

This chapter represents the core of this study and presents the main findings. The aim of this chapter is threefold. First, it offers in-depth explanations of the adverse drug reaction (ADR) reporting systems, and it describes relevant tasks and actors involved in all six countries under consideration (the United Kingdom, Finland, Poland, France, Portugal and Germany). Second, this chapter presents remaining challenges and best practices for each case as perceived by the interview partners. Third, it provides first recommendations on how to improve the existing systems in order to improve ADR reporting and help ensure public health.

5.1 ADR Reporting in the United Kingdom

5.1.1 The System

The United Kingdom has a long-established system of pharmacovigilance dating back to 1964, when the so-called Yellow Card Scheme was introduced there. Pharmacovigilance in the United Kingdom is based on a centralised system with the Medicines and Healthcare Products Regulatory Agency (MHRA) at its core.

The MHRA is the national competent authority and main regulatory body regarding medicines and pharmacovigilance and is an executive agency of the Department of Health, which is responsible for matters of legislation and finance.

Through the Yellow Card Scheme, a centralised reporting system reports on ADRs which are collected in the MHRA database. With the establishment of regional Yellow Card Centres, an element of decentralisation has been introduced. However, these centres do not play a direct role in the collection and processing of information; they aim to provide advice and training and to raise awareness (cf. below).

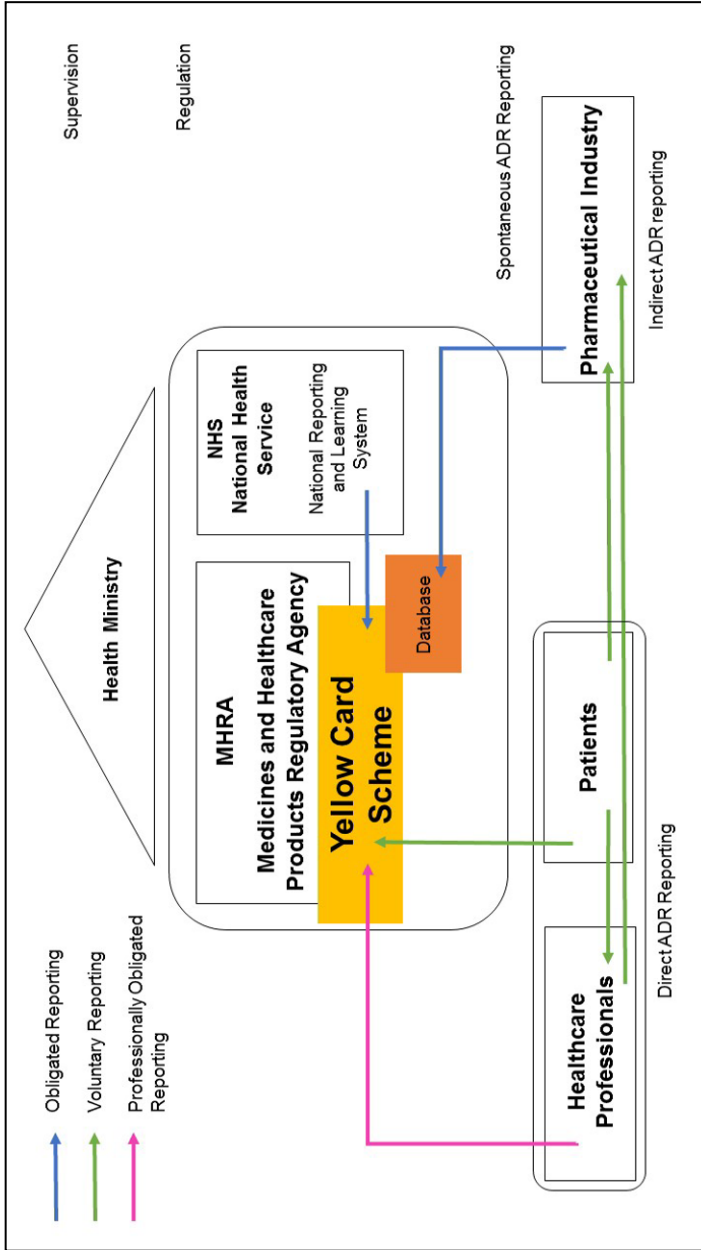


Fig. 5.1 ADR reporting in the United Kingdom (compilation by the authors)

There is no separate system for reporting ADRs arising from biologicals; the Yellow Card Scheme is used for synthetic and biological products alike. This system is shown in Fig. 5.1.

Reporting

In the 1960s, only physicians and dentists were allowed to report ADRs. However, more actors have been included over time. Since the 1990s, additional healthcare professionals (pharmacists, nurses and health visitors) have been allowed to report as well. After a pilot project, patient reporting was first introduced in 2005 and in revamped format in 2008, respectively. Hence, patient reporting in the United Kingdom was introduced before the reform of the EU pharmacovigilance system with Directive 2010/84/EU.

The way the system works is that both healthcare professionals and marketing authorisation holders submit reports to the national competent authority MHRA. Patients can report not only to the MHRA directly, but also to authorisation holders and healthcare professionals.

Healthcare professionals are not legally but professionally obligated to report ADRs and are particularly encouraged to report all serious suspected reactions to established medicines, even if the effects are already well recognised. In addition, they should report the reactions to the MHRA via the Yellow Card Scheme online form, but they can also report them to the marketing authorisation holder.

Moreover, healthcare professionals must report all suspected adverse reactions associated with black triangle products (▼), including non-serious ADRs. In the United Kingdom, all biological medicines are defined as black triangle products. Thus, even though there is no separate system for reporting ADRs related to biologicals, ADRs do receive special attention.

Marketing authorisation holders are legally obligated to report all suspected ADRs they are informed about through reports by healthcare professionals or patients or in the context of post-authorisation safety studies. Marketing authorisation holders process reports from either patients or healthcare professionals in individual case safety reports (ICSRs) and subsequently forward them to the MHRA database. Non-compliance by the industry might lead to sanctions.

Since 2005, patients are also allowed to report ADRs electronically via the Yellow Card Scheme, or by phone or regular mail to the national competent authority MHRA. In 2015, the MHRA even introduced the “Yellow Card App” for smartphones. Additionally, patients can report to healthcare professionals or the pharmaceutical industry, which must transfer the information to the MHRA database.

Furthermore, the National Health Service (NHS), as an active provider of healthcare, has its own database for medical errors and patient safety incidents, i.e. the

National Reporting and Learning System. The NHS and the national competent authority MHRA collaborate closely in order to ensure patient safety. Hence, when the National Research and Learning System identifies an ADR, the NHS forwards the information to the MHRA database.

As indicated by Fig. 5.2, healthcare professionals and marketing authorisation holders submitted roughly the same number of reports, while patient reporting remained at five to 10 percent in previous years.

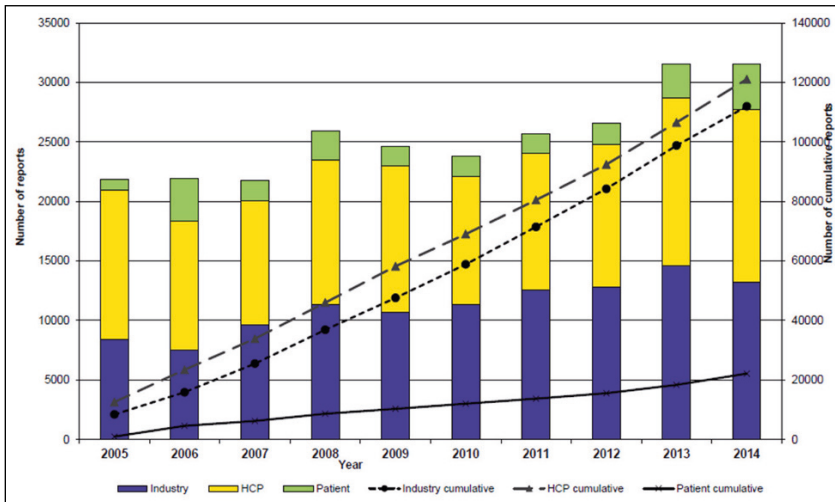


Fig. 5.2 ADR reporting by actors (2005-2014) (provided by the MHRA)

Between 2006 and 2012, there were roughly 25,000 reports per year. However, there have been substantial increases and the number of ADR reports reached 40,000 in 2015. The MHRA credits this to general promotion, integrating electronic reporting forms into clinical IT systems and the work of the Yellow Card Centres (MHRA 2016c Annual Report). In this respect, a significant increase in the reporting of both healthcare professionals and members of the public was noted by the MHRA.

Evaluation and Signal Detection

In contrast to pharmacovigilance systems in the other Member States, there is no comprehensive evaluation of reports before the stage of signal detection in the United Kingdom.

Therefore, the MHRA database consists of individual case safety reports (ICSRs) from the pharmaceutical industry, incidents from the National Report and Learning System, data from clinical trials and all ADR reports submitted via the Yellow Card Scheme. Additionally, the United Kingdom decided to include serious ICSRs from non-EU countries when ADRs relate to medicinal products authorised to be used in the United Kingdom.

As a result, the MHRA has to process extremely high numbers of ADR reports, and thus signal detection was automated. The MHRA database analyses the reports statistically with the Empirical Bayes Geometric Mean (EBGM) method, which is able to identify combinations of drug reactions that have been reported unusually frequently, and a “disproportionality score” is assigned to each combination (Foy 2015; MHRA 2016a).

The MHRA’s Vigilance Intelligence and Research Group meets twice weekly. In the first meeting, all synthetic medicines with alarmingly high disproportionality scores are discussed. In the second meeting, all serious reports regarding black triangle products (▼), i.e. biologicals, are assessed, again indicating that biological medicines receive special attention in the United Kingdom.

If signals are detected in either meeting, both statistical methods and a consultation with the Commission on Human Medicines prioritise further action (MHRA 2016a). This could include deciding to update the product information leaflet, changing the dosage, issuing warnings in periodic drug safety updates or taking the product off the market.

The MHRA has 15 days to report serious cases to EMA.

5.1.2 Perceived Challenges

It is widely assumed in the literature that underreporting is inherent in spontaneous ADR reporting. In the United Kingdom, it is estimated that around 10 percent of all ADRs are reported; yet, the precise number is dependent on a variety of factors and the seriousness of the ADR (see Cousins et al. 2015).

Lack of Awareness

Evidence suggests that the general awareness about pharmacovigilance is very high among healthcare professionals and recent polls show that around 80 percent of general practitioners and pharmacists are able to identify the Yellow Card Scheme as the ADR reporting scheme (see Cousins et al. 2015). However, public awareness regarding the Yellow Card Scheme is comparably low. A survey revealed that less than 10 percent had heard of the scheme (Fortnum et al. 2012). This number seems

to be fairly constant in recent years (Foy 2015) which is surprising, given that patient reporting had already been introduced in the United Kingdom in 2005. Yet, despite the long-established system of pharmacovigilance, a significant percentage of the general public seems to be unaware of it.

The interviews corroborate this evidence, pointing to a general patient unawareness regarding pharmacovigilance in general and ADR reporting in particular. Although the national competent authority MHRA is already engaged in various information campaigns (cf. below), public awareness and the knowledge of ADR reporting must be further enhanced. While the majority of people have heard of the Yellow Card Scheme through pharmacists, advertising in non-medical facilities such as public libraries has been suggested (Fortnum et al. 2012). One example of a more target-oriented approach would be to have healthcare professionals hand out information brochures when prescribing or administering drugs.

Recommendation: Awareness Raising – Patients

In order to tackle patient underreporting, European, national and regional authorities should invest in awareness-raising campaigns to increase the public knowledge about pharmacovigilance and reporting of ADRs. Authorities should raise awareness in the short term through various means of communication (e.g. websites, social media, leaflets) as well as in the long term through cooperation with schools to educate future generations.

Moreover, Member States should offer a wide range of possible communication channels, including web-based as well as paper-based formats. Both formats should be designed to be as user-friendly as possible. For web-based formats, IT solutions should be developed to guide patients through the format and to ensure the completeness of reports. All formats should be accompanied by accessible manuals written in layman's terms.

In addition to measures for facilitating patient reporting, national and regional competent authorities should also establish mechanisms to provide mandatory feedback to reporting patients.

However, unawareness is not only a challenge regarding patients, but also healthcare professionals, who often underestimate the importance of pharmacovigilance. Moreover, there seems to be a lack of sensitivity among healthcare professionals that non-serious and especially recurrent ADRs must be reported for an ongoing and expedient evaluation.

One respondent even indicated that some healthcare professionals appear to refuse engaging in ADR reporting because they consider product safety not the responsibility of practitioners but the industry producing the medications.

Recommendation: Awareness Raising – Healthcare Professionals

In order to tackle underreporting by healthcare professionals, national authorities and healthcare institutions should invest in awareness-raising campaigns to increase professional knowledge about pharmacovigilance and to sensitise relevant actors about its particular importance to ensure public health.

This lack of awareness should not come as a surprise, though, when considering academic education in this field (Smith and Webley 2013). In the United Kingdom, there is no nationwide curriculum covering pharmacovigilance in relevant studies. In undergraduate pharmacy degree programmes, pharmacovigilance is compulsory, although the amount of time dedicated to it is rather limited. And while pharmacy students discuss pharmacovigilance only sporadically, it is rather neglected for medical students. Hence, there are no mandatory classes on either pharmacovigilance or ADR reporting. It is argued that particularly causality assessment should be a basic subject in all medical schools (Edwards 2012).

Moreover, several interview partners indicated that there is not enough post-graduate training to keep up with the changing demands. They also lamented that the role of EMA and the impact of EU pharmaceuticals regulation on national pharmacovigilance is neglected (Smith and Webley 2013). We can thus assume that such neglect does not facilitate general awareness among healthcare professionals implementing EU regulation at the national level.

Awareness raising is therefore an issue in the long run in order to internalise the fact that all ADRs need to be reported for effective signal detection. Both pharmacy and medical academic programmes should include mandatory classes emphasizing the relevance of pharmacovigilance and imparting information on the practical management of ADR reporting. Additionally, the national competent authority and related research institutions should offer respective post-graduate training, constantly ensuring that practitioners understand the subject's significance and thus notify relevant actors about changing circumstances.

Recommendation: University and Post-University Training

In order to improve both the quantity and quality of ADR reports, university classes about the importance of pharmacovigilance and the need for constant ADR reporting should be mandatory for every medical and pharmacy student.

In addition, European, national or regional authorities should organise advanced post-graduate training on a regular basis to ensure that healthcare professionals acquire the necessary skills to cope with the complex task of ADR reporting.

Complexity of ADR Reporting

For biological medicines, the problems are even more severe. Even though United Kingdom law prescribes that batch numbers ought to be displayed on each package, the actual reporting of the number remains rather challenging. Healthcare professionals usually struggle with their daily routines in hospitals and do not have the time they would need to find and report the respective batch numbers. For patients, reporting the batch number is generally impossible because biologicals are generally administered directly in hospital settings, and therefore patients rarely see the respective packaging.

Recommendation: Facilitate Reporting Processes

Healthcare institutions, in line with the general health policies of their Member State, should facilitate reporting of ADRs through streamlined internal processes.

Lack of Interconnectivity

Several respondents addressed another concerning challenge, namely the use of two different electronic systems, i.e. one for managing patient data and one for reporting ADRs. This lack of connectivity between different IT systems renders the process of ADR reporting cumbersome and time-consuming and thereby severely impedes comprehensive reporting by physicians.

Note that the national competent authority MHRA already integrated the Yellow Card Scheme into two hospital systems (cf. below). This has two major advantages. First, it simplifies the reporting process because the system is able to complement large amounts of data automatically. Second, the system reminds healthcare professionals to report ADRs and makes non-reporting a more conscious decision.

Therefore, the integration of the Yellow Card Scheme into all hospital and general practitioner software programmes should be pursued further.

Recommendation: Harmonisation of IT Systems

In order to cope with information overload and to facilitate the process of submitting ADR reports, national and regional competent authorities should improve the interconnectivity of different IT systems, as for instance those of general practitioners, hospitals, pharmacies and the national competent authority's ADR reporting system.

5.1.3 Perceived Best Practices

In the United Kingdom's pharmacovigilance system, three best practices have been identified: active use of social media for awareness raising, interconnectivity regarding the Yellow Card Scheme and strong cooperation with other institutions.

Awareness Raising

The MHRA established five regional Yellow Card Centres to further promote the Yellow Card Scheme. These centres aim to raise awareness regarding ADR reporting and to improve communication between healthcare professionals and patients. In order to reach out to patients, the MHRA publishes an electronic newsletter called Drug Safety Update for interested patients.

The most important measures to date are as follows:

- In March 2013, the Yellow Card Centre of Wales launched the so-called "Yellow Card Hospital Champion Scheme" in order to increase awareness and provide further incentives for healthcare professionals to report (cf. Box 5.1).
- In 2014, a new Yellow Card website was launched as a single point of access to the reporting scheme, yielding an increase in the number of reports (MHRA 2016).
- In 2015, the 50th anniversary of the Yellow Card Scheme was celebrated with special events being held. The MHRA expects that these activities will bear fruit in the future due to systematic and cultural change regarding ADR reporting (MHRA 2016).
- In 2015, the MHRA launched the Yellow Card App (cf. Box 5.2) in order to offer a platform for information and further simplify patient reporting. Users of the smartphone app are able to create individual watch lists to receive official information and alerts about medicinal products that are relevant for them.

Furthermore, the MHRA is considerably engaged in awareness raising via social media, e.g. Facebook and Twitter. The hashtag *#ThinkPatientSafety*, for instance, is used to spread news, concerns or information via Twitter. Additionally, the MHRA not only uses social media to spread information, but also uses it as a source for signal analysis. By searching for specific keywords, statistical MHRA programmes are able to identify posts resembling ADR reports.

Although some respondents indicated a lack of sufficient pharmacovigilance training for practitioners, the MHRA is not inactive in this respect. For instance, it offers extensive guidance on pharmacovigilance and ADR reporting on its website, including free e-learning modules and particular courses for pharmacists and nurses to improve their pharmacovigilance skills. The MHRA also publishes general information about medical safety issues for all healthcare professionals as well as specific information for different specialist groups, if necessary.

Box 5.1 Best Practice: The Yellow Card App

The MHRA's Yellow Card App was introduced in 2015 as a supplement to the existing one-stop website and allows patients and healthcare professionals to directly report ADRs to the Yellow Card Scheme. The app was created in collaboration with the Innovative Medicines Initiative WEB-RADR project and is free to use for everyone who has iOS and Android. Besides ADR reporting, users can select specific medicines or vaccines to track and receive related news and alerts. More precisely, the app enables users to (1) create a watch list of medications in order to receive official news and alerts, (2) view numbers of Yellow Cards received by MHRA for medicines of interest and (3) receive immediate responses that a Yellow Card has been accepted (MHRA, iTunes store).

Interconnectivity

To begin with, most respondents are very satisfied with the MHRA's Yellow Card Scheme. It enables all actors to report ADRs and facilitates the central collection of reports, and the MHRA has already integrated the electronic Yellow Card Scheme into two out of five general practitioner software programmes. This profoundly simplifies the ADR reporting process, because physicians and pharmacists do not have to enter the relevant information twice. Additionally, this step is likely to further increase the number of ADR reports submitted by practitioners. Each time healthcare professionals intend to enter the termination of a certain medicine into the system, there will be a direct request about whether an adverse event ought to

be reported. Thus, the awareness about the need to report ADRs is increased and the decision not to report becomes much more conscious.

Compared with ADR reporting in other European countries, our respondents pointed out that the United Kingdom does not have problems concerning data duplication. The MHRA has a special duplication detection programme which is able to identify reports that were submitted twice.

Box 5.2 Best Practice: Yellow Card Hospital Champion Scheme Wales

In 2011-2012, the number of Yellow Cards submitted in Wales to the MHRA (Medicines and Healthcare Products Regulatory Agency) fell by 26 percent, i.e. the lowest annual number from Wales in the past 10 years. Reports submitted by hospital pharmacists – before the leading group of reporters – fell by 37 percent as compared with the previous year. Similarly, reports from hospital physicians fell by 24 percent over the same period.

As a reaction, the Yellow Card Centre Wales (YCC Wales) submitted a proposal to the All Wales Chief Pharmacist Committee recommending the introduction of a Yellow Card Hospital Champion Scheme as an attempt to improve declining reporting rates amongst hospital-based reporters.

All health boards in Wales were asked to nominate a pharmacist or pharmacy technician as their “Yellow Card Champion”. All 13 champions received training on the Yellow Card Scheme’s background, ADRs and their classification, how to complete a Yellow Card, and their new role. They also attended a workshop on how to overcome barriers to completing a Yellow Card. In addition, during a 12-month period, YCC Wales sent them regular e-mails outlining the latest pharmacovigilance news. Altogether, 438 additional healthcare professionals received training on the Yellow Card Scheme at 38 sessions.

In 2013-2014, the Wales region collected 1,177 reports of suspected ADRs, an increase of 81 percent from 2012-2013. More precisely, reports from hospital pharmacists rose by 189 percent, which represents the highest number of reports ever submitted since they have been able to report via the Yellow Card Scheme. Hence, the Yellow Card Hospital Champion Scheme has been extraordinarily efficient and enabled the YCC Wales to reach a wide audience across all health boards in Wales.

Cooperation

ADR reporting in the United Kingdom is based on the collaboration of all pharmacovigilance actors, including regulatory authorities and public and private organisations, including patients' organisations. The collaborative approach is expected to facilitate awareness and learning, and it has been suggested that it could serve as a template for other countries (Cousins et al. 2015).

Moreover, the United Kingdom is among the six Member States leading the main work packages of the SCOPE implementation project, particularly leading the topics in the work packages on ADR collection, signal management, quality management systems and risk communications (MHRA 2016). Taking steps in this direction – having both healthcare professionals and patients in mind – seems vital in order to address challenges relating to the underreporting of ADRs (Edwards 2012).

The steps taken in the United Kingdom are specifically geared towards medication errors, which are included in ADR reporting since the reform of the EU pharmacovigilance system. In this respect, large healthcare providers are now required to have medical safety officers (MSOs) and medical device safety officers (MDSOs). These MSOs or MDSOs are obligated to constantly improve the medication error-reporting system in their respective organisations and to act as the main contact for NHS England and the MHRA.

These MSOs and MDSOs are automatically members of the newly founded National Medication Safety Network which was set up by MHRA and NHS England; this network is a forum for discussing potential and recognised safety issues and identifying trends and actions to enhance the safe use of medicines.

Furthermore, the MHRA organises several projects in collaboration with the NHS England in order to improve patient safety. Among others, they jointly publish “Patient Safety Alerts” to inform the public, healthcare professionals and healthcare providers about current safety issues. Recently, the MHRA has also emphasized the reporting of ADRs observed in children and young people (MHRA 2016).

The Commission on Human Medicine is an advisory non-departmental public body which works independently and is only accountable to the Department of Health. One of the Commission's sub-committees is the Expert Advisory Group for Pharmacovigilance, whose task, *inter alia*, is to issue recommendations and advice on medicinal products to the MHRA.

5.2 ADR Reporting in Finland

5.2.1 The System

The Finnish pharmacovigilance system, which was established in 1982, is headed by the Ministry of Social Affairs and Welfare. The Ministry sets the legal guidelines but is not actively involved in the system of reporting adverse drug reactions (ADRs). The key actor in the Finnish ADR reporting system is the Finnish Medicines Agency (*Lääkealan Turvallisuus – Ja Kehittämiskeskus*, or Fimea) and it collects and evaluates the ADR reports it receives from healthcare professionals, patients, the pharmaceutical industry and the National Institute for Health and Welfare (*Terveyden Ja Hyvinvoinnin Laitos*, or THL) and forwards them to the European level.

As indicated in Fig. 5.3, the Finnish ADR reporting system differentiates between synthetic medicines and vaccines; a detailed account of this framework is also described below.

Reporting

The Finnish Medicines Agency emphasizes in its guidelines that any ADR ought to be reported to the national competent authority. However, Fimea also explicitly urges reporting serious and unexpected reactions (Fimea Administrative Guideline 2/2013). Each ADR report submitted by healthcare professionals, patients or marketing authorisation holders should include the following information:

- Description of the ADR
- The suspected drug or medication involved
- Drug user data
- The course of the event
- Information about the person reporting the adverse reaction
- The product trade name and the batch number of biological products

Hence, reporting both the trade name and batch number for biologicals is explicitly required by the Finnish authorities.

Reporting by healthcare professionals. In Finland, “persons authorised to prescribe or supply drugs *are advised* to report to Fimea any adverse reaction they find or suspect in association with the use of drugs” (Fimea Guideline 2/2010, emphasis added). Thus, healthcare professionals are not legally required to report ADRs related to synthetic products, although they are legally obligated to report ADRs resulting from vaccines.

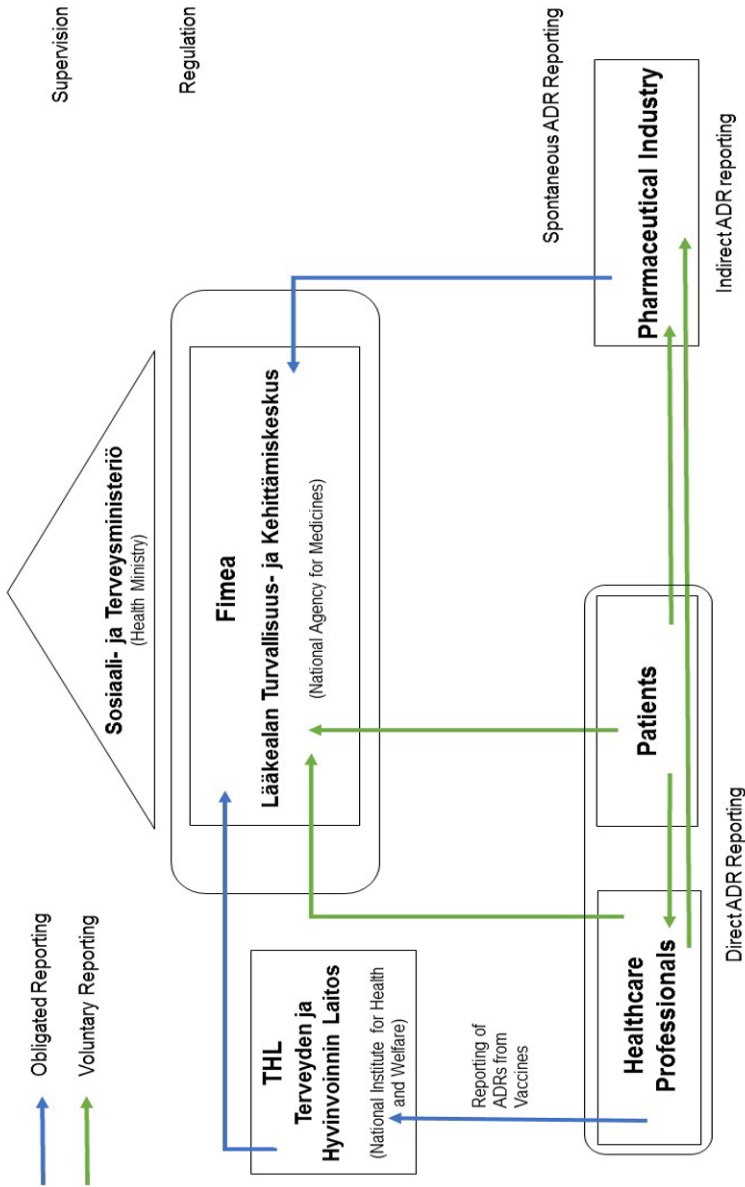


Fig. 5.3 ADR reporting in Finland (compilation by the authors)

ADRs of synthetic products should be reported to Fimea. Physicians and pharmacists can report via regular mail or download an online form on Fimea's homepage and then submit the completed form there. In order to report electronically, however, healthcare professionals need access to FIMnet; physicians and pharmacists receive their FIMnet user ID through membership in their respective professional associations.

Since 2012, nurses are also allowed to report. Yet, unlike physicians and pharmacists, they do not have access to FIMnet. Instead, they must print out an online form and then submit it via regular mail.

As already described above, ADRs caused by vaccines are treated differently. According to the Finnish Communicable Diseases Act (583/1986, 12b), "Healthcare professionals *must* notify all identified or suspected adverse effects of a vaccine that have come to their knowledge" (emphasis added). Here, instead of being advised to contact Fimea, healthcare professionals are required to inform the National Institute for Health and Welfare and the institute subsequently sends the respective data to Fimea.

Besides reporting to the national competent authority, all healthcare professionals, i.e. physicians, pharmacists and nurses, are allowed to inform the respective marketing authorisation holder about ADRs. The marketing authorisation holders are then legally obligated to forward the reports to Fimea. In the case of non-compliance, marketing authorisation holders risk the launch of infringement procedures or the imposition of sanctions. Thus, while healthcare professionals are only legally obligated to report ADRs related to vaccines, the pharmaceutical industry is under the obligation to report all adverse events to Fimea.

Patient reporting. Since the transposition of Directive 2010/84/EU in 2012, patients are also allowed to report ADRs. Similar to nurses, they cannot report electronically but need to contact Fimea via regular mail. In addition, patients can consult with their treating physician, pharmacist or the respective marketing authorisation holder in order to notify them about suspected ADRs. In fact, in their "Guidelines on Adverse Drug Reporting", Fimea specifies that it prefers that patients get in touch with healthcare professionals before sending reports directly to the national competent authority, arguing that reporting cannot be considered a substitute for consulting an expert (Fimea Guideline 2/2010).

Fig. 5.4 indicates that in 2015 Fimea received most reports by physicians, i.e. 1,230. Physicians especially report reactions to new medicines and those that are under special surveillance (e.g. black triangle products (▼)). In comparison, nurses filed 700 reports, which is an impressive number when taking into account that they must always jump through the bureaucratic hoops of printing the forms and sending them by regular mail. Pharmacists and patients submitted 270 and 400

reports, respectively. Thus, in 2015 a total number of 2,600 reports were submitted to Fimea (excluding reports by marketing authorisation holders).

Evaluation and Signal Detection

All reports received by Fimea are entered into the national Adverse Reaction Register. The data is coded by specialists and then medically evaluated by healthcare professionals and a database. Finally, after evaluation, Fimea forwards the details of all ADR reports via regular mail to the respective marketing authorisation holders, EMA and the WHO.

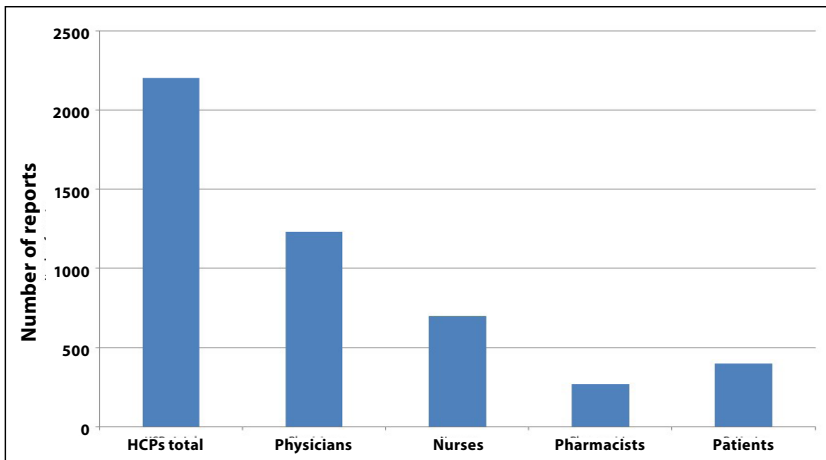


Fig. 5.4 ADR reporting by actors in 2015 (provided by Fimea)

5.2.2 Perceived Challenges

Several challenges have been identified by our interviewees, especially regarding Fimea's decision-making power, the actors who are able to report and the connection between different healthcare IT systems.

First, some respondents mentioned that they consider Fimea's dominance in the Finnish pharmacovigilance system problematic. Even though the agency is officially operating under the Ministry of Social Affairs and Welfare, it is *de facto* independent.

Thus, the result is that only very few people are responsible for making all decisions regarding pharmacovigilance and ADR reporting without elaborate supervision.

Lack of Awareness

Generally, our respondents were rather satisfied with the quantity of reports submitted to Fimea. Some of them, however, indicated that healthcare professionals are too focused on reporting serious and new ADRs. Recurrent and non-serious ADRs, they claim, are largely neglected and usually unrecorded.

Recommendation: Awareness Raising – Healthcare Professionals

In order to tackle underreporting by healthcare providers, national authorities and healthcare institutions should invest in awareness-raising campaigns to increase professional knowledge about pharmacovigilance and sensitise relevant actors about its importance to ensure public health.

Additionally, and considering Fimea's particular emphasis on the reporting of serious ADRs, reducing this emphasis from the guidelines on ADR reporting should be considered. Instead, more prominence should be given to reporting all ADRs, including recurrent and non-serious reactions.

Furthermore, our respondents were divided on the particular importance Fimea assigns to physicians and pharmacists, namely the only actors in the Finnish ADR system who are able to report electronically. Both patients and nurses have to resort to regular mail in order to report ADRs. This was perceived as rather unconstructive by several interviewees because nurses are particularly well trained regarding medication and identifying potential ADRs. Thus, *prima facie* there is no reasonable explanation why nurses are excluded from reporting electronically. Additionally, physicians are usually rather overworked which might render them unwilling to engage in ADR reporting. An additional group of reporters would presumably facilitate the process for all actors engaged.

Supposedly, this issue can be traced back to a more cultural explanation, i.e. a top-down relationship between physicians and nurses which has been customary in Finland for generations. In the Finnish healthcare system, physicians are still perceived as the most relevant actors and this status considerably impedes cooperation with other healthcare professionals. Thus, facilitating ADR reporting for nurses without medical confirmation from physicians would contradict the Finnish top-down relationship and impair the perceived “dominant” status of physicians.

Recommendation: Facilitate Reporting by Nurses

The prestige and perceived infallibility of physicians hinders the development of the Finnish pharmacovigilance system. Thus, cultural changes are necessary to adjust the level of competence and strengthen the appreciation of nurses to improve the process of reporting. The working relationship should be considered as cooperative rather than competitive. Nurses should therefore be enabled to report electronically, as they are sufficiently educated and would significantly reduce the duties and workload of physicians.

Yet not only nurses are impeded from reporting, but also patients are impeded; they have to go through the bureaucratic hurdles of searching, printing and mailing a reporting form to Fimea instead of using an electronic form. Accordingly, Finnish patients need to be very determined if they want to report an ADR to the national competent authority.

Despite this, most of our Finnish interview partners strongly support this method. They contend that reports submitted by physicians and pharmacists are of better quality regarding both completeness and content, while the majority of consumer reports include non-serious or already-listed events which these partners consider irrelevant from a signal detection point of view. Hence, impeding patient reports has been a conscious decision and is not perceived as a challenge by the relevant actors in Finland.

However, what is considered problematic is that patients are not informed about the possibility to report at all. Even if Fimea prefers not to be directly contacted by patients, the public ought to be informed about the possibility to report via consulting physicians and pharmacists.

Recommendation: Awareness Raising – Patients

In order to tackle underreporting by patients, Fimea, the national competent authority, should invest in awareness-raising campaigns to increase the public knowledge about pharmacovigilance and reporting of adverse drug reactions.

Authorities should raise awareness in the short term through various means of communication (e.g. websites, social media, leaflets) as well as in the long term through cooperation with schools to educate future generations.

Moreover, Member States should offer a wide range of possible communication channels, including web-based and paper-based formats. Both types of formats

should be designed to be as user-friendly as possible. For web-based formats, IT solutions should be developed to guide patients through the format and to ensure the completeness of reports. All formats should be accompanied by accessible manuals written in layman's terms.

Lack of Interconnectivity

ADR reporting for healthcare professionals has been identified as very time-consuming, particularly because there is no IT connection between Fimea's ADR reporting system and the various systems recording patient data. Therefore, our respondents regard more IT connectivity between different healthcare systems as a necessary step to facilitate ADR reporting. Thus, although most healthcare professionals are aware of the importance of reporting, they are impeded from doing so by the rather cumbersome reporting system.

However, it should be noted that connecting reporting systems with systems storing patient data is currently rather challenging in Finland. The responsibility to organise healthcare services is in the hands of 300 municipalities. Because each municipality individually decides which patient record system to use, there are numerous systems for recording patient data which considerably exacerbates their connection and the connection to Fimea's ADR reporting system.

In the years to come, the Finnish authorities plan to implement a significant healthcare reform aiming to transfer responsibilities from the municipal level to the regional level. Our respondents expect that afterwards the quality of patient record systems is likely to increase and render the connection to ADR reporting systems easier.

Recommendation: Harmonisation of IT Systems

In order to cope with information overload and to facilitate the process of submitting ADR reports, national and regional competent authorities should improve interconnectivity of IT systems, including those of general practitioners, hospitals, pharmacies and the national competent authority's ADR reporting system.

5.2.3 Perceived Best Practices

Awareness Raising

The importance of reporting ADRs is mainly accepted by physicians and pharmacists in Finland, even though it is not always easy for them to integrate ADR reporting into their daily working routine.

This can be mainly attributed to a very elaborate education system for healthcare professionals regarding pharmacovigilance. Pharmacovigilance and ADR reporting are part of the mandatory curriculum of both physicians and pharmacists. Moreover, pharmacists who are in contact with patients are required to have more advanced university degrees. Less-educated people are not allowed to work at the counter or to have direct contact with patients and are thus not allowed to report.

Additionally, Fimea offers voluntary advanced training for physicians, nurses and medical students, for example at the HUS hospital in Helsinki. During those training sessions, current trends, ADR reports and signals are thoroughly discussed, leading to high-quality reports.

Reporting of Batch Numbers

ADR reports related to vaccines need to contain not only the brand name, but also the product's batch number. Interestingly, there are barely any problems concerning missing information. As Table 5.1 reveals, most vaccines that have been in the register in 2015 have been identified by their batch number.

Tab. 5.1 How vaccines are identified (provided by THL) (in percent)

	2012	2013	2014	2015
Vaccines identified	98.7	99.1	99.4	99.7
...by batch number	93.9	95.4	96.3	97.2
...by trade name	3.8	3.0	2.9	2.2
Vaccines <i>not</i> identified	1.3	0.9	0.5	0.3

Interconnectivity

Finally, another positive example is the electronic connection between the IT systems of physicians and pharmacists. This IT connectivity allows physicians to ensure that patients pick up the prescribed drugs at the pharmacies. Even though this connectivity could be further improved, it is a promising starting point that should be considered by other pharmacovigilance systems across the EU.

5.3 ADR Reporting in Poland

5.3.1 The System

The Polish health ministry, although responsible for the health system's financing and its resources, only fulfils a supervisory role in the ADR reporting scheme and is not involved in its daily routines.

The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych, or URPL) is the Polish national competent authority for the reception and evaluation of all submitted ADR reports. Moreover, the URPL is also responsible for forwarding the relevant reports to European and international databases. It is affiliated with the national health ministry but acts largely independently from it. The URPL is also responsible for educating and training healthcare professionals as well as supervising the pharmaceutical industry. In addition, the URPL informs health professionals about new developments in pharmacovigilance and issues warnings. Because it is technically and professionally competent, it is able to influence political discussions on pharmacovigilance and initiates reforms in close cooperation with the health ministry.

Fig. 5.5 illustrates ADR reporting in Poland.

Reporting

Reporting by healthcare professionals. Healthcare professionals, including not only physicians, pharmacists and nurses, but also dentists, nurses, midwives, laboratory diagnosticians, paramedics and pharmaceutical technicians, are legally obligated to report any ADRs; however, there are no anticipated penalties for not doing so. Healthcare professionals must complete reports and submit them either to the national competent authority URPL or to the marketing authorisation holders in question. Moreover, they need to act as contact people for further questions and must provide additional information if required. Reports can be submitted by e-mail, fax, through regular mail or online.

Reporting by marketing authorisation holders. The pharmaceutical industry, which includes the marketing authorisation holders as well as the medicinal product manufacturers, is also legally obligated to submit reports on ADRs to the URPL. However, in contrast to healthcare professionals, actors in the pharmaceutical industry face non-reporting penalties ranging from paying severe fines to imprisonment.

Patient reporting. The patients, in contrast to the two former actors in the system, can submit their reports voluntarily and have three reporting options. They can either inform a healthcare professional (mostly the responsible doctor or pharmacist)

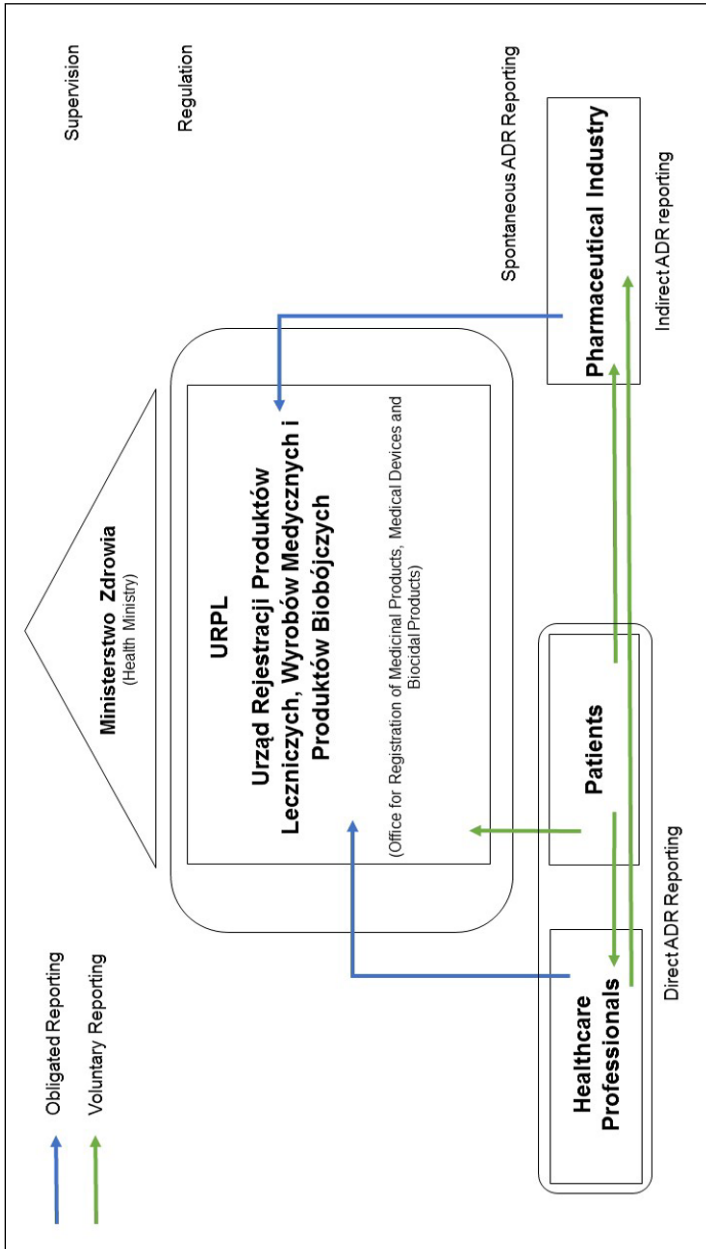


Fig. 5.5 ADR reporting in Poland (compilation by the authors)

or the marketing authorisation holder in question. Moreover, the patient also has the option to report the ADR directly to the URPL office. The report can be submitted by e-mail, fax, through regular mail or online.

Evaluation and Signal Detection

The national competent authority URPL receives the ADR reports from patients, healthcare professionals and the pharmaceutical industry alike and carries out the causality assessment of the reported incidents, evaluating them scientifically in order to detect signals. The agency is also able to contact the reporters for additional questions or to fill in missing information. Once the report is completed and scientifically evaluated, it is forwarded to EudraVigilance and the database of the WHO. Moreover, the agency sends feedback to the reporters.

The ADR reporting scheme in general does not differentiate between biological and non-biological medicines. However, there is one exception to this rule: Vaccines and possible negative side effects stemming from vaccinations are treated in a separate system. In Poland, vaccines are administered by healthcare professionals mostly working in centres responsible for public health issues. Therefore, the majority of the vaccines are given by personnel who deal with vaccines on a daily basis and are both well-informed about possible negative side effects and well-trained to identify possible symptoms. If any ADR is detected, a report is submitted to the responsible Regional Sanitary Board, which is obligated to send a copy of the report to the URPL. In the case of serious ADRs, the Regional Sanitary Board has to inform the State Sanitary Inspectorate which in turn forwards the report to the Chief Sanitary Inspectorate (c.f. Fig. 5.6).

5.3.2 Perceived Challenges

One of the challenges of the Polish pharmacovigilance system is underreporting, although the overall reporting quality is perceived as being good. A number of reasons for the non-reporting of ADRs have been identified and are discussed in the following paragraphs.

Lack of Awareness

Lack of time and awareness, and the fact that the reporting procedure is perceived as being complex and burdensome, lead to non-reporting among healthcare professionals. Moreover, a strong hierarchical order within hospitals, which is part of the Polish social culture, further impedes efficient reporting. There is the

widespread misconception that ADRs only occur in the case of medication errors, and thus healthcare professionals are afraid of damaging their own reputations by reporting ADRs. Medical supervisors and management boards are also considered to be rather restrictive about reporting adverse reactions, trying to avoid reports because others' possible misbehaviour medical errors could be exposed, possibly leading to legal consequences such as claims for damages.

Recommendation: Awareness Raising – Healthcare Professionals

In order to tackle underreporting by healthcare providers, national authorities and healthcare institutions should invest in awareness-raising campaigns to increase professional knowledge about pharmacovigilance and sensitise relevant actors about its particular importance to ensure public health.

Additionally, training should include practical and legal counselling in order to alleviate the fear of litigation. While respecting national diversity in health-related and legal terms, it is important to recognise that fault-based systems are a significant impediment to ADR reporting. A general and cautious recommendation would be to enable healthcare professionals to report ADRs without fear of liability. This could be pursued not only by practical and legal counselling for healthcare professionals, but also by legal means through strengthening confidentiality or setting up compensation schemes for patients' claims.

The Polish pharmacovigilance system faces the insufficient education of professionals on the topic, because pharmacovigilance is not taught in a coordinated manner at the medical and pharmaceutical faculties at the country's universities. Instead, education and training for students remain dependent on the personal engagement of single professors. A systematic organisation for training is also lacking for healthcare professionals. In addition, the options for continuous training and professional development programmes are very limited.

Recommendation: University and Post-University Training

In order to improve both the quantity and quality of ADR reports, university classes about the importance of pharmacovigilance and the need for constant ADR reporting should be mandatory for every medical and pharmacy student.

In addition, the URPL should organise advanced post-graduate training on a

regular basis to ensure that healthcare professionals acquire the necessary skills to cope with the complex task of ADR reporting.

The lack of a sound academic and professional network of pharmacovigilance in Poland is also perceived as a challenge to the system. Although a number of institutes and organisations are engaged in the national pharmacovigilance system and research in this field, there is only a very limited, informal exchange of information and study results. Experience and new insights can get lost because of the lack of academic and professional interconnections.

Patients are not sufficiently educated on pharmacovigilance and know very little about the possibilities to report ADRs. Although first steps have been taken to educate the public about pharmacovigilance and adverse events (cf. Box 5.3), many gaps remain. Moreover, better-educated patients can also possibly monitor healthcare professionals and motivate them towards more active ADR reporting. The patients' advantage is that the repercussions of the hierarchical hospital system and possible professional consequences do not affect them.

Recommendation: Awareness Raising – Patients

In order to tackle underreporting by patients, the URPL should invest in awareness-raising campaigns to increase the public knowledge about pharmacovigilance and the reporting of ADRs.

Authorities should raise awareness in the short term through various means of communication (e.g. websites, social media, leaflets) as well as in the long term through cooperation with schools to educate future generations.

Moreover, Member States should offer a wide range of possible communication channels, including web-based and paper-based formats. Both web-based and paper-based formats should be designed to be as user-friendly as possible. For web-based formats, IT solutions should be developed to guide patients through the format and to ensure the completeness of reports. All formats should be accompanied by accessible manuals written in layman's terms.

Incomplete Reports

The Polish pharmacovigilance scheme is relatively inexperienced in tracking and using biologicals. Because the Polish pharmaceutical industry is focused on producing generic drugs, professionals and also predominantly the national competent

authorities are rather inexperienced in monitoring and supervising biological medicines. Hence, the ADR reporting scheme does not differentiate between biological and non-biological medicines, except for vaccinations. Thus, not only risks, but also benefits of biological medicines can be underestimated and warning signs can be overlooked due to inexperience in the field. Moreover, these both lead to problems in ADR reporting. Due to the relative inexperience with biologicals and a lack of training, batch numbers are not coherently reported and traceability is hampered.

Recommendation: Training on Biological Products

European, national or regional authorities should organise advanced post-graduate training on a regular basis to ensure that healthcare professionals acquire the necessary skills to cope with the complex task of ADR reporting.

In order to tackle underreporting of batch numbers and thereby facilitate the correct and timely traceability of biologicals, healthcare professionals should receive additional training to both increase awareness about the particular relevance of ADR reporting related to biologicals and to acquire the necessary skills to do so.

Budgetary Constraints

The national competent authority URPL has very limited personnel capacities and limited financial resources which both restrain its scope of actions; each year, the number of submitted reports increases while the workforce remains the same. Hence, reports cannot be evaluated as fast as would be desired. In addition, ADR reporting by telephone cannot be done because it would take too much time.

Recommendation: Sufficient Financial Means for Relevant Actors

National and regional competent authorities working under the auspices of national ministries should be endowed with sufficient financial means to fulfil their functions. Likewise, healthcare institutions should be endowed with sufficient means. Sound finances enable healthcare institutions to rely on a stronger workforce which reduces the workload of individual healthcare professionals and increases the possibility of extended the reporting of ADRs.

5.3.3 Perceived Best Practices

Awareness Raising

The URPL aims at spreading information and raising awareness in the general public, not only to educate patients, but also to reach healthcare professionals. The agency uses different social media accounts (cf. Box 5.3), and has produced two animated movies (URPL 2016) which explain how to report ADRs and offer training for professionals.

Box 5.3 Best Practice: URPL on social media

The Polish URPL is very active on social media with a Twitter and Facebook account as well as a YouTube channel. The authority posts news, interesting insights and information on pharmacovigilance, among other URPL topics. It uses the hashtag #safedrug to promote knowledge about ADR reporting and pharmacovigilance. Moreover, URPL published two animated movies which explain how to report an ADR and adverse events to the authority (URPL 2014, 2015).

Reporting System for Vaccines

A positive example, especially for the ADR reporting of biological medicines, is the reporting scheme for negative effects deriving from vaccines (cf. Fig. 5.6). The system is different from the general ADR reporting scheme because it follows a decentralised approach for reporting vaccine ADRs. Physicians and feldshers are legally obligated to report ADRs stemming from vaccines to the Regional Sanitary Board. Other healthcare professionals can voluntarily file an ADR report but are not obligated to do so.

The Regional Sanitary Board receives the ADR report, adds it to a database that stores ADR reports on vaccines for 10 years, and is obligated to forward a copy of the report to the national competent authority URPL. With a serious ADR event, the regional unit has to inform the State Sanitary Board (*Wojewodzki Inspektorat Sanitarny*, or WIS) within an hour after receiving the report. The WIS in turn informs the Chief Sanitary Inspectorate (*Główny Inspektorat Sanitarny*, or GIS). The GIS keeps records of all ADRs caused by vaccines and publishes a yearly report. This system enables a close monitoring of ADRs resulting from vaccinations, and it ensures high numbers of reporting because it is well-known and broadly accepted among professionals. In addition, batch number reporting functions well because the personnel is trained accordingly.

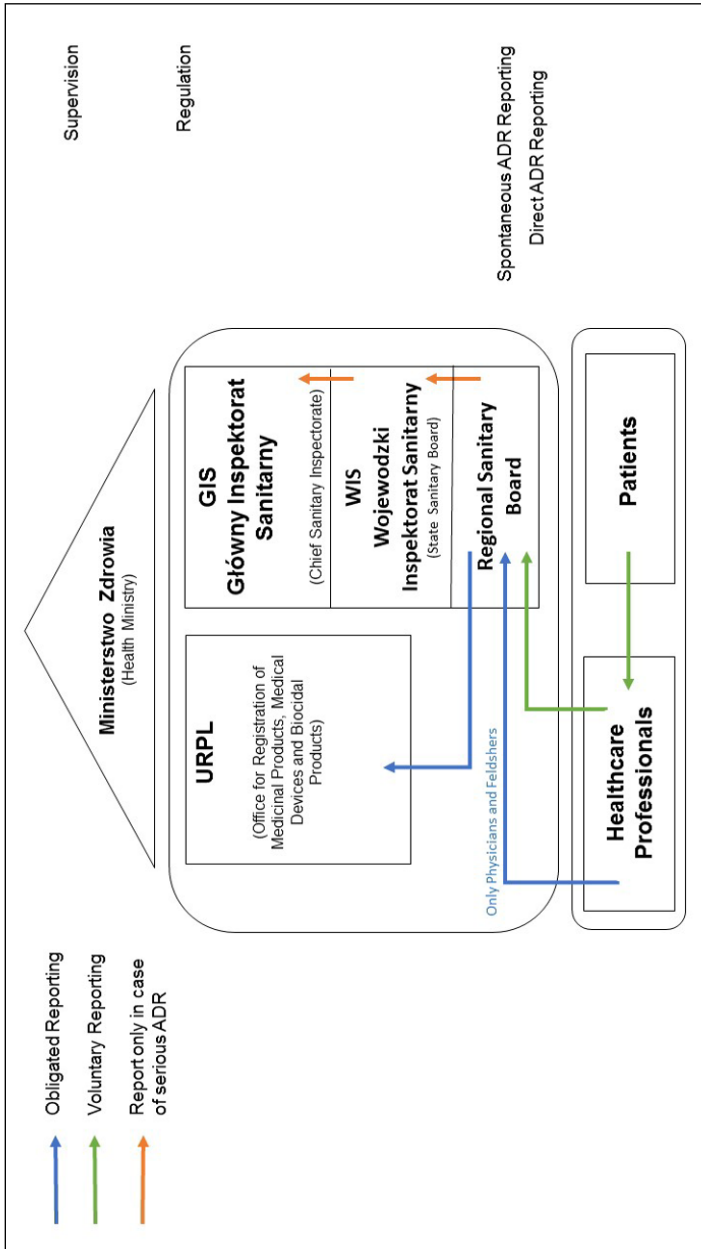


Fig. 5.6 Reporting of ADRs stemming from vaccines (compilation by the authors)

5.4 ADR Reporting in France

5.4.1 The System

Since 1973, pharmacovigilance in France has been organised by a decentralised network of 31 regional centres (*Centres Régionaux de Pharmacovigilance*, or CRPVs) and the national competent authority, namely the Agency for Drug Safety and Health Products (*Agence Nationale de Sécurité de Médicament et des Produits de Santé*, or ANSM). While the CRPVs are in charge of data collection and validation, the ANSM is responsible for data evaluation and overall decision-making processes. The French Ministry for Health and Social Security is responsible for the legal framework, finances, and the overall supervision of the French pharmacovigilance system.

The process of adverse drug reaction (ADR) reporting in France is illustrated by Fig. 5.7 and explained in the following sections. Currently, there is no separate system for reporting ADRs arising from biologicals, so the system outline below refers to the reporting of both synthetic and biological medicines.

Reporting

Reporting by healthcare professionals. Healthcare professionals constitute one of the major pillars of the French ADR reporting system. Physicians, dentists, pharmacists and midwives are legally obligated to report any ADR they encounter (*Loi de l'état 2011-2012 du 29 décembre 2011 relative au renforcement de la sécurité sanitaire du médicament et des produits de santé*); non-compliance can lead to three years of imprisonment and a fine of up to €45,000 (*ibid.*, Article 28).

According to French legislation, healthcare professionals must file a report to the regional CRPV where the patient is based that contains all the necessary information. Reports can be submitted via regular mail, e-mail, via an online form or by fax. During the evaluation procedure in the regional centres, healthcare professionals act as contact points and must be open to follow-up questions from the regional CRPV's experts.

Reporting by the pharmaceutical industry. In addition, the pharmaceutical industry has the legal obligation to file a report on every ADR it is informed about and any failure to comply can result in a fine of up to €150,000 and two years' imprisonment (*Code de la santé publique*, Article L. 5421-5). The respective marketing authorisation holders must send the report directly to the national competent authority ANSM, again by regular mail, e-mail or via an online form.

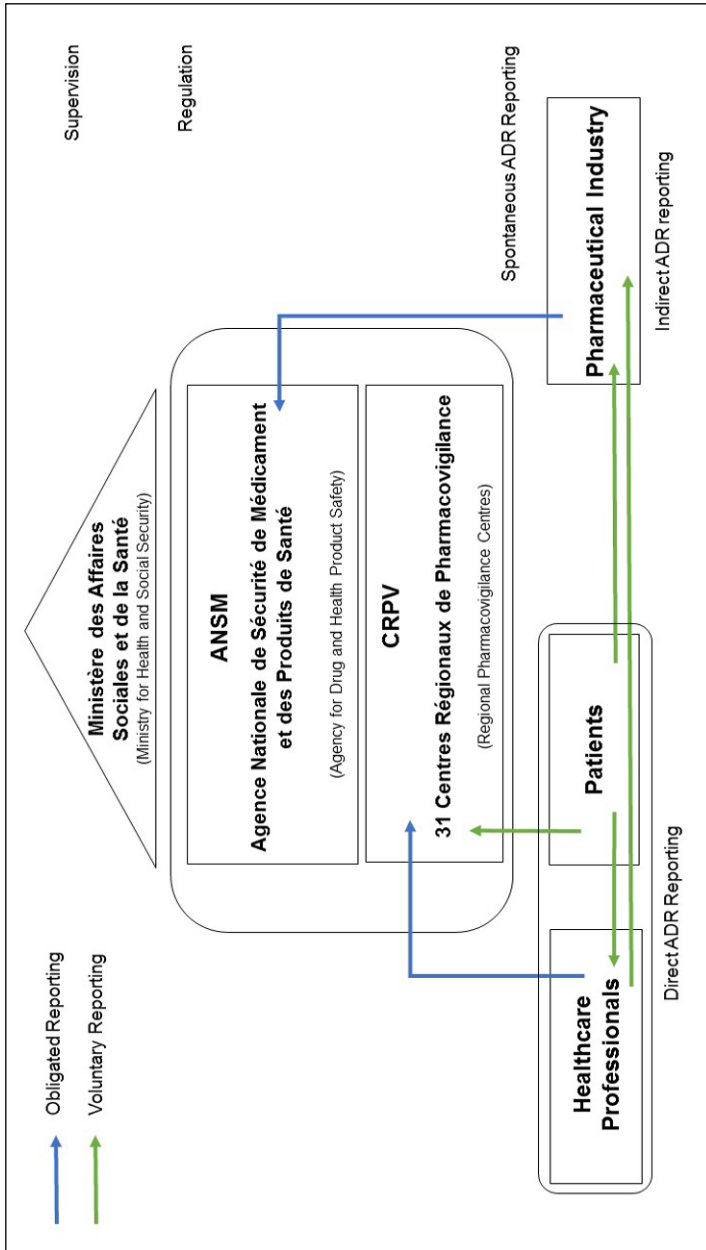


Fig. 5.7 ADR reporting in France (compilation by the authors)

Patient reporting. Finally, since June 2011, patients have also been empowered to report ADRs, although they can report on a voluntary basis. If a patient suspects an ADR, he or she has different options for reporting. First, the patient can choose to inform the regional pharmacovigilance centres or the ANSM by mail, fax and often via an online form. Interestingly, a study by Health Action International (Santos n.d.: 13) found that “in France, about half of the regional pharmacovigilance centres did not appear to have their own website to report ADRs” and only very few were found to allow direct online reporting. Further, a patient has the possibility to directly contact the marketing authorisation holder for the medicinal product in question. Third, the patient can consult a healthcare professional for advice and assistance in reporting.

Some regular centres provide feedback to reporters. As Health Action International (Santos n.d.: 8) summarised: “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”.

Evaluation and Signal Detection

All reports submitted by healthcare professionals and patients are collected by the 31 regional pharmacovigilance centres which are located in university hospitals all over the country. The regional CRPVs’ pharmacovigilance units scientifically evaluate the reports and conduct the causality assessments. After verification by CRPV experts, the reports are collected in the French pharmacovigilance database (FPD) which is hosted by the ANSM; the reports submitted by marketing authorisation holders are directly sent to the FPD.

There are monthly meetings between the heads of the regional centres and the ANSM’s Technical Committee (Caron et al. 2014). This committee is responsible for collecting and evaluating further information about ADRs, assessing the evaluated reports for trends in order to detect larger signals and, subsequently, forwarding these to the ANSM’s general director. If deemed necessary, the committee forwards their findings to the EMA and the international database of the WHO.

In 2014, the ANSM received 46,497 ADR reports (initial and follow-up) from the regional centres, 1,983 of which were submitted by patients (ANSM Annual Report 2015).

5.4.2 Perceived Challenges

The French pharmacovigilance system is suffering from the aftermath of the so-called Mediator scandal which cost more than 2,000 deaths as a consequence of serious delays in ADR reporting and an inadequate reaction from the national competent authority (cf. Box 5.4). Many of our respondents emphasised that this scandal has still not been entirely processed by the French pharmacovigilance system and the actors involved. Instead, the respondents pointed out that many systematic difficulties remain, considerably impeding efficient and independent pharmacovigilance. For instance, it is not explicitly prohibited to work for the pharmaceutical industry and to be a member of the national competent authority at the same time. Consequently, conflicts of interest of ANSM committee members regarding the monitoring medicinal products are still present. And even though conflicts of interests formally need to be declared, there is no penalty for not doing so.

All of our respondents indicated that the French pharmacovigilance system currently faces numerous challenges. Again, underreporting is considered one of the major weaknesses. Several reasons for this have been identified by our interviewees and are discussed in the following sections.

Lack of Awareness

First, the relevant actors in the French pharmacovigilance system are often unaware either of their obligation to report ADRs or the importance of reporting ADRs, especially those arising from biological medicines. This leads many healthcare professionals to completely neglect this issue in the course of their daily routines.

Recommendation: Awareness Raising – Healthcare Professionals

In order to tackle underreporting by healthcare providers, national authorities and healthcare institutions should invest in awareness-raising campaigns to increase professional knowledge about pharmacovigilance and sensitise relevant actors about its importance to ensure public health.

This training should especially increase understanding about the particular relevance of ADR reporting related to biologicals and impart the necessary skills to do so.

Complexity and Lack of Interconnectivity

In addition, several interview partners mentioned that the workload of healthcare professionals was already considerable; therefore, healthcare professionals often refuse to engage in ADR reporting, perceiving it as a time-consuming and complex task which is difficult to integrate into daily routines. Administrative hurdles also make it difficult for healthcare professionals to report. First, reports need to be submitted via a separate online portal, and thus information needs to be collected from different IT systems. Patients must also be informed. In addition, practitioners are expected to be available for any follow-up questions from the regional centres. In summary, ADR reporting turns into a long process which cannot simply be reduced to the mere submission of a report.

Recommendation: Facilitate ADR Reporting Processes

Healthcare institutions, in line with the French general health policies, should facilitate ADR reporting through streamlined internal processes.

In order to cope with information overload and to facilitate the process of submitting ADR reports, national and regional competent authorities should improve the interconnectivity of IT systems, such as those of general practitioners, hospitals, pharmacies and the ANSM's ADR reporting system.

Additionally, all stakeholders at the national level should improve mechanisms of cooperation. This not only includes competent authorities, but also industry and patients' associations as well as research and training facilities such as universities.

Box 5.4 The 2009 Mediator scandal in France

From 1976 to 2009, the French manufacturer *Laboratoires Servier* sold the drug benfluorex under the brand name Mediator on the French market. The product was originally designed to control the weight of patients suffering from diabetes or obesity. However, it was often prescribed off-label to people with no other medical indications as an appetite suppressant for facilitating weight loss. In the early 2000s, the first studies found that the medication causes cardiac valve damage and pulmonary hypertension. Despite repeated warning signs and studies pointing at the causality between taking the drug and cardiac illnesses, however, neither the French authorities nor *Laboratoires Servier* reacted. Only in 2009 did the national agency AFSSAPS (now the national competent authority ANSM) finally ban the drug and investigations were started by an independent

commission. The final report argues that both the company as well as the country's regulatory system are responsible for this medical scandal, which caused an estimated 2,000 deaths and led to many more patients being hospitalised with cardiac problems (Mullard 2011; Casassus 2016).

Fear of Litigation

ADRs can occur despite medications being correctly prescribed and correctly administered. However, our respondents indicated that French healthcare professionals still often consciously avoid reporting ADRs due to a fear of litigation and loss of reputation. Reporting an ADR is still often considered akin to confessing to a medical error.

Recommendation: Legal Counselling

The previously suggested pharmacovigilance training should include both practical and legal counselling in order to alleviate the fear of litigation. While respecting national diversity in health-related and legal terms, it is important to recognise that fault-based systems are an important impediment to the reporting of ADRs. A general and cautious recommendation is to enable healthcare professionals to report ADRs without fear of liability. This could be pursued not only by practical and legal counselling for healthcare professionals, but also by legal means through strengthening confidentiality or setting up compensation schemes for patients' claims.

Incomplete Reports

Another closely related problem identified by our interviewees is the weak quality of submitted reports. Frequently, brand names or relevant patient information is either inaccurate or completely omitted, and reported batch numbers appear to be the exception, especially with biological medicines. The varying quality of ADR reports thus exacerbates sound causality assessments and often renders them impossible. This emphasizes the need for a separate system regarding the reporting of biological medicines in order to guarantee sound monitoring and an appropriate risk-benefit assessment.

Recommendation: Training on Biological Products

European, national or regional authorities should organise advanced post-graduate training on a regular basis to ensure that healthcare professionals acquire the necessary skills to cope with the complex task of reporting ADRs.

In order to tackle underreporting of batch numbers and thereby facilitate the correct and timely traceability of biologicals, healthcare professionals should receive additional training to both increase awareness about the particular relevance of ADR reporting related to biologicals and to acquire the necessary skills to do so.

Budgetary Constraints

Finally, public health seems not to be an economic priority. This is visible not only from the Mediator scandal, but also in the dependencies faced by the regional centres that rely on financing from the state budget and political priorities set by the Health Ministry. Thus, regional budgets are rather limited and pharmacovigilance does not appear to be high on the political agenda.

Recommendation: Sufficient Financial Means for Relevant Agencies

National and regional competent authorities working under the auspices of national ministries should be endowed with sufficient financial means to fulfil their functions. Likewise, healthcare institutions should be endowed with sufficient means. Sound finances enable healthcare institutions to rely on a stronger workforce which reduces the workload of individual healthcare professionals and increases the possibility of extended reporting of adverse drug reactions.

5.4.3 Perceived Best Practices

However, besides these challenges and the system's shortcomings, the French pharmacovigilance system also exhibits very positive aspects, as discussed below.

Decentralisation

As emphasized by our respondents, one of the major advantages is the decentralised approach to ADR reporting. The close proximity of the 31 regional pharmacovigi-

lance centres situated in hospitals all over the country allows the experts to be close to both healthcare professionals and patients. Moreover, the regional experts are able to keep in contact with both medical and pharmacy students. This profoundly facilitates communication between the relevant reporting and evaluating actors, and the experts remain visible in the healthcare professionals' daily working routine.

Besides collecting and evaluating the reports as well as acting as contact points between reporting actors and the ANSM, the regional centres are also active in research and education. They offer training on pharmacovigilance for healthcare professionals, provide information and expert advice, and serve as the first contact points for patients and practitioners alike. The regional units also provide information on the efficacy and safety of the medicinal products to healthcare professionals and patients.

Furthermore, the reports' assessment and evaluation has been pointed out as advantageous by our interviewees. For each individual case, a causality assessment is conducted. Each report is scientifically evaluated by the regional units before it is forwarded to the ANSM. Thus, low-quality and invalid reports can be largely eliminated before they are entered into the FPD, EMA or WHO databases.

As one of our respondents emphasized, leaving the evaluation to pharmacovigilance experts, usually pharmacists or physicians, was a conscious decision by the relevant actors. Collecting huge amounts of data and leaving signal detection to an algorithm, as for instance in the United Kingdom, was perceived as rather unconstructive.

Awareness Raising

In addition, our respondents identified several good examples regarding education. First, there are some university professors who are specialised in pharmacovigilance. Although they are few, they have a positive influence because they put pharmacovigilance on the agenda of medical faculties and academia. Pharmacovigilance professors enhance the healthcare professionals' knowledge through academic publications, conferences and awareness raising.

Second, a master's programme on pharmacovigilance (cf. Box 5.5) with different specialisations was established by the University of Bordeaux. This programme aims not only at training future professionals in pharmacovigilance and pharmacoepidemiology, but also focuses on establishing an international network of academics and professionals alike which fosters the exchange of knowledge and expertise.

Box 5.5 Best Practice: Master's Degree in Pharmacovigilance and Pharmacoepidemiology

This master's programme is coordinated by the University of Bordeaux and aims at training future professionals in pharmacovigilance as well as fields connected with this issue. Aside from offering basic courses in pharmacovigilance and epidemiology, the programme provides courses in risk identification, pharmacovigilance regulations, public health and risk communication. Moreover, workshops with experts from regulatory agencies and the pharmaceutical industry are held in order to ensure the subjects' practical relevance, as the graduates are expected to work in industry, regulatory bodies and academia alike. Universities from other European countries also participate in this programme to ensure high academic expertise and an international exchange of knowledge.

5.5 ADR Reporting in Portugal

5.5.1 The System

The Portuguese pharmacovigilance system was introduced in 1992. The National Authority of Medicines and Health Products (*Autoridade Nacional do Medicamentos e Produtos de Saúde, I.P.*, or INFARMED) is the country's national competent authority. It supervises and coordinates the regional units and maintains the national ADR database, and is affiliated with the National Health Ministry which is responsible for legislative matters.

The Portuguese pharmacovigilance framework was initially devised as a centralised system, but in the early 2000s turned into a decentralised system (see Duarte et al. 2015; Marques et al. 2015). Today, it is based on four regional pharmacovigilance centres that are in line with Portugal's administrative regions (North, Centre, Lisbon, South). The four regional centres are responsible for collecting, processing and evaluating adverse drug reaction (ADR) reports and maintain their own databases (Mendes et al. 2014).

In doing so, the regional centres collaborate with INFARMED. The Risk Management for Medicines Directorate (*Direção de Gestão do Risco de Medicamentos*) of INFARMED coordinates the national pharmacovigilance database.

There is no separate system for reporting ADRs arising from biological medicines. The Portuguese ADR reporting system is shown in Fig. 5.8.

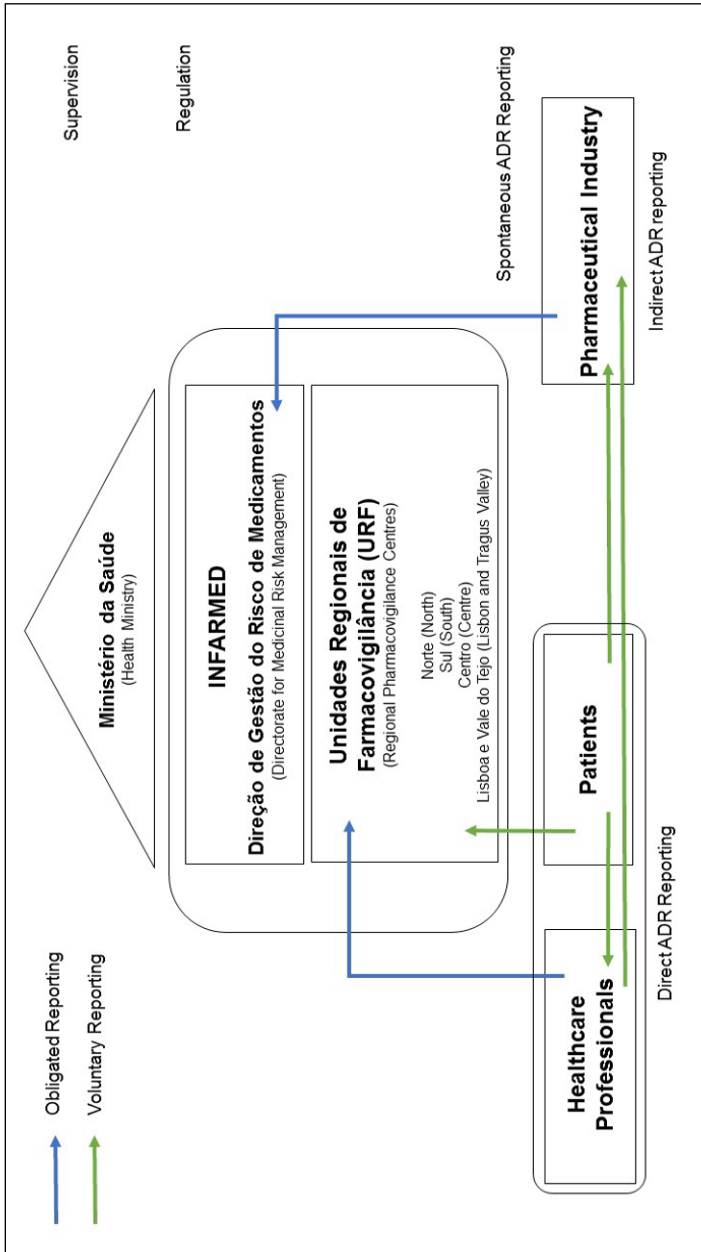


Fig. 5.8 ADR reporting in Portugal (compilation by the authors)

Reporting

In recent years, Portugal has developed a robust pharmacovigilance system, with several actors being allowed to report ADRs (Marques et al. 2016). At the time of system creation in 1992, only physicians were allowed to submit reports. However, pharmacists and nurses were included in 1995 and 1999, respectively. With Directive 2010/84/EU, patients have become the latest addition; today, ADRs can be reported by market authorisation holders, healthcare professionals and patients.

While healthcare professionals and patients submit their reports to the regional pharmacovigilance centres, the respective marketing authorisation holders directly report to the INFARMED sub-unit that is responsible for medicinal risk management.

Reporting by healthcare professionals. All healthcare professionals are legally obligated to report any ADR. Officially, non-compliance is sanctioned. In practice, however, sanctions are not enforced. Healthcare professionals, i.e. physicians, dentists, pharmacists, nurses and medical-technical assistants, are a vital part of the pharmacovigilance system. Depending on their postal code, they have to report adverse reactions to the respective regional centre and need to be available for follow-up questions. A majority of reports is issued by physicians and pharmacists, although some reports are submitted by nurses and medical-laboratory assistants. Healthcare professionals can submit their reports via online forms, e-mail, fax or regular mail.

Reporting by marketing authorisation holders. Marketing authorisation holders are under a legal obligation to report any ADR as well. Yet, while healthcare professionals and patients report to the regional units, the pharmaceutical industry submits its reports directly to INFARMED.

Patient Reporting. Since 2013, patients are also allowed to report suspected ADRs to the regional pharmacovigilance centres. In contrast to professionals and the industry, however, their reports are optional. Reports can be submitted by a number of options, including by telephone, fax, regular mail, e-mail or the online forms provided by the regional centres or INFARMED.

As illustrated by Fig. 5.9, since 2005, marketing authorisation holders submit the majority of reports to INFARMED, followed by physicians and pharmacists. Nurses and patients bring up the rear.

The number of reports has been steadily increasing since the introduction of the system in 1992 (INFARMED 2010). In 2013, the year in which patient reporting was introduced, the number was around 3,400 (Santos n.d.) and in 2014, the number was around 4,600 (Matos et al. 2015). In 2015, the number was around 5,600 (INFARMED 2016). The number of reports submitted by patients, however, is very small, with only 175 reports in 2014 (Santos n.d.). There is also considerable variation in terms of reporting by the regional pharmacovigilance centres (Ribeiro-Vaz et al. 2016).

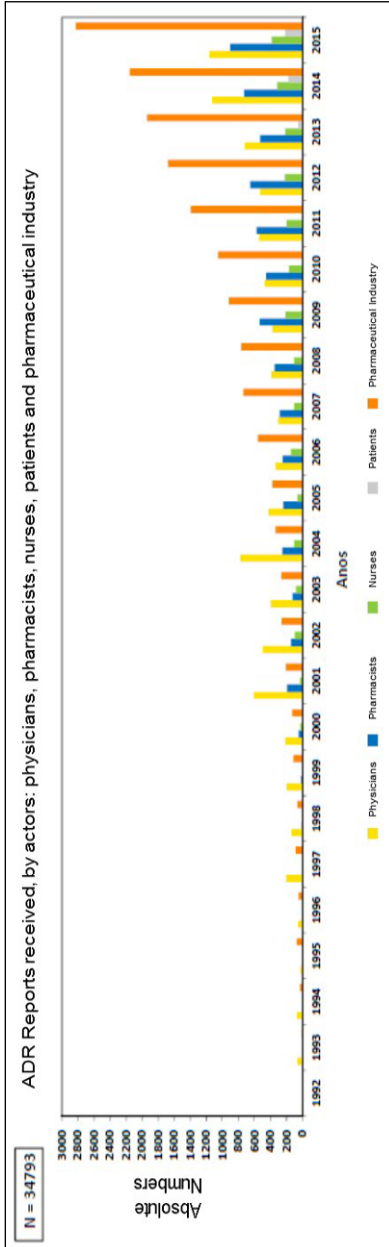


Fig. 5.9 ADR reporting by actors (provided by INFARMED)

Evaluation and Signal Detection

ADR reports submitted by healthcare professionals and patients are collected by the four regional pharmacovigilance centres. The centres receive reports by patients and healthcare professionals assigned by postal code and evaluate them with a team of physicians and pharmacists. Reports submitted by marketing authorisation holders are directly sent to and assessed by INFARMED's Directorate of Risk Management for Medicines.

During the processing of ADR reports, the centres keep in touch with the reporters or directly with the patient, and the necessary information is cross-checked regarding the causality assessment and final review of the adverse reactions. The causality assessment is usually done by clinicians (Inácio et al. 2015). Usually, the regional centres have 30 days from the report's submission for a comprehensive causality assessment before forwarding the report to INFARMED.

Signal detection includes the identification and management of signals and is conducted by the Risk Management for Medicines Directorate of INFARMED. To this end, individual case safety reports (ICSRs), literature and other sources are considered.

In terms of methodology, INFARMED uses multiple approaches, including computerised signal detection methods. However, despite these methods, the assessment of ICSRs remains the most relevant information (INFARMED 2010).

5.5.2 Perceived Challenges

Similar to other countries, underreporting by both healthcare professionals and patients was perceived by our interview partners as a significant shortcoming. The reasons for underreporting are twofold: lack of awareness and time constraints.

Lack of Awareness

First, it has been lamented that the relevant actors are not sufficiently informed that they are able to report. In Portugal, this refers especially to patients. Because patients could only submit reports after Directive 2010/84/EU was transposed into Portuguese legislation in 2013, they are still not yet sufficiently aware of both the possibility to do so and the subject's importance. Despite the fact that patient reporting increased in 2014 and 2015 (cf. Fig. 5.8), indicating that awareness raising is in fact taking place, patients should be more thoroughly informed about the possibility to report ADRs.

Recommendation: Awareness Raising – Patients

In order to tackle underreporting by patients, European, national and regional authorities should invest in awareness-raising campaigns to increase the public knowledge about pharmacovigilance. Even though awareness raising is already taking place in Portugal, efforts in this regard should be enhanced.

However, unawareness is not only a challenge regarding patients, but also regarding healthcare professionals. Here it is important to note that the Portuguese pharmacovigilance system was initiated in the 1990s as a top-down project, and therefore education on this subject is also rather new. Hence, many healthcare professionals are simply not informed about their legal obligation to report every single ADR they encounter.

Moreover, even if healthcare professionals know that they are obligated to report, many physicians and pharmacists are unaware of the importance of reporting all ADRs, and not only new or serious ones. More precisely, while patients are often not aware of the fact that they are able to report, healthcare professionals tend to report only serious or formerly unknown ADRs. Recurrent and non-serious ADRs are largely neglected.

In addition, numerous healthcare professionals do not seem to be aware of the need to report batch numbers in order to ensure the accurate and timely traceability of biological medicines.

All this is especially problematic if the hospital management is also not adequately educated and hence does not consider ADR reporting sufficiently important. Sufficient ADR reporting also depends on the hospital management boards because they can make pharmacovigilance a priority in the working environment and train their medical staff accordingly. However, the management is often perceived as impeding education on the topic and neglecting the issue's importance. Although it is already impeding ADR reporting if practitioners do not consider it relevant, it might be even more dangerous if their superiors label it as insignificant and therefore do not offer practitioners the respective time, information and training they need to report in a responsible manner. This insufficient sense of importance often leads to insufficient prioritisation of the task, which in turn continues to hinder effective ADR reporting in Portugal.

Recommendation: Awareness Raising – Healthcare Professionals

National authorities and healthcare institutions should invest in awareness-raising campaigns to increase professional knowledge about pharmacovigilance and sensitise relevant actors about its particular importance to ensure public health.

In order to improve both the quantity and quality of reports on adverse drug reactions (ADRs), university classes about the importance of pharmacovigilance and the need for ADR reporting should be mandatory for every medical and pharmacy student.

Further, healthcare professionals – including hospital management – should receive additional training to both increase awareness about the particular relevance of ADR reporting related to biologicals and to acquire the necessary skills to ensure the reporting of batch numbers, thereby facilitating the correct and timely traceability of biologicals.

Fear of Litigation

Finally, our interview partners mentioned another issue potentially resulting in the underreporting of ADRs. Even if healthcare professionals are aware of the importance of reporting and have sufficient time to report, they might be unwilling to do so in cases of off-label use. Regardless of the underlying cause of adverse effects, off-label use, medication errors or otherwise, the legal repercussions are a serious concern for healthcare professionals. Hence, it is vital to emphasize that any reporting system should be geared towards the quality of healthcare services and thus be separated from legal proceedings (see EMA 2013). From this perspective, healthcare providers must be assured that ADR reporting has no legal repercussions.

Recommendation: Legal Counselling

The suggested training should include practical and legal counselling in order to alleviate the fear of litigation. While national diversity in health-related and legal terms should be respected, it is important to recognize that fault-based systems are a significant impediment to reporting ADRs. A general and cautious recommendation is to enable healthcare professionals to report ADRs without fear of liability. This could be pursued not only through practical and legal counselling for healthcare professionals, but also by legal means through either strengthening confidentiality or setting up compensation schemes for patients' claims.

Budgetary Constraints

Another challenge pointed out by our respondents is the lack of time to report. This is particularly the case in hospital environments in which physicians and nurses are usually rather overworked. According to our interviewees, adding the comprehensive reporting of every ADR to the usual workload therefore appears to be too challenging. Again, this is a particular obstacle for ADR reporting of biological medicines, the majority of which are dispensed in hospitals.

Thus, there is a perceived shortage of financial and especially human resources which mainly results from lean budgets following the economic crisis in Southern Europe. During the crisis, relevant actors even feared that the pharmacovigilance system could be suspended altogether due to the lack of resources and lack of political priority. The Portuguese pharmacovigilance system is only slowly recovering from the deep financial and personnel cuts in the recent years.

Recommendation: Sufficient Financial Means for Relevant Agencies

National and regional competent authorities working under the auspices of national ministries should be endowed with sufficient financial means to fulfil their functions. Likewise, healthcare institutions should be endowed with sufficient means. Sound finances enable healthcare institutions to rely on a stronger workforce which reduces the workload of individual healthcare professionals and increases the possibility of extended reporting of adverse drug reactions.

5.5.3 Perceived Best Practices

In Portugal's pharmacovigilance system, identified best practices are associated primarily with the four regional pharmacovigilance centres. These best practices concern awareness raising and cooperation.

Awareness Raising

The regional pharmacovigilance centres actively engage in awareness-raising campaigns in order to increase the knowledge and perceived importance of pharmacovigilance in general and ADR reporting in particular. In order to sensitise these actors about the importance of ADR reporting, regional centres offer internships for pharmacy and medical students, provide lectures and training on pharmacovigilance, and disseminate further relevant information. The southern

unit, for instance, educates selected pharmacists on pharmacovigilance and the ADR reporting system.

However, healthcare professionals are not the only target group as many activities are geared towards the general public. One respondent, for instance, mentioned cooperation with public schools aiming to educate both children and their parents.

Cooperation

The aforementioned decentralisation has proven to be vital to strengthen the cooperation of pharmacovigilance centres with universities (Inácio et al. 2015). All regional centres are located within research institutions allowing for close cooperation with the relevant actors in ADR reporting. While the units for Lisbon, South and North are located directly within the universities' medical or pharmacy faculties, the pharmacovigilance unit of the centre region is located within the Association for Innovation and Biomedical Research on Light and Image, a research technology organisation dedicated to the development and clinical research of new products for medicinal therapy and diagnostic imaging.

The regional centres seek to increase the available data on ADRs by collaborating with healthcare organisations. After the initially low number of ADR reports, the northern centre, for instance, established a collaboration protocol with nearby hospitals to collect every suspected case of ADR (Ribeiro-Vaz et al. 2016). This approach requires close collaboration at the personal level between the staff of the pharmacovigilance centre and hospitals. As another instance, respondents identified the collaboration between the southern centre and the rheumatology association. Such close collaboration between the pharmacovigilance centres and other healthcare providers can lead to more and reliable data which considerably facilitates the reports' evaluation and respective signal detection.

Hence, the work by the four regional pharmacovigilance units and especially their strong cooperation with other relevant actors and active engagement in awareness-raising activities has been perceived as particularly conducive to the Portuguese pharmacovigilance system.

5.6 ADR Reporting in Germany

5.6.1 The System

Pharmacovigilance in Germany is based on a highly complex and centralised system that was initiated in the 1970s. Regarding ADR reporting, there are two separate *modus operandi*, depending on whether the product under suspicion is synthetic or biological. Whereas ADRs related to synthetic medicines are centrally collected by the Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, or BfArM), ADRs resulting from biologicals must be reported to the Federal Institute for Vaccines (*Paul-Ehrlich-Institut*, or PEI). Even though both agencies are independent and act as centralised agencies, they have a nearly identical legal basis and have similar instruments at their disposal when it comes to pharmacovigilance and ADR reporting (Hagemann and Paeschke 2014).

BfArM and PEI are both under the supervision of the Federal Ministry of Health (Hagemann and Paeschke 2014). Both systems are presented in Fig. 5.10 and 5.11 and are described in the following sections.

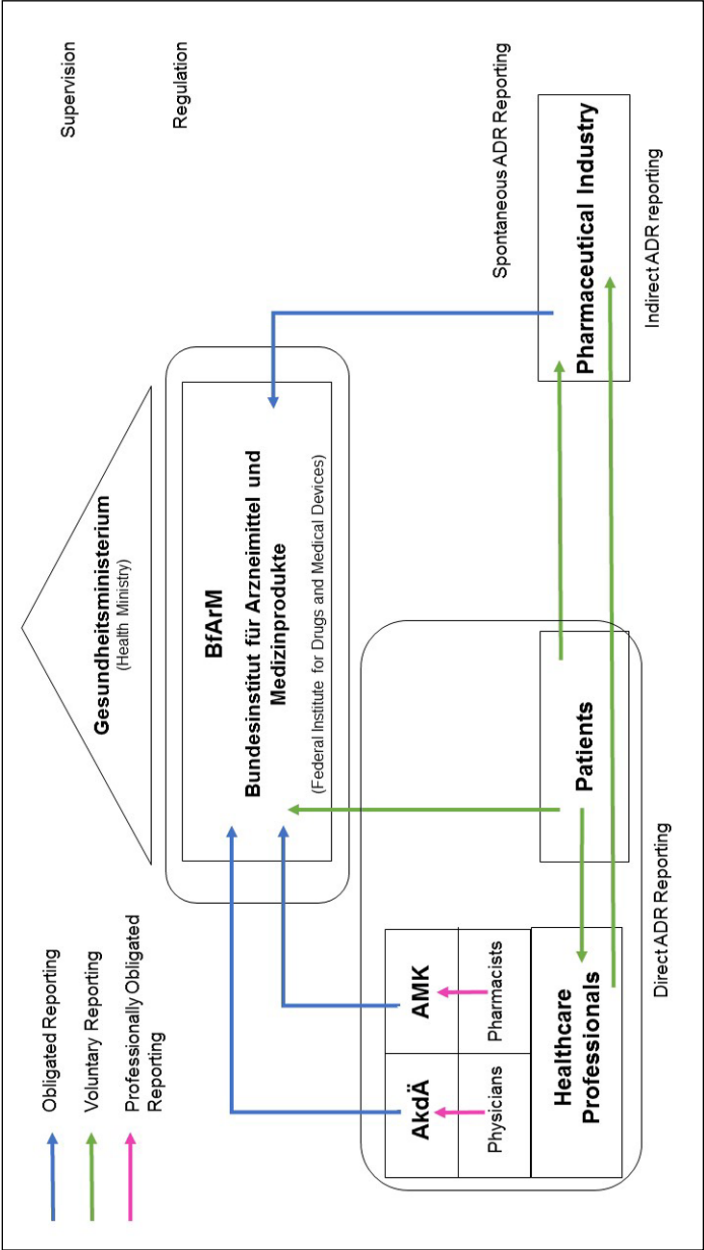


Fig. 5.10 ADR reporting in Germany for synthetic medicines (compilation by the authors)

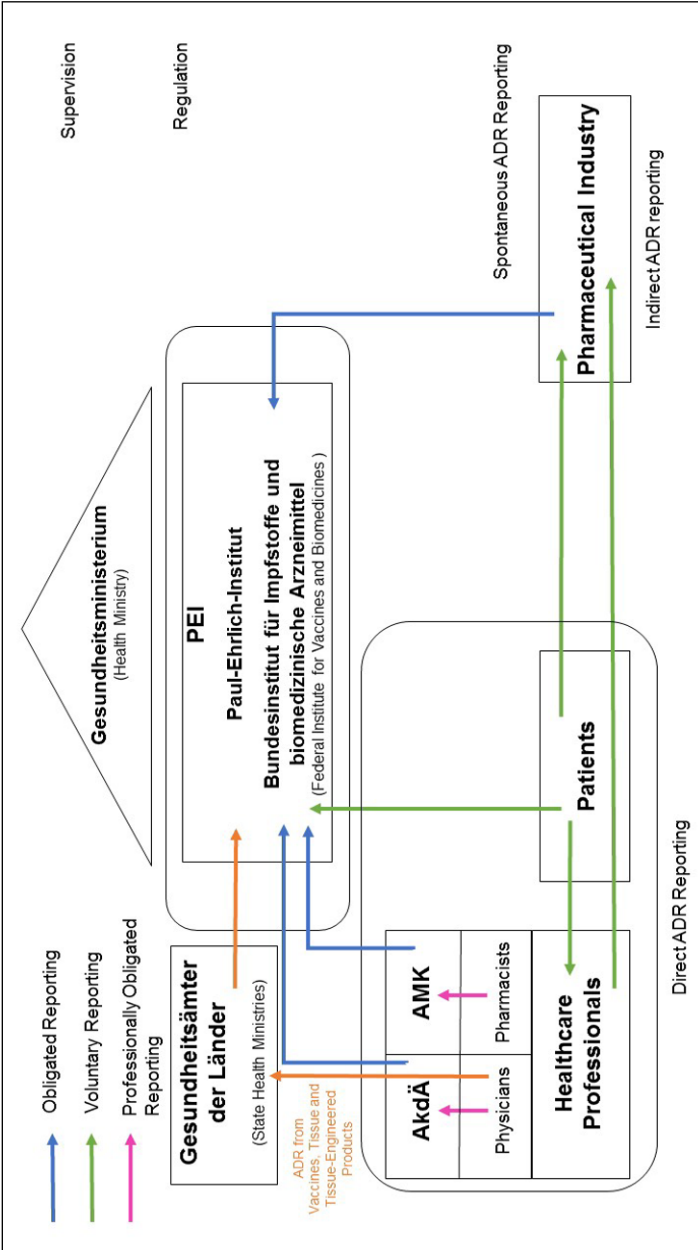


Fig. 5.11 ADR reporting in Germany for biological medicines (compilation by the authors)

Reporting

Healthcare professionals are not legally obligated to report ADRs, neither for synthetic nor biological medicines. They are merely bound by their professional codes of conduct (Ärztliche Berufsordnung, Article 6). Accordingly, there are no sanctions for non-reporting.

Reporting by healthcare professionals. While physicians must report ADRs to the Drug Commission of the German Medical Association (*Arzneikommision der deutschen Ärzteschaft*, or AkdÄ), pharmacists are expected to submit their reports to the largest national association of pharmacists, the Drug Commission of German Pharmacists (*Arzneikommision der Deutschen Apotheker*, or AMK). To facilitate data collection, reports can be submitted online, via regular mail or fax. Physicians and pharmacists receive confirmations of receipt for every submitted report, complemented with additional information and literature regarding the respective ADR. In urgent cases, reporters might be requested to provide further information, such as hospital reports. Sometimes, reporters are contacted via phone for further consultation or follow-up questions in case of lack of clarity.

The physicians' and pharmacists' associations in turn collect, evaluate and – excluding information regarding reporters – forward the reports they receive to BfArM, PEI and marketing authorisation holders. The collaboration between BfArM and the associations is regulated by an agreement created in 1995. Since 2011, there is an additional agreement governing the collaboration with the PEI. Collaboration includes the electronic exchange of ADR reports and reciprocal information exchange regarding newly discovered drug risks. Additionally, the Medical Committee on Drug Safety (*Ärzteausschuss Arzneimittelsicherheit*, or ÄAAS) was initiated at BfArM and PEI, which consists of AkdÄ experts (AkdÄ Tätigkeitsbericht 2015).

Alternatively, healthcare professionals can voluntarily submit reports directly to the respective marketing authorisation holders or the national competent authority BfArM. Submitted reports are disseminated between the different actors so that double reporting is not necessary. In the end, all reports are centrally collected and saved in pseudonomised form by the BfArM, which forwards their reports to the respective marketing authorisation holder and to EMA as well as the WHO.

ADR reporting concerning biologicals works rather similarly. However, instead of reporting to the BfArM, AkdÄ and AKM need to forward the physicians' and pharmacists' reports to the Paul Ehrlich Institute for Vaccines.

However, there is one important difference when it comes to tissues, tissue-engineered products and vaccines. In the case of ADRs related to these products, healthcare professionals do not submit the reports to their respective associations but to the state health authorities (*Gesundheitsämter der Länder*), which carry out

a first examination. Subsequently, these health authorities forward the reports to the PEI for central collection.

Reporting by marketing authorisation holders. In contrast to healthcare professionals, marketing authorisation holders are legally obligated to report every case they are informed about to the BfArM or, as regards biologicals, to the PEI (German Drug Law, Chapter 17). In the case of non-compliance, sanctions can be imposed.

Patient Reporting. Patients have various options to report since the transposition of Directive 2010/84/EU in 2012. They can submit reports directly to the national competent authorities, namely the BfArM or the PEI, via phone, e-mail or an online form. Additionally, they can call the respective marketing authorisation holder in order to report an unexpected side effect, or they can consult their physician or pharmacist.

Evaluation and Signal Detection

The evaluation of ADR reports takes place within the AkdÄ and AKM pharmacovigilance units. After the reports' completeness is verified, the reports are scientifically assessed regarding severity, causality and the necessity of further risk-minimising measures, including consultation of a database, medical advisers and research assistants. Evaluation and signal detection is carried out by a software program called ARTEMIS (Adverse Drug Reactions Electronic Management and Information System), which is used to look for similar cases in the shared BfArM and AkdÄ database. In cases of particularly severe ADRs or ambiguous causality assessments, additional scientific statements from experts are collected. Based on these evaluation procedures, selected cases are debated in the respective pharmacovigilance units in order to decide on further procedures. In these settings, relevant public safety issues and necessary measures for risk minimisation – such as additional information for physicians and pharmacists or an alteration of market authorisation – are debated. Relevant safety issues are communicated via the *Deutsches Ärzteblatt*, a weekly magazine, or via drug safety mails (Bronder and Stammschulte 2013).

5.6.2 Perceived Challenges

Even though all respondents considered ADR reporting to work rather efficiently in Germany, several of them emphasized that there are still instances of underreporting, especially by healthcare professionals. As per the interviewees, this can predominantly be attributed to a general lack of awareness and sensitivity regarding ADR reporting as well as insufficient time and personnel.

Lack of Awareness

According to our respondents, the healthcare professionals' lack of awareness regarding ADR reporting can be traced back to various shortcomings in the academic education of the relevant actors. Pharmacovigilance is only included in the curriculum of pharmacy studies, while other medical curricula do not impart any knowledge on drug safety in general and on pharmacovigilance in particular.

Recommendation: Awareness Raising – Healthcare Professionals

In order to tackle underreporting by healthcare providers, national authorities and healthcare institutions should invest in awareness-raising campaigns to increase professional knowledge about pharmacovigilance and sensitise relevant actors about its particular importance to ensure public health.

To improve both the quantity and quality of ADR reports, university classes about the importance of pharmacovigilance and ADR reporting should be mandatory for every medical and pharmacy student.

In addition, European, national or regional authorities should organise advanced post-graduate training on a regular basis to ensure that healthcare professionals acquire the necessary skills to cope with the complex task of ADR reporting.

It was further indicated that patients are not sufficiently aware that they are able to report and do not know how to do so. This suggests that the quantity of ADR reports could be increased if patients were better informed. Additionally, respondents pointed out that reporting mechanisms for patients were still rather complex.

In addition, the quality of submitted ADR reports has been criticized by several interview partners. More precisely, it was pointed out that reports submitted via the national competent authority's online forms are frequently incomplete. This leads to severe problems for data evaluation and signal detection. Incomplete reports cannot be processed adequately and are therefore invalid. Accordingly, missing information needs to be gathered in a follow-up process and this means a considerable increase in workload for the relevant actors.

In line with this, our respondents generally suggested that direct patient reporting was rather unconstructive. Instead, they agreed that patients who suspect an ADR should consult their physician first and file their reports in collaboration with them.

Recommendation: Awareness Raising – Patients

In order to tackle underreporting by patients, European, national and regional authorities should invest in awareness-raising campaigns to increase the public knowledge about pharmacovigilance.

Authorities should raise awareness in the short term through various means of communication (e.g. websites, social media, leaflets) as well as in the long term through cooperation with schools to educate future generations.

In order to facilitate ADR reporting by patients, Member States should offer a wide range of possible communication channels, including web-based and paper-based formats. Both web-based and paper-based formats should be designed to be as user-friendly as possible. For web-based formats, IT solutions should be developed to guide patients through the format and to ensure the completeness of reports. All formats should be accompanied by accessible manuals written in layman's terms.

A first step in this direction is indicated by ongoing discussions about introducing a smartphone app intending to render ADR reporting more accessible to the public and thereby reduce reporting hurdles for patients. We consider this a good approach which should be pursued further.

Lack of Interconnectivity

Moreover, some respondents pointed out that the IT infrastructure of hospitals, pharmacies, associations and institutes is by no means connected. In some cases, there is still the need to manually transfer data from one system to another. This is a very time-consuming, complex and resource-intensive process, which is prone to mistakes and transcription errors.

A closely related problem is the duplication of ADR reports that occurs when identical reports are submitted by different actors, e.g. when patients report ADRs directly to the national competent authority and subsequently consult healthcare professionals, who then report the incident to the national competent authority a second time. Due to the particularly restrictive data protection laws in Germany, it is practically impossible to identify these duplications. In addition, unique characteristics are omitted from the reports at a very early stage of the process. Even though this ensures proper data protection, at the same time the detection of duplications is rendered impossible.

Recommendation: Harmonisation of IT Systems

In order to cope with information overload and to facilitate the process of submitting ADR reports, national and regional competent authorities should improve interconnectivity of IT systems, as for instance those of general practitioners, hospitals, pharmacies and the ADR reporting system.

In addition, the process of “who reports to whom” could be further facilitated and clarified, allowing for a more streamlined process and less data duplication.

Budgetary Constraints

Several interviewees described challenges regarding financial resources. Both national competent authorities, i.e. BfArM and PEI, are financially dependent on the Federal Ministry of Health. Accordingly, there is no room for quick and independent decision-making, resulting in delayed and insufficient reactions to changing demands.

Recommendation: Sufficient Financial Means for Relevant Actors

National and regional competent authorities working under the auspices of national ministries should be endowed with sufficient financial means to fulfil their functions. Likewise, healthcare institutions should be endowed with sufficient means. Sound finances enable healthcare institutions to rely on a stronger workforce which reduces the workload of individual healthcare professionals and increases the possibility of extended reporting of ADRs.

Incomplete Reports

Finally, our respondents are largely satisfied with the functioning of ADR reporting and the identification and traceability of biologicals. The only caveat identified is that the product name and batch number cannot be reported in all cases. *Inter alia*, this can be attributed to rather vague legal requirements. However, the currently discussed Fourth Amendment to the German Drug Law (4. *Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften*) requires that both the brand name and batch number must be reported for ADRs relating to biologicals, which is a step in the right direction.

5.6.3 Perceived Best Practices

The German pharmacovigilance system is deeply entrenched and well-appointed with manifold experts in the field. Because the pharmacovigilance system has been in place for more than 40 years, experience and routine both contribute to effective ADR reporting. Moreover, identification and traceability of biological medicines works particularly well because there is a separate system for biologicals.

Even though the German pharmacovigilance system is centralised, the national competent authorities are usually not directly contacted by healthcare professionals. Instead the physicians' and pharmacists' associations collect the reports and subsequently forward them. Hence, these associations act as points of contact between reporters and the authorities, thereby assuming a mediating role and allow for better communication between the relevant actors.

Awareness Raising

The national competent authorities provide several possibilities for engagement and educational activities for actors in the pharmacovigilance system. Healthcare professionals, patients and pharmaceutical companies can contact the authorities at any time in order to receive additional information on certain products or ADR reporting.

Additionally, Germany established several systems for spreading new information on risks of medicinal products to healthcare professionals. The so-called red-hand letter (*Rote-Hand-Brief*) is distributed via regular mail. The red hand printed on the cover signals that the letter does not contain an advertisement but important information related to pharmacovigilance (for further information see cf. Box 5.6).

Further, since December 2016, the so-called blue-hand letter (*Blaue-Hand-Brief*) has been introduced. Blue-hand letters contain additional and relevant educational information and material on specific medicines (cf. Box 5.6)

Additionally, the AMK established, together with the Confederation of the Pharmaceutical Wholesale Trade (PHAGRO), an efficient fax information system aiming to inform pharmacists and other healthcare professionals about urgent risks (cf. Box 5.7).

Cooperation

Pharmacovigilance educational and research centres are important for improving ADR reporting. A particularly good example in Germany is the Institute for Clinical Teratology and Drug Risk Assessment in the Pregnancy and Nursing Period (*Pharmakovigilanzzentrum Embryonaltoxikologie*, or Embryotox), which is located in the Charité hospital in Berlin. This institute serves as a consultancy centre for healthcare professionals working in hospitals and advises the national competent authorities whenever problems or questions referring to ADRs in pregnancy and nursing periods arise. It also maintains an online database which is accessible to everyone.⁶ Moreover, it can forward ADRs to the national competent authorities.

Another advisory body in the German pharmacovigilance system is the Medical Committee on Drug Safety (ÄAAS), which also advises the national competent authorities with expertise on specific risks of medicinal products.

Box 5.6 Red- and blue-hand letters

In 1969, the German Pharmaceutical Industry Association introduced the red hand as a symbol to indicate the importance of the information provided in the letter. These letters with the red hand are distributed to all healthcare professionals. The unique red hand logo signals that the letter does not contain an advertisement but important information on newly detected risks of medicines or a defective batch. The red-hand letters are distributed in consultation with BfArM and PEI and are a common way to communicate medicinal risks in Germany.

The newly introduced blue-hand letter (in December 2016) contains educational material that has been approved by BfArM and PEI. More precisely, the letters provide additional information complementing the package leaflets and the summary of product characteristics and are directed to physicians, pharmacists or patients in order to alert them about certain risks. It is expected that the blue-hand letters will contribute towards improving the safe and correct use of medicinal products.

6 www.embryotox.de.

Box 5.7 AMK/PHAGRO Schnellinformationssystem

Moreover, the AMK, in collaboration with the association of pharmaceutical wholesaler trading companies (PHAGRO), distributes information to pharmacies via a fax information system (*AMK/PHAGRO Schnellinformationssystem*). This system was established in 1996 aiming at providing important and urgent information on drug safety risks on short notice. In the case of an emergency, the AMK, in close cooperation with the marketing authorization holder and the responsible national competent authority, drafts an informational notice, which includes the medicine's name, the batch number and a description of the potential dangers. Moreover, recommended actions are enclosed. The informational notice is distributed via fax to every wholesale trader in Germany; these traders print them and enclose them with the invoices and delivery notes accompanying every single shipment to pharmacies. Because pharmacies are usually supplied every day, the informational notices reach end consumers very quickly.

An additional e-mail and fax system sends the information notices to the AkdÄ, hospital pharmacies, the German army medical service, public institutes, and diverse competent authorities at the state and federal levels. In addition, the informational notice is published, often including additional information, in the next AMK newsletter.

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