Direct Patient Reporting in the European Union

A Snapshot of Reporting Systems in Seven Member States

hai Health Action International

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I. Introduction

Adverse drug reactions (ADRs) are a serious public health concern. It is estimated that 5% of all hospital admissions in the European Union (EU) are due to an ADR, and that ADRs are the fifth leading cause of hospital death. This represents approximately 197,000 deaths a year.[1] Although the most common adverse reactions to medicines may be identified in clinical trials, rarer ones might only be recognised when numerous patients have used the medicine in normal clinical practice, over the long term, or even after the end of treatment—and only if reported.

By collecting reports on suspected adverse drug reactions after medicines are made available to patients and evaluating these data, regulatory authorities can identify whether harms outweigh benefits and take necessary action to protect patient safety. In spite of the fact that spontaneous reporting is crucial for signal detection, under-reporting is common. It is estimated that only 1% to 10% of serious adverse reactions are reported.[2]

Healthcare professionals are a key source of information about medicines safety, but they do not report as much as they should. Doctors often cite lack of time as a barrier to reporting and sometimes only report adverse reactions when completely confident that they are related to the use of a drug.[3] Additionally, whilst patients consider certain ADRs to be very significant in terms of impacting their quality of life, healthcare professionals do not to the same extent.[4]

The combination of reports from healthcare professionals with first-hand information from patients is of great added value because it increases chances to identify new safety issues. Reports initiated by patients often provide more detailed information about experienced ADRs and their impact on patients' everyday lives. This also has important implications for patients, empowering them to participate more actively in their treatment instead of being passive recipients of medical interventions. [5, 6,7]

The advantages posed by complementing reports from healthcare professionals with reports from patients have been facilitated by a number of changes to established systems of pharmacovigilance in Europe. In 2003, Denmark and the Netherlands became the first countries to allow patients and consumers to report suspected ADRs directly to their regulatory agency. These countries were followed by Italy (2004), the United Kingdom (2005) and Sweden (2008).[8]

With the implementation of new EU pharmacovigilance legislation in 2012, patient reporting has been expanded throughout the EU.[9] [10] The EU now mandates Member

States to encourage patients to report suspected ADRs directly to the regulatory agency and to enable reporting through web-based formats and alternative means. The new legislation also states that marketing authorisation holders (MAHs) shall not refuse to consider ADR reports received from patients through appropriate means.

Direct patient reporting to regulatory authorities is of particular relevance in that it avoids the conflict of interest situation that arises when patients report suspected adverse reactions directly to MAHs. Without independent verification, there is a higher risk that spontaneous ADR reports received by a pharmaceutical company are stripped of clinical significance when encoded and subsequently transferred to the regulatory authorities.[11] [12]

By introducing a legal right for patients to report suspected ADRs directly to regulatory authorities, the EU acknowledges patients and consumers as key sources of information on medicines safety and paves the way for a faster—and more comprehensive—collection of data on adverse drug reactions.

But to maximise the benefits of direct patient reporting, appropriate reporting systems must be in place. The general public must also be made aware of the possibility to initiate ADR reports and guided throughout the process. To contribute knowledge on patient reporting, particularly on direct reporting to regulatory authorities, we aim to describe the reporting systems of selected EU Member States to identify best practices and issue recommendations for improvement.

This publication follows Health Action International's 2010 report, *Direct Reporting of Adverse Drug Reactions: A Twelve-country Survey and Literature Review*, which advocated for the implementation of direct patient reporting in EU pharmacovigilance legislation.

II. Methodology

We describe and analyse systems of direct patient reporting in seven EU Member States: Bulgaria, Denmark, France, the Netherlands, Portugal, Romania and Sweden. This sample includes countries with the most experience in patient reporting (Denmark, the Netherlands and Sweden) and others with less. It also represents a balanced EU geographical coverage.

The selected countries' systems for direct patient reporting were assessed by conducting a literature review, interviewing national regulatory agencies and searching their websites.[i] Feedback was also sought from patient and consumer organisations.[ii] Patient reporting

[i] Accessed July 2015, in original language and translated.
[ii] Sources of information: Bulgarian Drug Agency, Bulgarian Organization for Patients with Rheumatology Diseases, Danish Consumer Council, Danish Health and Medicines Authority, French National Agency for Medicines and Health Products Safety, UFC Que-Choisir, Lareb, Dutch Institute for the Rational Use of Medicine, Portuguese National Authority of Medicines and Health Products, DECO Proteste, Romanian

mechanisms were evaluated and distinctive characteristics were highlighted. Patient reports refer to reports initiated by patients, their relatives, caretakers or representatives.

III. Country Overviews

Bulgaria

The Bulgarian pharmacovigilance system has been in place since 1995. Patient reports without medical validation were not part of the signal detection process, but this changed when Directive 2010/84/EU became part of national law in 2012. According to the Bulgarian Drug Agency (BDA), the pharmacovigilance system was then strengthened; however, it has proved difficult to adequately enlarge the Agency's staff for the new tasks.

The BDA received few reports directly from patients in the years following the implementation of the new EU legislation. In 2013, only 11 of 450 ADR reports were direct patient reports. In 2014, the BDA received a total of 403 ADR reports; 12 were directly notified by patients.

Patients can report through an electronic reporting form (e-form) that is available on the Agency's website. The report form can also be printed and sent by fax or post. Free letters (i.e., no report form) are also allowed, and instructions about the minimal information that should be reported (i.e., reporter's contact details and personal health data, such as age, weight and height; name of the medicinal product; description of the reaction) are provided on the website's section on information for citizens. Further information and help can be sought by phoning the pharmacovigilance department.

An icon indicating the e-form for patients can be found on a sidebar on the right side of the website's main page (Bulgarian version). It is simple and easy to fill out. Multiple-choice and open questions are provided in one page, including a free text box that allows for the description of the reaction. The BDA asks for permission to contact the patient's doctor if necessary. Patients are encouraged to first share their experiences with their doctor and, if the healthcare professional also suspects a link between the drug and the observed reaction, to make one report.

In addition to communicating on pharmacovigilance through its website, the BDA publishes a drug bulletin and an information sheet on ADRs but only for healthcare professionals. Additional information is provided on request. Patients can also seek advice

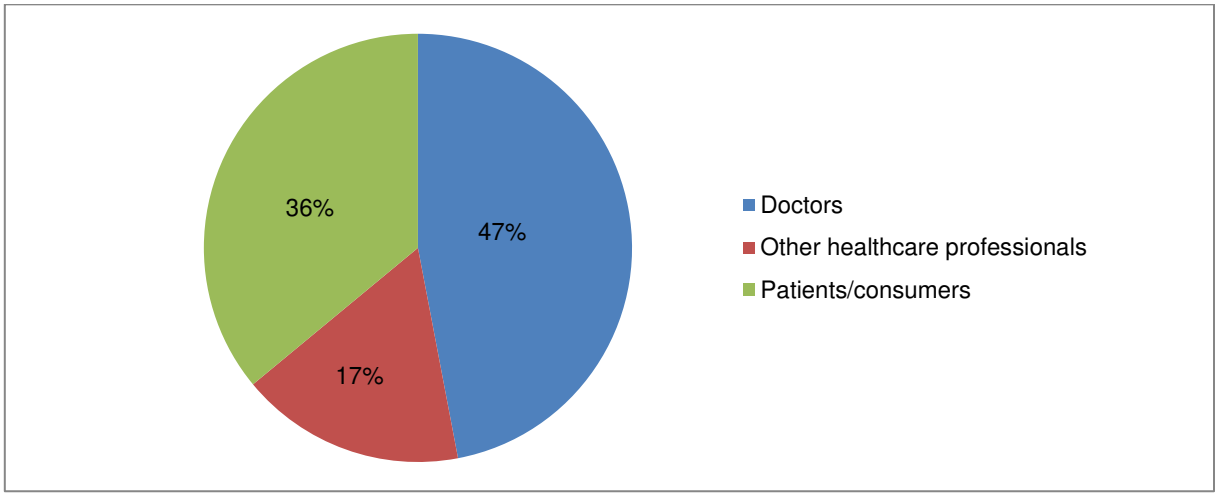
National Agency for Medicines and Medical Devices, UNOPA (National Union of Persons Affected by HIV-AIDS).

about ADR reporting through patient organisations. It was reported that patients are not actively informed about the possibility to report ADRs by their physicians and other healthcare professionals.

Denmark

Direct patient reporting to the Danish Health and Medicines Authority (DHMA, Sundhedsstyrelsen) has been possible since 2003. Demands from civil society organisations contributed to this development. The ADR reporting system has been continuously improved and online tools have been made easier to use. No new elements have been introduced specifically as a result of the new EU Directive. In 2013, the DHMA received 6,681 reports of suspected ADRs, which represents an increase of 35% compared to the previous year.[13] It was reported that a proliferation of stories concerning side effects from HPV vaccinations contributed to high reporting levels.

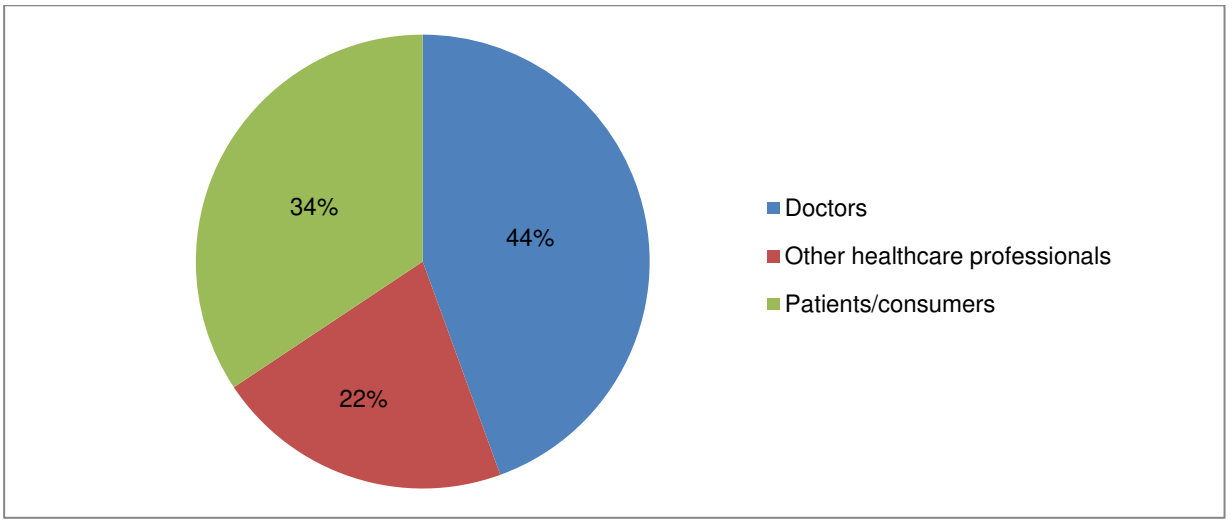
Chart 1: Number of ADR reports by type of originating reporter in 2013*



* Some of these reports were received from marketing authorisation holders (MAHs) and not directly from patients and doctors/other healthcare professionals. According to the DHMA, a small portion of the percentage of patient reports was received from MAHs.

In 2014, the DHMA received 6,499 reports, slightly fewer than the previous year.

Chart 2: Number of ADR reports by type of originating reporter in 2014*



* Some of these reports were received from marketing authorisation holders (MAHs) and not directly from patients and doctors/other healthcare professionals. According to the DHMA, a small portion of the percentage of patient reports was received from MAHs.

Patients can report a suspected ADR to the DHMA electronically and in paper form. According to interviewees, reporting by phone is possible, but it does not appear to be actively promoted on the DHMA site. The website (Danish version) is relatively easy to navigate, although it takes seven clicks to reach the e-form for patients. The form comprises six steps, but can be quickly completed in approximately 10 minutes. Reporters are advised to have the medicine package with them before starting the process. After submission, the DHMA sends an email confirming the receipt with a reference number.

The DHMA seeks medical validation for patient reports on serious ADRs by directly contacting the reporting patient's healthcare professional; otherwise, the case handling process does not differ compared to non-patient reports. In Denmark, citizens' social security numbers are used to link all reports concerning the same patient to minimise the risk of unnoticed duplicate reports. Patients are encouraged to write their identification number in the reporting form.

As in many other countries, under-reporting is a problem in Denmark. To encourage the spontaneous notification of ADRs, the DHMA has run several major information campaigns. In 2007, a leaflet distributed to pharmacies and general practitioners encouraged patients to report ADRs electronically. Similar activities were undertaken in 2010, including support programmes for patient organisations' phone counselling services to address questions on ADRs.[14]

In 2013, patient reporting was further encouraged through an awareness-raising campaign called, “Not everybody reacts the same”. The campaign was launched in pharmacies and health centres in collaboration with patient organisations. The DHMA considered it a success. In 2014, the focus of the campaign shifted towards increasing ADR reporting amongst patients, relatives and doctors within mental health care.[15] [16]

Campaigns by the DHMA are complemented by activities from consumer and patient groups (e.g., the Danish Consumer Council, Forbrugerrådet Tænk). The organisation conducts awareness-raising activities using networks and the media wherever possible. Consumer representatives emphasise, however, that while awareness is improving, many patients remain inadequately informed about ADR reporting and a cultural change is needed.

France

The National Agency for Medicines and Health Products Safety (ANSM) has accepted reports from patients since June 2011. In France, patients/consumers and healthcare professionals report ADRs to the Regional Pharmacovigilance Centres (CRPVs) where the patient is based. CRPVs collect, analyse, document and transfer ADR reports to the ANSM and can assess potential signals and contribute to signal detection by tracing a report or several reports as a potential signal.

The number of direct patient reports has remained stable over time, representing around 5% of all reports transferred by the CRPVs to the national database. In 2013, the ANSM received 46,843 ADR reports from CRPVs (initial and follow-up).[iii] Of those, 2,151 had been directly submitted by patients. In 2014, the number of ADR reports sent by CRPVs fell slightly to 46,497 reports (initial and follow-up). There were 1,983 direct patient reports.

There are 31 regional pharmacovigilance centres in France. A list with all 31 CRPVs can be found on the ANSM website; however, only around half of the regional centres appear to have their own website. Notably, the CRPVs from Besançon, Nice, the Paris region, Reims and Toulouse offer the possibility to report through electronic forms.[iv] Patients can also download a reporting form from the ANSM website and send it by e-mail or mail to their pharmacovigilance centre.

[iii] After de-duplication. CRPVs check whether there are duplicates between reports received from patients and healthcare professionals before sending the reports to the ANSM database. In case of duplicates, the report is considered to originate from a patient or healthcare professional taking into account the initial reporter.

[iv] Some CRPVs might offer additional reporting means. The pharmacovigilance centre in Toulouse, for example, has developed a smart phone application, VigiBIP, to complement reporting through an e-form. More information about VigiBip can be found at http://www.bip31.fr/.

The ANSM reporting form can be completed electronically and comprises two pages, the second of which allows for an extensive description of the adverse reaction. Instructions about essential information that must be included are indicated at the bottom of the second page in small type. Patients are reminded that they can complete the template with the help of a patient organisation. Other documents, such as the results of medical tests, can be sent with the reporting form. Reporters are asked to provide the contact details of the patient's healthcare professional, particularly to whom the adverse reaction was notified.

Some CRPVs send regular feedback to reporters. The pharmacovigilance centre of Toulouse, for example, sends a letter to patients who report an ADR. It includes a summary of the report and its assessment and the extent to which the report has been transferred to the national database. Relevant scientific publications can also be attached.[17]

General information about pharmacovigilance and direct patient reporting can be found on the national medicines agency and CRPV websites. ANSM uses social media tools, such as Twitter, to raise awareness about ADR reporting. Spontaneous reporting is also promoted in events, and informational materials are distributed amongst patient and consumer organisations. These organisations also have their own initiatives. The consumer organisation, UFC Que-Choisir, for example, uses publications and its website to raise awareness within the general public about adverse drug reactions and patient reporting.

The Netherlands

Direct patient reporting to regulatory authorities in the Netherlands began with a pilot project in April 2003. Patients and consumers can submit reports of suspected ADRs to Lareb, an independent foundation responsible for the spontaneous reporting system in the Netherlands. Lareb analyses reports received from patients, healthcare professionals and MAHs. It reviews the reports in weekly signal detection meetings and informs the College ter Beoordeling van Geneesmiddelen, the Medicines Evaluation Board (MEB), of new signals. When necessary, the MEB takes further action.

Existing reporting mechanisms have been improved since 2012, mostly as a result of Lareb's continuous evaluation and improvement, rather than the new EU Directive. In 2013, Lareb received a total of 17,057 reports, including 3,961 (23%) directly from patients/consumers. In 2014, 4,393 (20%) of 21,713 ADR reports received were direct patient reports. Of all direct reports received in that year, 95% were submitted electronically. Sending reports by paper is not actively promoted and this option is only available on request.

The patients' reporting e-form is advertised on the main page of Lareb's website (Dutch version). Patients, or their relatives/caretakers, must choose whether they wish to report an adverse reaction to a medicine or a vaccine. Each report consists of five steps. Help function icons next to the questions guide the patient on how to accurately complete the template. There is a blank space to describe the adverse reaction. Reporters can either upload relevant documents (e.g., prescription, pictures) or send them via email or mail with a reference number. Specific contact details of the healthcare professional are not required but might be asked in subsequent follow ups.

In the last section of the e-form, patients have the option to provide tips on how to improve the reporting form. Reporters are also asked whether they wish to receive a receipt confirmation email with the report summary. Lareb provides individualised feedback in the event of serious reports, in response to a specific question, to issue a recommendation to the patient to visit a doctor, and in relation to reports that may have legal implications.[18]

Statistical summaries of all ADR reports received are available online. Information is listed by brand name or international non-proprietary name. In the past, it was also possible to access anonymised summaries of individual cases, but this information has been removed due to concerns about patient privacy.

Lareb's Board is comprised of 10 members, including two patient representatives. The Foundation works with patient and consumer organisations to promote direct patient reporting. It has also collaborated with non-governmental organisations that manage online registers of medicine users' experiences with medications (www.mijnmedicijn.nl and meldpuntmedicijnen.nl).[v] Specific efforts have also focused on promoting the reporting of over-the-counter (OTC) medicines. In joint campaigns with the Central Bureau for Drugstores, consumers buying OTC drugs were given information leaflets explaining how to report. The campaigns led to a 170% increase in the number of reports on OTC medicines.[19] Additional efforts are needed, however, to increase awareness of spontaneous reporting in the general population. A survey revealed that only 17% of the general public in the Netherlands knew that ADRs could be reported to Lareb.[20] Lack of funding for awareness-raising activities appears to be an issue.

As the World Health Organization Collaborating Centre for Pharmacovigilance in Education and Patient Reporting, Lareb also conducts training courses for staff working in pharmacovigilance and conducts research.

[v] Technical work is underway to re-establish the transfer of information from meldpuntmedicijnen.nl, managed by the Dutch Institute for the Rational Use of Medicine (IVM), to Lareb.

Portugal

The pharmacovigilance system in Portugal was established in 1992. The framework has been updated since then to incorporate subsequent legislative changes. The national pharmacovigilance system is comprised of the Directorate of Risk Management for Medicines (DGRM), the National Authority of Medicines and Health Products (INFARMED) and four regional pharmacovigilance units. Each regional unit is responsible for evaluating ADRs that occur in their territory. The system is coordinated by DGRM.

Direct patient reporting began in 2012 as a result of the new EU pharmacovigilance legislation. INFARMED established a web-based portal allowing patients to report suspected ADRs electronically. They can also submit a paper form or report over the phone.

In 2013, INFARMED received only 50 direct patient reports from a total of 3,461 reports. In 2014, the number of ADR reports increased to 4,618. Of these, 175 had been directly submitted by patients.

To access the e-form on INFARMED's website, reporters must click the 'Portal RAM' box (ADR portal in English) at the bottom of the main page (Portuguese version). There are different tabs at the top of the portal for contacts, general information about pharmacovigilance, questions and answers and 'report reaction'. Before the e-form displays, patients are reminded that they should have the package or product information leaflet with them. The reporting form comprises several steps, but the system does not easily allow reporters to move from one tab to another. The help function did not display correctly. Only 14% (21 out of 154) of direct patient reports to INFARMED were received through the online reporting form in 2014.[21]

For patients wishing to use another method of reporting, a link to a paper form can also be found online. Very little space is provided in the paper form to describe the adverse reaction and report other relevant data (e.g., test results). INFARMED asks patients whether the adverse reaction was communicated to a healthcare professional. If so, they are asked to provide the doctor's contact details.

Reports submitted through the e-form are initially followed up by a confirmation email upon receipt. After validation, INFARMED sends a second email with a unique identification number for the reporter to use in any future contact about the report. Once the pharmaceutical and clinical assessors have evaluated the report, INFARMED sends another email to the reporter with the results of the assessment. The same feedback is provided to reporters who use other reporting means.

To further increase awareness in the general population about patient reporting, INFARMED has developed communication materials and organised informative meetings with patient and consumer organisations. However, according to consumer representatives, more could be done to implement comprehensive public awareness campaigns. INFARMED is also involved in the European Commission project, Strengthening Collaborations in Operating Pharmacovigilance in Europe (SCOPE). INFARMED is one of the seven regulatory agencies that are part of the 'ADR Collection' work group, which aims to provide an overview of national ADR reporting systems to identify best practices and develop a media toolkit to raise awareness of spontaneous reporting.

Consumer organisations can also play an important role in informing the general public on spontaneous reporting. DECO Proteste, the Portuguese consumers' organisation, provides information about the various methods of patient reporting through its magazines and website. The website offers practical information on how to use the 'RAM Portal' and what happens with ADR reports after submission. Consumers are also invited to visit adrreports.eu, the public website for Eudravigilance.

Romania

Romania's National Pharmacovigilance Network was established in 1973. The current system has been in place since 1999 alongside the establishment of the National Agency for Medicines and Medical Devices (NAMMD). Patient reporting to NAMMD was introduced as a result of the new EU pharmacovigilance legislation, which led the amendment of Law 95/2006 on healthcare reform.

The number of ADR reports is increasing every year, but more must be done to encourage spontaneous reporting, particularly direct patient reporting to NAMMD. In 2013, the agency received 295 reports directly from doctors and 1,552 from MAHs. Of those submitted by MAHs, 100 came from patients, 34 from pharmacists, 59 from nurses and the remainder from doctors, including from literature articles.[22]

Since March 2015, a printable ADR reporting form for patients can be found on NAMMD's website. Prior to that, patients had to use the same template as healthcare professionals. An icon on ADR reporting is now displayed on the website's main page (Romanian version). Patients can download a sheet with general information on spontaneous reporting and the ADR reporting form, which must be manually completed and sent by e-mail, mail or fax. Patients have little space to describe the adverse reaction and there are no instructions that help the patient to respond to the questions accurately. Reporters have the option, however, to receive assistance by phone.

Reports from patients and healthcare professionals are kept in the same database, but patients' reports are marked as 'not medically confirmed'. NAMMD asks patients whether the ADR was notified to a healthcare professional and requests permission to contact the doctor for additional information.

The Romanian pharmacovigilance system is being strengthened through the allocation of additional staff. Direct patient reporting is relatively new in the country and NAMMD has started promoting it through presentations at relevant events. Following the launch of the patient ADR reporting form, the Romanian agency organised some roundtable meetings with patient organisations on spontaneous reporting. Participating organisations expressed openness to raising public awareness and promoting the patient reporting form (e.g., by posting it on their websites). Information about these roundtable meetings can be found on NAMMDs website and Facebook page. NAMMD has said it will continue organising such meetings with patient organisations.

The relatively limited experience on patient reporting in Romania may explain why, according to the patient organisation, UNOPA (the Romanian federation representing people affected by HIV/AIDS), the public knows little about it. However, the information campaign launched by NAMMD on ADR reporting amongst healthcare professional and patient organisations can contribute to increased levels of spontaneous reporting in the years to come. UNOPA was one of the organisations participating in roundtable meetings held by the regulatory agency. Information about patient reporting can be found on its website.

Sweden

In Sweden, formal direct patient reporting to the Swedish Medical Product Agency (MPA, Läkemedelsverket) has been possible since 2008. A new system was implemented in October 2013, which replaced two parallel systems for healthcare professional and patient reports and facilitated signal detection.[23] In that year, the MPA received 6,190 ADR reports, of which 18% and 83% were received directly by patients and healthcare professionals, respectively. In 2014, the MPA received 6,933 ADR reports. Of those, 21% were received directly from patients and 79% from healthcare professionals.[vi] [24]

Reporting mechanisms have been improved throughout the years. Patients can report ADRs to the MPA through an e-form or printable form. The e-form is very easy to find; a link is positioned on the main page of the website (Swedish version). Clear instructions with examples on how to complete the template guide the reporter through the process (e.g., "Form and strength: This information can be found on the package – e.g., tablet

[vi] After de-duplication data for 2013 and 2014.

50mg"; "Doses: Specify how much and how often the drug is used – e.g., 2 tablets, 3 times per day or 2 ml per day for 10 days").

Patients can specify in the ADR report whether they informed a healthcare professional about the adverse reaction. Social security numbers are used to facilitate the identification of duplicates. The MPA asks consumers whether they may be contacted for additional information. After the submission, an electronic acknowledgement of receipt is provided with a reference number; however, the MPA does not provide personalised feedback.

Since 2008, the MPA has promoted direct patient reporting with a number of campaigns, including information seminars organised with healthcare professionals. The increase in ADR reports received by the MPA from 2013 to 2014 is believed to be the result of successful information and education campaigns, as well as improved online reporting mechanisms.[25]

IV. Analysis

The new EU pharmacovigilance framework has helped expand spontaneous patient reporting across Europe. Patients and consumers in all Member States can now report ADRs directly to their regulatory authority. In countries that already had established direct patient reporting systems, new elements have been introduced to varying degrees (e.g., improved online reporting tools in Denmark and Sweden); however, these are likely not the result of EU legislative changes. Instead, local stakeholders believe these changes result from the continuous process of monitoring and improvement.

ADR reporting forms for patients could be found on regulatory agencies' websites in all countries examined. Direct online reporting (through an e-form) is generally enabled with few exceptions (i.e., Romania and France). In France, about half of the regional pharmacovigilance centres did not appear to have their own website to report ADRs. Only five were found to allow direct online reporting. This reporting method should be readily available. It can improve reporting effectiveness by incorporating dynamic help functions for more accurate reporting, expediting the process for reporters, and facilitating the readability of reports by assessors.

Electronic reporting should always be complemented with alternative means of reporting (e.g., paper forms, telephone). In general, reporting by phone was not found to be actively promoted by regulatory agencies. Phone numbers were usually provided for additional information on how to report an ADR and to get technical support with electronic reporting. Sending reports by paper was not actively promoted in the Netherlands.

In general, electronic reporting forms were not found to be overly time-consuming. Help function icons beside the questions or sidebars with examples of information that should be reported were found to provide useful guidance on how to complete the e-form accurately. In general, paper forms provide few instructions. This could be easily solved by adding footnotes where space is lacking in the body of the template, or including an additional page with examples.

To facilitate patient reporting and maximise its added value, ADR reporting forms should include layperson language and address the right questions. A specific reporting form for patients, however, was not available in Romania before March 2015. Prior to that, patients had to use a template designed for healthcare professionals. The launch of the new patient ADR reporting can contribute to increased levels of direct patient reporting in the years to come. Whilst all assessed reporting forms provide a text box to describe the adverse reaction, none specifically ask for qualitative data about the impact of the adverse reaction on the patient's daily life. There is, of course, more to ADRs than symptoms, but some patients could think that they are only supposed to provide information about symptoms.

Individualised follow-up information regarding the assessment of the ADR report appears only to be available in the Netherlands, Portugal and in some CRPVs in France (e.g., Toulouse). In the Netherlands, Lareb also provides public access to summary statistics of its ADR database. However, Lareb no longer provides access to anonymised summaries of individual cases due to concerns about patient privacy.

Patient and healthcare professional reports are stored together and the process of handling these two types of reports is similar. To facilitate the de-duplication process, social security numbers are used in Denmark and Sweden to link reports initiated by different sources. ADR report forms in France (ANSM template), Portugal, Romania and Sweden ask patients whether they have informed a healthcare professional about the adverse reaction. In Bulgaria, patients are encouraged to first share their experience with a healthcare professional and to make one report.

The number of ADR reports received from patients by regulatory agencies indicates that the lack of awareness about direct patient reporting is more acute in countries with lesser experience (i.e., Bulgaria, Portugal and Romania). However, lack of awareness amongst the public has also been found to be a problem in countries with greater experience (e.g. Denmark and the Netherlands).

Denmark is a good example of what can be achieved by comprehensive campaigns involving general practitioners, pharmacies and patient organisations, including the provision of support for phone counselling services. According to consumer

representatives, more could be done to implement comprehensive public awareness-raising campaigns in Portugal.

V. Recommendations

The following recommendations are provided to regulatory authorities to strengthen direct patient reporting:

1. Actively promote direct patient reporting through awareness-raising activities, including comprehensive campaigns with patient and consumer organisations and healthcare professionals.

2. Contribute to strengthening the knowledge of patient and consumer organisations about pharmacovigilance (e.g., provide training sessions). Support patient and consumer groups in their role as informers and promoters of direct patient reporting. Enable discussions with these groups on how to improve awareness-raising activities and reporting mechanisms. Conflict of interest situations should be avoided and the responsibility for further information should not be deferred to manufacturers.

3. Make ADR reporting forms easy to find on regulatory agencies' websites. Ideally, there should be an icon on the home page. Provide information sections for citizens with general information about the importance of pharmacovigilance and ADR reporting, how it can be done and the steps of the process.

4. Facilitate effective reporting mechanisms, such as direct online reporting. Alternative means of reporting should also be enabled, particularly those that are most likely to be used by vulnerable populations, like the elderly. This may result in the need to allow reporting by phone, or paper form, which can be returned by mail or fax. Patients should be made aware that they could seek support to complete the reporting form and be given a list of contacts (e.g., patient and consumer organisations, pharmacies). Direct ADR reporting to regulatory authorities through mobile phone applications should be explored; pilot projects can help determine the added value of such tools from quantitative and qualitative perspectives.

5. Ensure that ADR report forms are specifically addressed to patients, contain easily understandable language and questions that allow the added value of patient reporting to be captured. In particular, enable comprehensive reporting of qualitative data about adverse reactions and their impact on patients' daily lives. Provide guidance and examples on how to complete the report accurately. Reporters should have the option to provide feedback on reporting tools' ease of use for improvement.

6. Patients should have the right to receive regular feedback after submitting an ADR report. Individualised feedback can be particularly important for serious ADRs and when reporters ask specific questions. Patients should be informed about the processing of the ADR report and the outcome of the evaluation. They should also receive an overview of similar adverse reactions that have been reported for the medicine. New regulatory safety measures could be notified through a system of collective feedback.

7. Facilitate public access to pharmacovigilance data. National regulatory agencies should set up public interfaces of their ADR databases and provide a general overview of stored ADR reports, including qualitative information (e.g., de-identified summaries of individual cases) to better enable independent assessment. Transparency of clinical data enhances accountability and can strengthen rational use of medicines.

8. Share best practices with Member States on mechanisms for direct patient reporting and information campaigns for raising awareness amongst consumers.

References

[1] European Commission. Strengthening pharmacovigilance to reduce adverse effects. December 10, 2008. Available at http://europa.eu/rapid/press-release_MEMO-08-782_en.htm?locale=en

[2] Prescrire International. ''The reorganisation of European Pharmacovigilance''. 24.157 (2015):50-54

[3] Herdeiro, Maria T et al. "Physicians' Attitudes to Adverse Drug Reaction Reporting. A case control study in Portugal" *Drug safety* 28.9 (2005): 825-833.

[4] Frankenfeld, Christian. ""Serious" and "severe" adverse drug reactions need defining." *BMJ* 329.7465 (2004): 573.

[5] van Hunsel, Florence et al. "The proportion of patient reports of suspected ADRs to signal detection in the Netherlands: case–control study." *Pharmacoepidemiology and drug safety* 20.3 (2011): 286-291.

[6] Avery, Anthony J et al. "Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys." *Health Technology Assess*, 2011;15(20): 1-234

[7] Herxheimer, A, R Crombag, and TL Alves. "Direct f reporting of adverse drug reactions. A twelve-country survey & literature review." *Health Action International Europe.* May 2010.

[8] Herxheimer, A, R Crombag, and TL Alves. "Direct f reporting of adverse drug reactions. A twelve-country survey & literature review." *Health Action International Europe*. May 2010

[9] Directive 2010/84/EU amending as regards pharmacovigilance Directive 2001/83/EC on the Community code relating to medicinal products for human use.

[10] Regulation (EU) 1235/2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products

[11] Prescrire International. '' The reorganisation of European Pharmacovigilance''. 24:157 (2015):50-54

[12] Prescrire International. ''European pharmacovigilance: increasingly outsourced to drug companies''. 23:155 (2014): 302-307.

[13] Danish Health and Medicines Authority. Danish Health and Medicines Authority's annual pharmacovigilance report 2013. Available at: http://sundhedsstyrelsen.dk/en/publications/2014/~/media/8D5A61AE65E84D8BA246A9837B56E39B.ashx

[14] Danish Health and Medicines Authority. Adverse drug reactions reported by consumers in Denmark- compared with reports from health professionals. (2013) Available at: http://sundhedsstyrelsen.dk/en/publications/2014/~/media/B71CB7AF2879471ABE9DCF23BF853B18.ashx

[15] Danish Health and Medicines Authority. Danish Health and Medicines Authority's annual pharmacovigilance report 2013.

[16] Danish Health and Medicines Authority. DHMA Annual Pharmacovigilance Report 2014

[17] Prescrire International. ''The reorganisation of European Pharmacovigilance. 24:157 (2015):50-54.

[18] Härmark L, van Hunsel F, Grundmark B. ''ADR Reporting by the General Public: Lessons Learnt from the Dutch and Swedish Systems.'' *Drug Safety*, 2015 DOI: 10.1007/s40264-015-0264-1

[19] Härmark L, van Hunsel F, Grundmark B. ''ADR Reporting by the General Public: Lessons Learnt from the Dutch and Swedish Systems.'' *Drug Safety*, 2015 DOI: 10.1007/s40264-015-0264-1

[20] Härmark L, van Hunsel F, Grundmark B. ''ADR Reporting by the General Public: Lessons Learnt from the Dutch and Swedish Systems.'' *Drug Safety*, 2015 DOI: 10.1007/s40264-015-0264-1

[21] INFARMED. Sistema Nacional de Farmacovigilância (SNF): Notificações e Casos de RAM - Ano/2014 (2014).

[22] NAMDD activity report 2013. Available at http://www.anm.ro/anmdm/_/RAPORT%20ACTIVITATE/Raport_ANMDM_2013.pdf

[23] Härmark L, van Hunsel F, Grundmark B. ''ADR Reporting by the General Public: Lessons Learnt from the Dutch and Swedish Systems.'' *Drug Safety*, 2015 DOI: 10.1007/s40264-015-0264-1

[24] Medical Products Agency (MPA). Läkemedelsverkets årsredovisning 2014. https://lakemedelsverket.se/upload/om-lakemedelsverket/publikationer/arsredovisning_2014.pdf

[25] Medical Products Agency (MPA). Läkemedelsverkets årsredovisning 2014. https://lakemedelsverket.se/upload/om-lakemedelsverket/publikationer/arsredovisning_2014.pdf