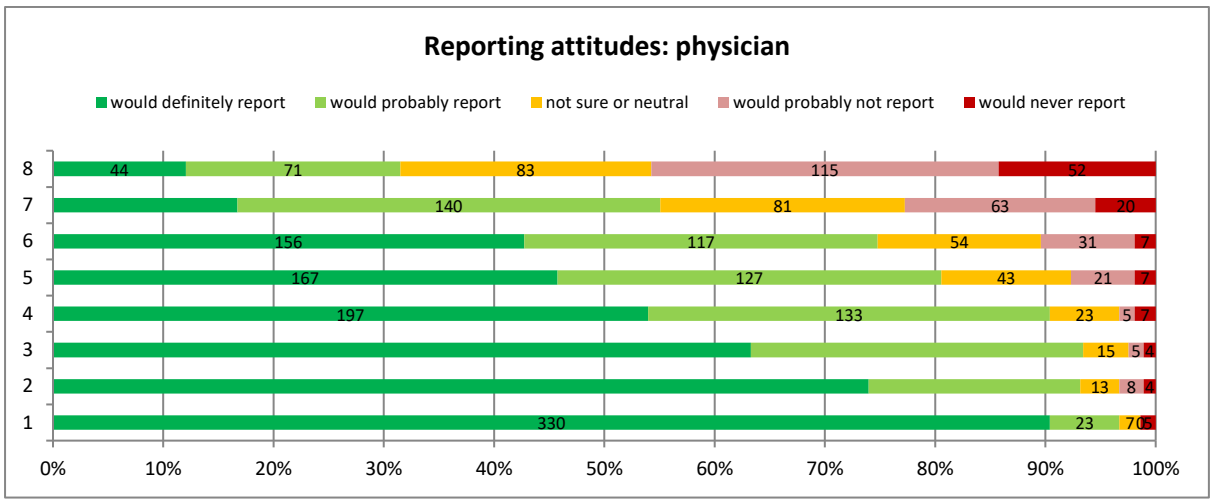
Reporting attitudes: physician
would definitely report
would probably report
not sure or neutral
would probably not report
would never report
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