Sundhedsstyrelsen

Danish Health and Medicines Authority

ADVERSE DRUG REACTIONS REPORTED BY CONSUMERS IN DENMARK – compared with reports from healthcare professionals

2013

Adverse drug reaction reported by consumers in Denmark – compared with reports from healthcare professionals

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1 Introduction

Consumers must be confident that the medicine they receive is as safe and effective as possible. Medicine safety issues must be identified, evaluated and handled quickly, and adverse drug reaction reporting is a key element of this process.

In this report, the Danish Health and Medicines Authority (DHMA) has chosen to use the expression 'consumer' instead of 'patient', since a patient is a person receiving treatment in the health care sector. Consumer is a broader expression than patient, as it includes a consumer buying contraceptive pills or over-the-counter medications without being considered a patient.

Since 2003, it has been possible for consumers or their representatives to report any suspected adverse drug reactions (ADRs). This possibility was implemented in response to the large number of ADRs experienced by consumers from the use of the weight loss product Letigen® during 2002.

The definition of an ADR was recently expanded due to new legislation that came into force in the summer of 2012. However, in this review it is relevant to apply the former definition of an ADR, because it was the valid definition during the period covered by this analysis. An ADR in this review is thus a reaction to a medicinal product which is noxious and unintended and that occurs at a dose normally used for prophylaxis, diagnosis or treatment.

The DHMA has reviewed all ADR reports received during the years 2003–2011 to clarify how consumer reports differ from reports from healthcare professionals and how they contribute to improving patient safety.

2 The purpose of a reporting system

The purpose of a system aimed at receiving reports of spontaneous ADRs from consumers is to enable the DHMA to discover new safety issues. Therefore, it is important to receive as many reports as possible – of the best possible quality.

An ADR report recorded in the DHMA's ADR database does not mean that there is a correlation between the medicinal product and the ADR. ADRs are reported to and recorded in the database even if it is only suspected that there is a correlation between the medicinal product and the ADR. Accordingly, the database contains reports of suspected ADRs.

Doctors have a duty to report certain suspected ADRs[1] (ref. 1), and consumers have an opportunity to do so, but not all suspected ADRs are reported. Underreporting is a well-known problem in Denmark as well as internationally, and reports received from consumers help to reduce this problem.

[1] Doctors and dentists must report suspected ADRs experienced by patients in their care. Within the first two years following placement of a new medicinal product on the market, all ADRs must be reported. After that period only serious ADRs must be reported.

However, the level of under-reporting varies between different medicinal products. ADRs of public interest that may have received attention from newspapers or television are reported more frequently than less exposed ADRs. Therefore, the incidence of an ADR cannot be estimated solely based on the number of spontaneous reports.

For the purposes of interpretation, spontaneous ADR reports should always be seen in the light of other available information such as the background occurrence of the events and the consumption of the medicinal product.

Consumer reports are not an alternative to reports from healthcare professionals – but the two types of reports complement each other. The general awareness of the fact that consumers can report ADRs is still limited, so there remains a need to spread information about this opportunity to consumers.

3 Consumer reports

It is possible for consumers to report directly to the DHMA electronically, in paper form or by telephone. Also, they can report to the company responsible for the product, which will then forward the report to the DHMA.

Reports from consumers and others, e.g. doctors, are processed almost in the same way in terms of follow-up and analysis. The difference is that consumer reports are not medically confirmed.

When receiving a consumer report on a serious ADR, the DHMA tries to obtain a medical confirmation of the ADR from the patient's doctor (GP or hospital doctor), i.e. to obtain a statement from a doctor that he/she believes there is a correlation between the medicinal product taken by the patient and the ADR in question. The doctor may also be contacted for further information about the patient's medical history.

The DHMA briefs the companies responsible for the products when receiving reports directly from doctors, nurses, consumers and others. In addition, the information is submitted to the common European pharmacovigilance database, EudraVigilance, and to the WHO in Uppsala, Sweden, ensuring that the medicines regulatory authorities in other countries may benefit from the information.

Assessment of the ADRs plays an important role in the DHMA's safety monitoring of medicines (pharmacovigilance). In addition to a daily assessment of all ADRs reported, each ADR is included in, e.g., the DHMA's analyses where data are compared electronically (signal generation).

The signals are analysed and compared to other data from, e.g., the EudraVigilance database and to information from the periodic safety update report (PSUR) for the product in question. The result may be that the issue will be further discussed at a European level in the European Pharmacovigilance Risk Assessment Committee, PRAC. The result may also be published on the DHMA's website and in the newsletter Danish Pharmacovigilance Update. Finally, it may be communicated to healthcare professionals, patient organisations etc.

4 Information campaigns

In 2007 and 2010, the DHMA completed information campaigns aimed at increasing the number of consumer reports. In 2007, a leaflet was distributed to pharmacies and GPs, in which consumers were encouraged to report ADRs from their medicine electronically. This leaflet included examples of ADRs, and it was pointed out to the reader that it is worthwhile to report ADRs, because they are included in the overall safety assessment of medicinal products.

In 2010, the campaign was aimed at hospital doctors among others, who received detailed information about how to report ADRs and why it should be done. Also, an e-learning programme concerning ADR reporting was developed in cooperation with the Danish Medical Association. In addition, the campaign involved various materials for use in training of pharmacy staff, i.a. leaflets to be handed out to consumers, help for the patient organisations' phone counselling in order to handle questions on ADRs, and input for the organisations for articles in member magazines and on websites.

5 Danish Council for Adverse Drug Reactions

Through the Danish Council for Adverse Drug Reactions, consumers may impact on the way ADRs are monitored by the DHMA. The Council consists of 11 members. The members should include representatives of healthcare professionals, pharmaceutical companies, pharmacies and other retail distributors of medicinal products, patients and consumers.

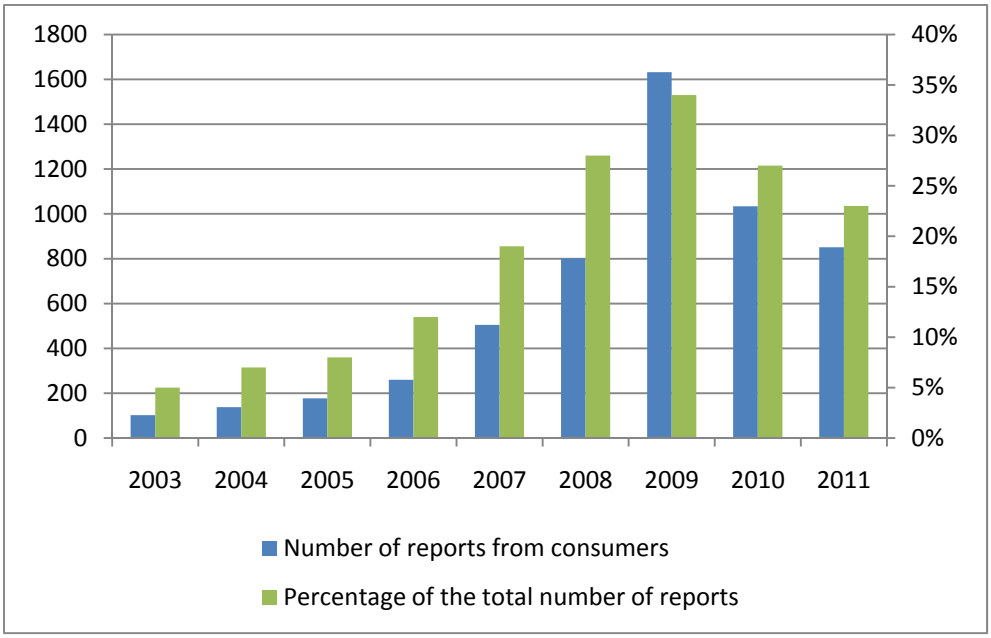
The Council was established by the DHMA. It provides consultancy regarding general questions on ADRs and makes recommendations and solution proposals on how to improve the DHMA's prevention and monitoring of ADRs.

6 Number of consumer reports received from 2003-2011

As shown in Figure 1, consumer reports increased during the years 2003–2011 in number as well as percentage of the total number of reports until 2009. Within the last two years studied, there has been a slight decrease.

The calculations comprise all reports where a consumer is recorded as reporter including reports that have also been reported by, e.g., a doctor or nurse either before, simultaneously or subsequently.

Figure 1. Consumer reports received from 2003-2011.



The number of consumer reports increased drastically in 2009 – mainly due to ADR reports associated with the Pandemrix® vaccine and Eltroxin®.

The Pandemrix® vaccine, which was used prophylactically against 'swine influenza', was introduced in 2009.

Also in 2009, the manufacturer of Eltroxin® changed the product excipients, and this change was sufficient to cause ADRs from the product in a number of patients. The symptoms corresponded to either overdosage or underdosage. The number of reports concerning Eltroxin® increased drastically that year and comprised 47% of the total number of consumer reports in 2009.

The Gardasil® vaccine was introduced into the childhood immunisation programme in 2009 and the number of ADRs reported was pronounced during an initial period following the introduction.

In 2009, there was a lot of public information as well as press coverage of ADRs from the use of the above-mentioned three drugs.

The DHMA concludes that the heavy focus on these three drugs contributed to increasing consumer awareness of ADRs and the public information available provided consumers with instructions on how to report.

For the product Eltroxin®, consumer reports were decisive for acknowledging the issue, and for Gardasil® and Pandemrix® consumer reports contributed to a quick solution of the ADR issues related to these products in practice.

The consumer reports in all three cases contributed significantly to the DHMA's communication.

7 Comparison of data between different reporters

In the reports, the reporting person is recorded as:

- Consumer
- Doctor[2]
- Other healthcare professional[3]
- Pharmacist

[2] Reports received from the Patient Insurance Association are recorded as ADRs from a doctor, because their case management involves a doctor who has thereby contributed to the description of the ADR.

[3] Other healthcare professionals are: nurses, dentists, social and healthcare assistants etc.

Hereafter, the following factors are compared across reporter type:

- Number of reports
- Gender and age of the consumer
- Time lag between ADR occurrence and reporting
- Number of ADRs
- System Organ Classes
- ADRs
- Medicinal products
- Most frequently reported combinations of substance and ADR
- Seriousness
- Outcome of the ADR.

7.1 Number of reports

During the period 2003-2011, a total of 26,162 reports were received. 1262 of these reports had more than one reporter (e.g. a consumer and a doctor). These latter reports are excluded below, because the aim was to look into characteristics of consumer reports as compared with reports from healthcare professionals.

Table 1. Reports sorted by reporter type. The percentage is shown in brackets.

Reporter type	Number
Consumers	4631 (18.6)
Doctors	17,746 (71.3)
Other healthcare professionals	2178 (8.7)
Pharmacists	345 (1.4)
Total	24,900 (100)

As shown in Table 1, 18.6% of reports from the period 2003-2011 were received from consumers.

Working with ADRs is an integral part of a doctor's job, and, according to the rules on ADR reporting, doctors have a duty to report certain ADRs, which can explain the fact that the majority of the reports are submitted by doctors. ADRs to be reported by doctors are described in reference 1.

7.2 Gender and age

For all reporter types, the DHMA received more reports concerning women than men. This is particularly pronounced for consumer reports, in that only around every fourth of these reports concern a man (Table 2).

Table 2. Percentage distribution of the reports according to gender of the consumer, by reporter type.

Reporter type	Gender		
	Male	Female	Not specified
Consumers	26.8	72.5	0.7
Doctors	37.0	60.5	2.5
Other healthcare professionals	40.1	56.4	3.5
Pharmacists	35.4	59.7	4.9

The proportion of ADR reports concerning male consumers is between 35.4% and 40.1% for reports from doctors, other healthcare professionals and pharmacists. The corresponding proportion is significantly lower for reports from consumers (26.8%) ($p < 0.0001$, chi^2).

For nearly all groups of drugs (ATC groups), the volume of medicine prescribed in the primary care sector is higher for women than men (ref. 2). There are no existing corresponding listings for the secondary care sector. Additionally, international studies show that women may be more prone to ADRs from certain types of medicine (ref. 3). Whether women also have a higher tendency than men to report ADRs is not known.

The age of the consumer at the time of onset of the ADR sorted by reporter type was also considered (Table 3).

Table 3. Average age of the consumer, by reporter type. The proportion of the reports for which the age of the consumer is known is shown in brackets

Reporter type	Average age of consumer in years. The proportion for which the age is known is shown in brackets.
Consumers	45.6 (82.7)
Doctors	47.4 (82.5)
Other healthcare professionals	46.6 (88.0)
Pharmacists	56.5 (65.0)

The average age of the consumer was between 45.6 and 47.4 years for ADR reports from doctors, other healthcare professionals and consumers, whereas it was significantly higher (56.5 years) ($P < 0.0001$, ANOVA) for reports from pharmacists. The explanation could be that elderly people receive more information about medicinal products at pharmacies than younger people, who search for this type of information on the internet instead.

Table 4. Average age of the male and female consumers, sorted by reporter type.

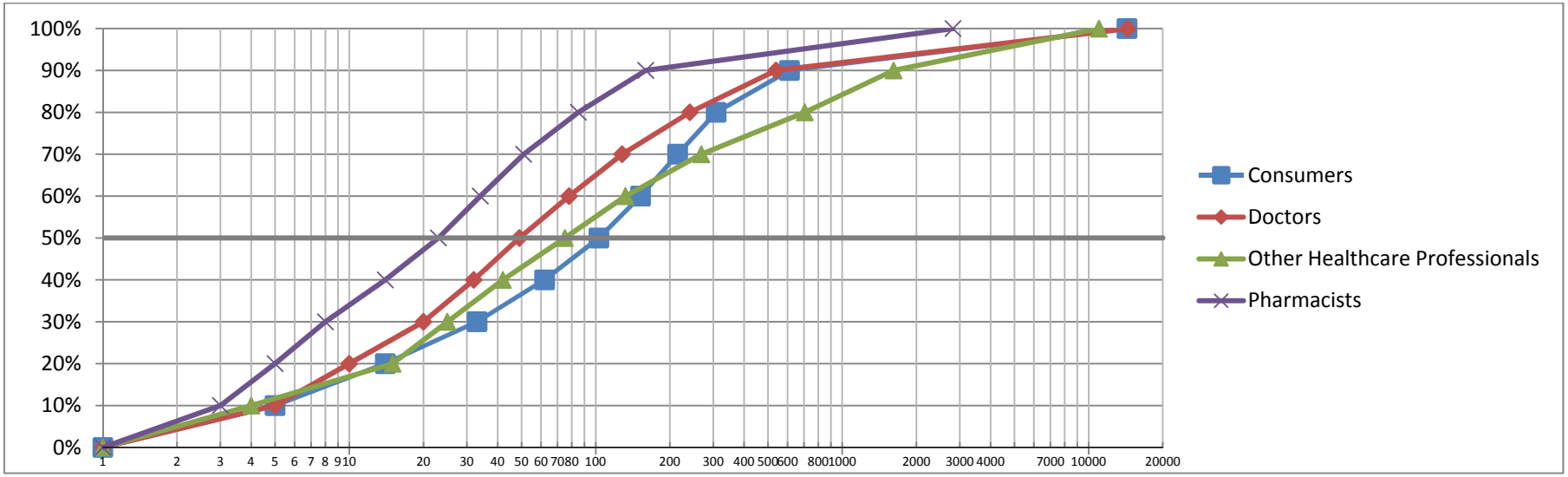
Reporter type	Male (years)	Female (years)	Proportion of reports in %, for which the gender and age are known.
Consumers	48.0	44.8	82.4
Doctors	47.4	46.9	82.0
Other healthcare professionals	46.1	47.0	77.0
Pharmacists	57.8	56.1	63.8

Table 4 shows differences in the average age of female and male consumers for the different reporter types. There are significant differences within all reporter types ($P = 0.0189$, ANOVA). The difference is smallest among doctors and largest among consumers.

7.3 The time lag between ADR occurrence and reporting

In Figure 2, the time lag between the occurrence of the ADR and the reporting to the DHMA has been calculated – see the next page.

Figure 2. Percentage of ADRs received as a function of days from their occurrence (semilogarithmic scale)[4] by reporter type.



The above figure shows that the 50% percentile, i.e. the time lag between the occurrence and the reporting to the DHMA of 50% of the ADRs reported, was 103 days for consumers, 49 days for doctors, 75 days for other healthcare professionals and 23 days for pharmacists.

[4] The figure comprises a total of 46,877 out of 61,884 possible ADRs. 29,391 (76%) from doctors, 13,729 (81%) from consumers, 3277 (62%) from other healthcare professionals and 480 (65%) from pharmacists. The remaining ADR reports provided either no date of occurrence or the date stated in the report was invalid.

As shown, consumers took the longest to report the ADRs. It may be due to the fact that a consumer is unaware that the condition in question may be caused by an ADR or that he/she is unaware of the existence of the reporting system. The delayed reporting may lead to a delay in the DHMA's analyses. Delayed reporting may also be problematic, because the factual circumstances of the ADR are easier to remember just after the occurrence.

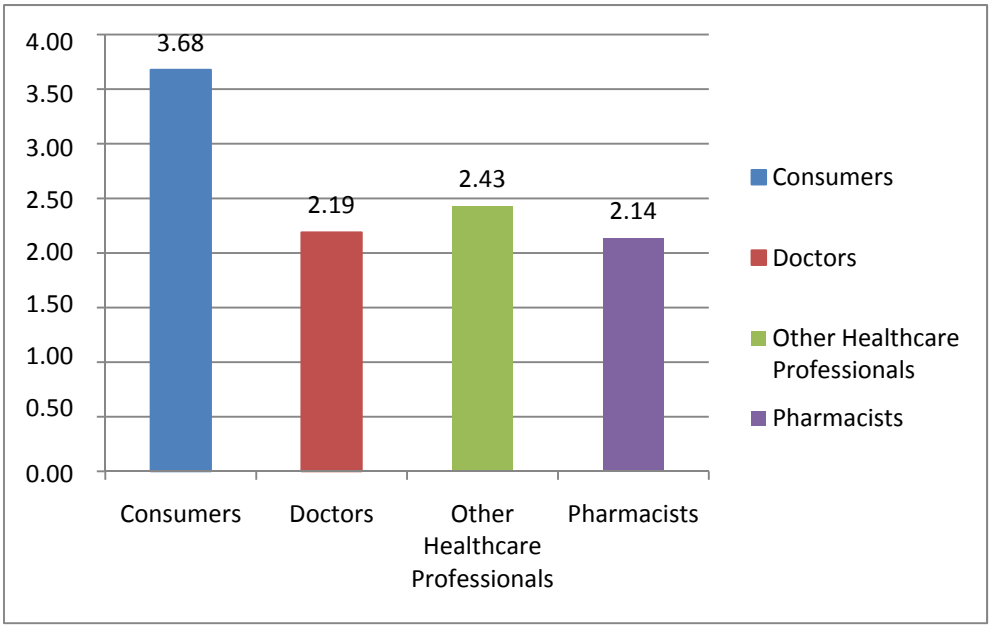
A pharmacist meets the customer at the time of redeeming or renewing a prescription at a pharmacy and provides customer guidance on ADRs among other things. At the pharmacy, the consumer may become aware that some of his/her symptoms may be related to ADRs and the pharmacist can then report them. Also, many consumers find it natural to contact a pharmacy, if they experience ADRs. This might explain why the time lag between the occurrence of the ADR and the reporting to the DHMA is shortest for ADRs reported by pharmacists.

Doctors have a duty to report and will quickly identify a correlation between a medicinal product and the consumer's symptoms by virtue of their education. This might explain why the time lag from the occurrence to the reporting is shorter for ADRs reported by doctors than for reports from consumers and other healthcare professionals.

7.4 Number of ADRs

A report may cover several ADRs. The average number of ADRs covered by a single report, by reporter type, has been examined (Figure 3).

Figure 3. Average numbers of different ADRs in a single report, by reporter type.



Consumer reports were found to cover more ADRs per report than reports from the other reporter types. One reason could be that consumers mainly reported disorders, whereas others reported disorders grouped in diagnoses.

7.5 System Organ Classes

Additionally, the frequency of System Organ Classes (SOCs) involved in ADR reports, by reporter type, has been examined (Table 5).

Table 5. The five most frequent SOCs involved in ADR reports, by reporter type.

Reporter type	System Organ Class	Percentage distribution of ADRs within each reporter type
Consumers	Nervous system disorders	19.6
	General disorders and administration site conditions	15.5
	Gastrointestinal disorders	14.3
	Psychiatric disorders	10.4
	Skin disorders	8.5
Doctors	General disorders and administration site conditions	16.4
	Skin disorders	14.2
	Nervous system disorders	13.7
	Gastrointestinal disorders	10.6
	Muscular disorders	6.3
Other healthcare professionals	General disorders and administration site conditions	17.2
	Nervous system disorders	14.2
	Gastrointestinal disorders	10.9
	Skin disorders	8.6
	Poisoning, injury and procedural complications	6.2
Pharmacists	General disorders and administration site conditions	21.4
	Gastrointestinal disorders	15.9
	Nervous system disorders	13.4
	Skin disorders	12.6
	Psychiatric disorders	6.8

Consumers most frequently reported ADRs within the SOC 'nervous system disorders', whereas doctors, other healthcare professionals and pharmacists most frequently reported ADRs within the SOC 'general disorders and administration site conditions'.

All reporter types have at least four SOCs in common as shown in the above list.

The five most frequent SOCs involved in ADR reports are the same for consumers and pharmacists, but placed in different orders.

For consumers and doctors, four SOCs are identical in the list of the five most frequent SOCs involved in ADR reports. The fifth SOC is 'muscular disorders' for doctors and 'psychiatric disorders' for consumers.

Consumers and other healthcare professionals also have four SOCs in common in the above list of the five most frequent SOCs. The fifth SOC is 'poisoning, injury and procedural complications' for other healthcare professionals and 'psychiatric disorders' for consumers.

7.6 ADRs

Also, the most frequently reported ADRs for the different reporter types have been determined. (Table 6).

Table 6. The five most frequently reported ADRs, by reporter type.

Reporter type	ADR	Percentage distribution of ADRs within each reporter type
Consumers	Headache	17.5
	Fatigue	16.8
	Dizziness	14.4
	Nausea	12.5
	Muscle pain	7.0
Doctors	Nausea	5.0
	Fever	4.7
	Urticaria	4.7
	Headache	4.6
	Dizziness	4.6
Other healthcare professionals	Nerve injury	5.1
	Injection site pain	4.6
	Headache	4.6
	Oral hypoaesthesia	4.0
	Nausea	4.0

Pharmacists	Lack of effectiveness	11.6
	Dizziness	8.1
	Nausea	7.0
	Unexpected therapeutic response with substitution	5.8
	Abuse	5.5

As shown in the above table, the most frequent ADRs are headache and fatigue in consumer reports, nausea and fever in reports from doctors, nerve injury and injection site pain in reports from other healthcare professionals and lack of effectiveness and dizziness in reports from pharmacists.

Furthermore, the table shows that the ADRs nausea, headache and dizziness appear in the list of the five ADRs most frequently reported by consumers as well as in the corresponding list for doctors.

ADRs such as headache, fatigue, dizziness, nausea and muscle pain are the ADRs most frequently reported by consumers, which most likely reflects the effect of the ADRs on their quality of life. However, the background occurrence of these disorders in the general population is high.

For consumers, differences between men and women for the ten most frequently reported ADRs were studied. Weight gain, heart palpitations and abdominal pain are only included in the list of female ADRs. On the other hand, diarrhoea, itching and fever are only included in the list of male ADRs. (Data not shown.)

For all four reporter types, the proportion of the ADRs describing disorders associated with the sexual life (e.g. erectile dysfunction, reduced libido and sexual dysfunction) was also examined. The proportion is 0.68% for consumers, 0.37% for doctors, 0.13% for other healthcare professionals and 0.68% for pharmacists. Even though the numbers are small, there are indications that consumers report these ADRs themselves or mention them to a pharmacist at a pharmacy – rather than informing their GP.

7.7 Medicinal products

Number of substances reported

In this report, a substance refers to the active part of the medicine.

A report may comprise more than one suspected substance for one or more suspected ADRs. However, as specified in Table 7, the majority of reports comprised one substance only, and the consumer reports comprised one substance more often than the reports from the other groups.

Table 7. Percentage distribution of the reports according to whether they comprised one or more than one suspected substance, by reporter type.

Reporter type	One suspected substance in the report	More than one suspected substance in the report
Consumers	95.5	4.5
Doctors	92.0	8.0
Other healthcare professionals	88.2	11.8
Pharmacists	95.4	4.6

As shown in Figure 4, only few ADR reports (out of thousands) comprised more than two different substances across all reporter types. The highest number in a report was 12. This number appeared in a single consumer report.

Figure 4. Percentage distribution of the reports according to the number of substances per report, by reporter type.

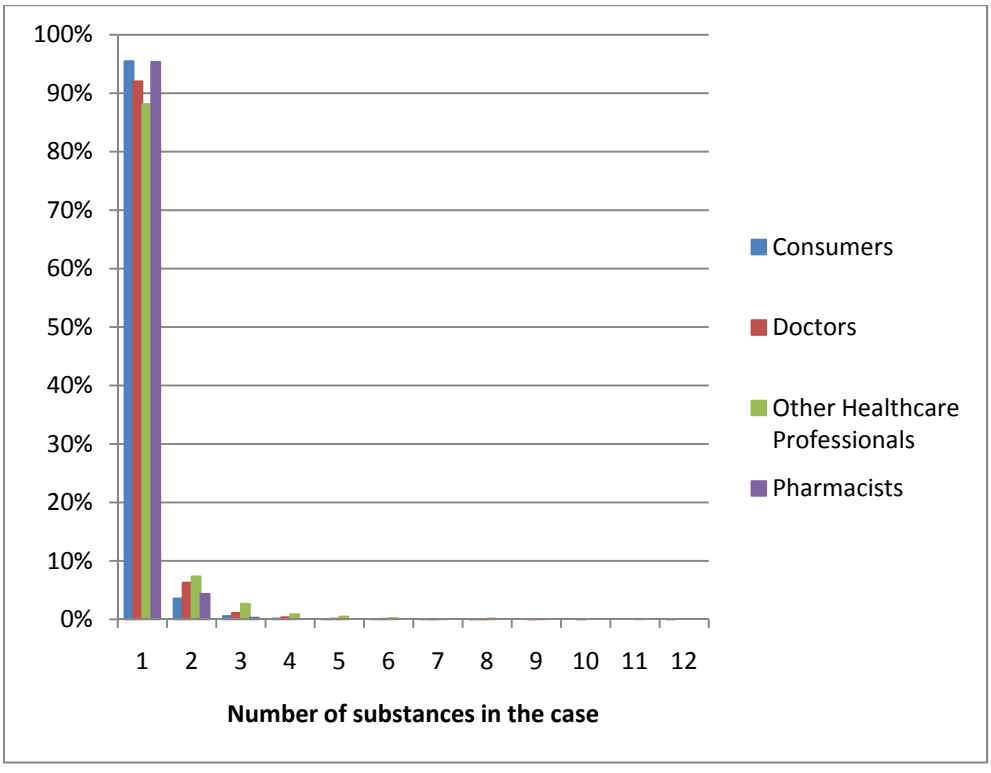


Table 8. Average number of substances per report and reported ADRs per substance, by reporter type.

Reporter type	Number of substances per report	Number of ADRs per substance
Consumers	1.06	3.45
Doctors	1.11	1.98
Other healthcare professionals	1.21	2.01
Pharmacists	1.05	2.04

As shown in the above table, consumer reports comprised the second-lowest number of substances per report, but the highest number of ADRs per substance. As described earlier, consumers may have mainly reported disorders, whereas doctors and other healthcare professionals may have reported disorders grouped in diagnoses.

Consumer reports were expected to comprise more substances per report than the other types of reports, as one might assume that they had had difficulties distinguishing the product causing the ADR and therefore reported all the products received. However, that is not the case. 95.5% of consumer reports comprised one substance only, and the average number of substances per report was low.

The most frequently reported product groups

The most frequently reported product groups have been determined and subsequently grouped according to ATC codes (Anatomical Therapeutic Chemical Classification) in the table below.

Table 9. The ten most frequently reported product groups by reporter type. The percentage of reports comprising at least one product from the stated ATC code is shown in the appropriate cells below, sorted by reporter type [5]. See also Annex I, where the ATC codes mentioned in Table 9 are explained.

	Product groups (ATC codes)																
Reporter type	J07	N06	L04	N05	L01	C09	M01	C10	G03	J01	H03	N02	N03	N01	R03	A10	R06	A02
Consumers	6	9		4		3		5	5	6	22	3	3					
Doctors	14	10	8	5	5	4	4	4	4	4								
Other healthcare professionals	9	6	12	6	7				3	3			4	9	3			
Pharmacists		6				7		4	4	5		4			8	5	4	4

[5] Unambiguous ATC group: 27. 099
ATC group chosen on the basis of the route of administration, indication or information in the narrative 664
Uncertain ATC group. The most likely group is chosen. 31
Unknown ATC group. Medicinal product not known - or not filled in – e.g. if the only information available is 'NSAID' or 'antipsychotic' 11
In total : 27. 886

As shown in the above table, products from the ATC group H03 (thyroid therapy) appear most frequently in the consumer reports. The most frequent ATC groups are J07 (vaccines) from doctors, L04 (immunosuppressants) from other healthcare professionals and R03 (drugs for obstructive airway diseases) from pharmacists.

The most frequently reported substances within the ATC codes in Table 9, have been determined. The table below shows the three most frequently reported substances.

Table 10. The three most frequent substances within the most frequently reported ATC code, sorted by reporter type.

Reporter type	ATC code	Substance
Consumers	H03	Levothyroxine sodium (98%), including Eltroxin® (98%), thiamazole (1%) and propyl thiouracil (0.5%).
Doctors	J07	Influenza, purified antigen (28%), including Pandemrix® (71%), diphtheria-Haemophilus influenzae B-pertussis-poliomyelitis-tetanus (16%) and human papillomavirus (types 6, 11, 16, 18) (15%).
Other healthcare professionals	L04	Infliximab (43%), etanercept (15%) and adalimumab (9%).
Pharmacists	R03	Budesonide (33%), formoterol and other products for obstructive pulmonary disease (23%), terbutaline (17%).

The most frequently reported substances

The most frequently reported substances have been determined for the four reporter types. Annex II lists the ten most frequently reported substances for each reporter type. Figure 5 shows the ten substances most often found in ADR reports from doctors and their frequencies. This figure also shows the frequencies of these substances in consumer reports.

Figure 6 shows the ten substances most often found in consumer reports and their frequencies. This figure also shows the frequencies of these substances in reports from doctors.

Figure 5. The ten substances most frequently found at least once in reports from doctors. The frequencies of these ten substances found in reports from consumers are shown for comparison.

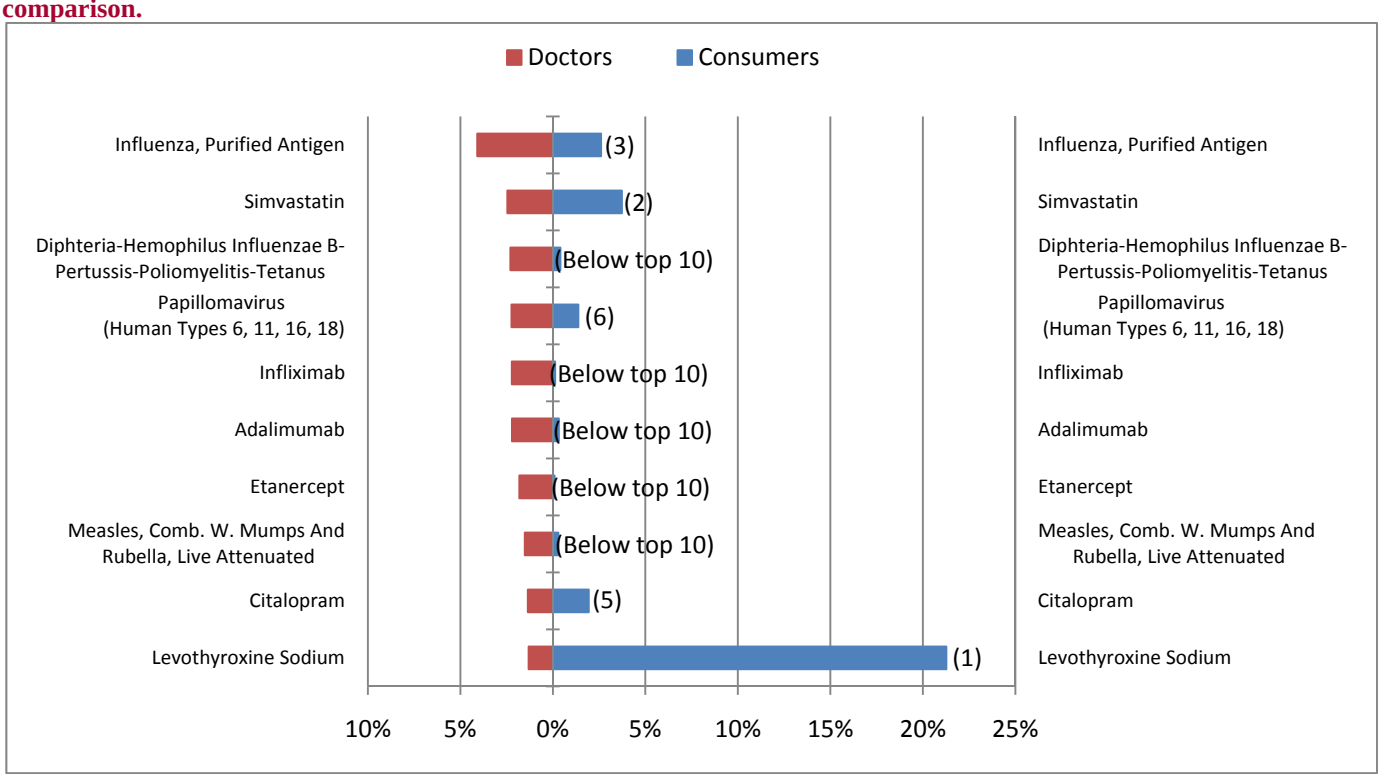
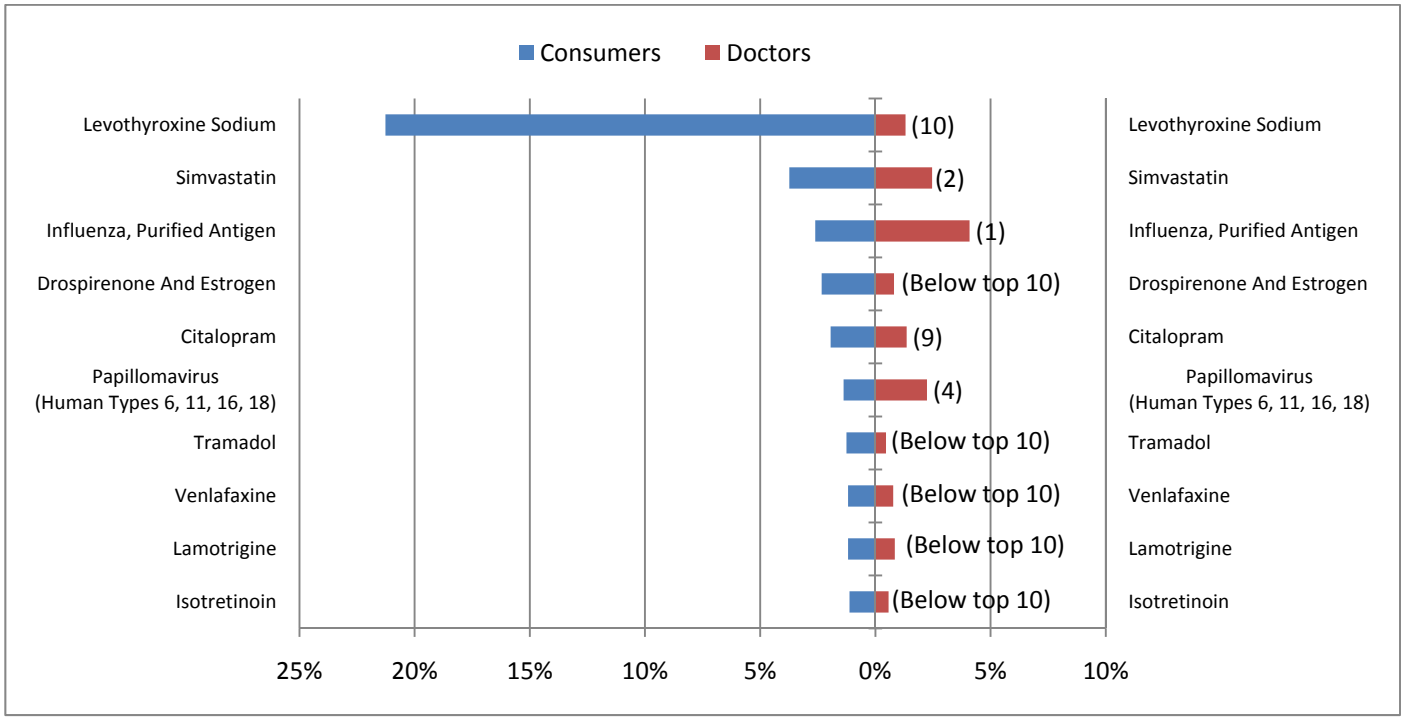


Figure 6. The ten substances most frequently found at least once in reports from consumers. The frequencies of these substances found in reports from doctors are shown for comparison.



Figures 5 and 6 show that the following five substances are included in the list for consumers as well as the list for doctors: simvastatin, levothyroxine sodium, influenza, puri-

fied antigen, citalopram and papillomavirus. Influenza, purified antigen, is also included in the corresponding list for other healthcare professionals.
Simvastatin and citalopram are also included in the list of the ten substances most frequently found in ADR reports from pharmacists[6].

The number of ADR reports for the different substances should be seen in the light of the consumption, which is high for citalopram and simvastatin. Furthermore, the number of ADR reports concerning a particular substance reflects the concept stimulated ADR reporting: The number of ADR reports received by the DHMA for a particular substance increases with the media focus on that substance. This is evident for the year 2009 for the substance levothyroxine sodium (see page 7). This implies that consumers become aware that they are experiencing an ADR and, not least, that their knowledge about the opportunity to report ADRs is increased.

7.8 Most frequently reported combinations of substance and ADR

The DHMA has looked into differences between the ADRs reported for the five above-mentioned substances most frequently reported by consumers and doctors. For each reporter group Annex III lists the ADRs for which the difference in reporting frequency was 1% or more between doctors and consumers.

For these five substances, presence of ADRs reported only by consumers was shown. However, these ADRs are only described in a few percent / parts per thousand of the reports for the substance in question (0.2-1.5%). (Data not shown.) Examples are shown below.

Table 11. Examples of ADRs reported only by consumers.

Substance	Examples of ADRs reported only by consumers
Simvastatin	Weight loss, change in the sense of taste, inflammation of the eye
Levothyroxine sodium	Increased heart rate, night sweats, dysphonia
Influenza, purified antigen	Ear pain, thirst, stomach discomfort
Citalopram	Change in the sense of taste, somnolence, increased appetite
Papillomavirus	Patchy baldness, dry skin, food allergy

Also, the most frequently reported combination of substance and ADR for each reporter group has been determined.

[6]Annex II lists the ten most frequently reported substances for all four reporter types.

Table 12. The most frequently reported combination of substance and ADR for each reporter type.

Reporter type	Substance – ADR combination (%)
Consumers	Levothyroxine sodium – fatigue (2.7)
Doctors	Diphtheria-Haemophilus influenzae B-pertussis-poliomyelitis-tetanus – fever (0.4)
Other healthcare professionals	Anthrax - injection site pain (1.1)
Pharmacists	Insulin aspart – ineffective product (0.8)

Consumers reported many ADRs in association with a change of Eltroxin® excipients by the manufacturer in 2009 (see above).

The vaccine DTaP-IPV/Act-Hib is included in the Danish childhood immunisation programme (3 months, 5 months and 13 months) and, to a large extent, is administered by doctors.

It comes as a surprise that injection site pain in association with anthrax vaccination is the most frequently reported combination for other healthcare professionals.

The DHMA has studied these reports in detail.

They were reported during the years 2003–2004. Based on the Danish political decision to join the war against Iraq, the Danish Defence decided to vaccinate all personnel to be deployed in Iraq against anthrax. During the period from March 2003 to February 2004, 1,899 vaccinations of a total of 755 persons were recorded at the Defence vaccination sites (ref. 4). All ADRs were recorded, which explains the high frequency of the above-mentioned combination of substance and ADR.

Insulin aspart is an injection fluid (fast-acting insulin analogue). When renewing a prescription at a pharmacy, the consumer most likely will inform the staff if the previously redeemed product was ineffective.

7.9 Seriousness

A report is recorded as serious, if one or more of the ADRs reported resulted in death, were life-threatening, required hospitalisation or prolonged hospitalisation, or caused persistent or significant disability or incapacity, or were a congenital anomaly or birth defect. A report may comprise more than one seriousness criterion.

However, a report could also be recorded as serious, even if none of these criteria are met, in case it is found medically significant. For reports submitted directly to the DHMA, this seriousness criterion is ticked off upon receipt by the DHMA, when judged – based on the information in the report – that the condition would have developed to meet one or more of the seriousness criteria if the patient had not received treatment. Furthermore, the European Medicines Agency, EMA, has decided that all reports of certain ADRs must be recorded as serious reports. Companies have similar guidelines for use of the seriousness criterion 'medically significant'.

Through all the years studied, the ADR reporting form for healthcare professionals has included tick boxes for the above-mentioned seriousness criteria. The ADR reporting form for consumers changed over the years 2003-2011. Previously, it was possible for consumers to tick off any of the above-mentioned seriousness criteria. On the present form, they can only tick off whether the ADR required hospitalisation. The other seriousness criteria are ticked off upon receipt by the DHMA based on the text written in each report by consumers.

Table 13. Percentage distribution of the reports according to seriousness (serious or non-serious) by reporter type.

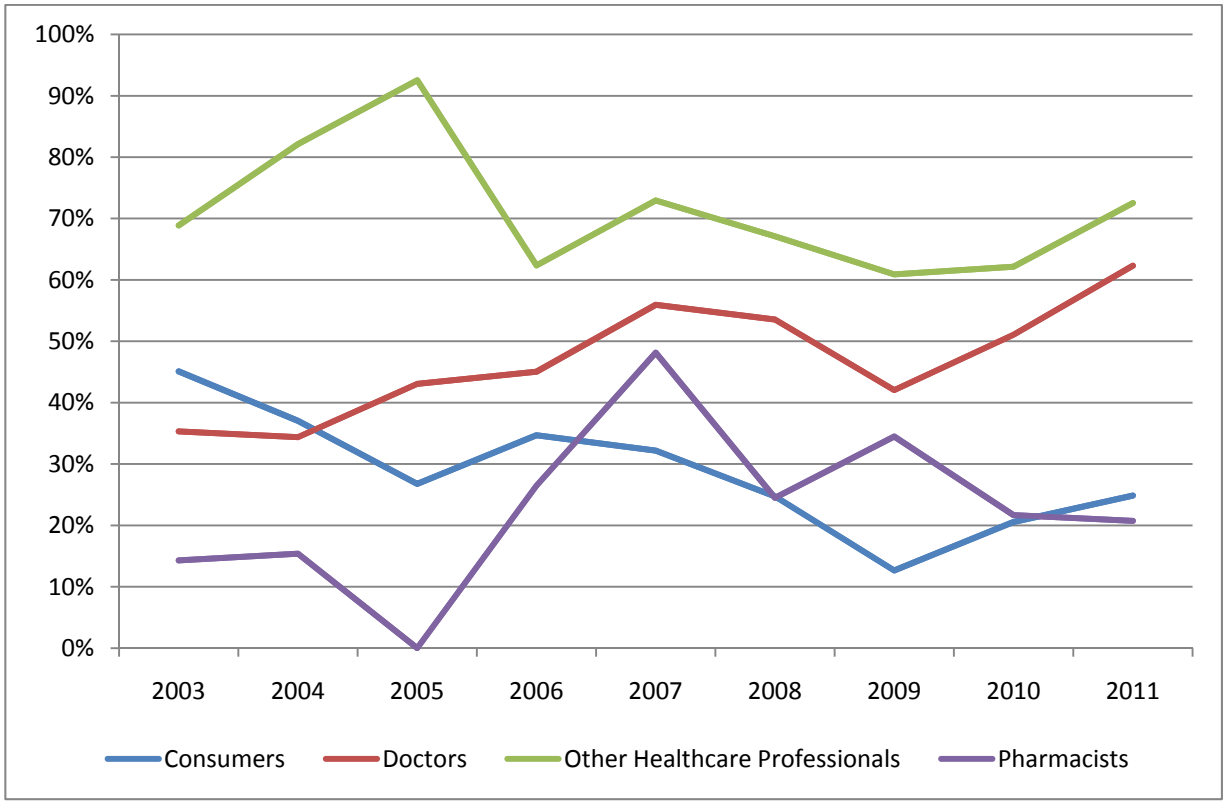
Reporter type	Serious reports	Non-serious reports
Consumers	22.2	77.8
Doctors	47.7	52.3
Other healthcare professionals	71.7	28.3
Pharmacists	25.2	74.8

Around a fourth of the consumer reports and the reports from pharmacists are characterised as serious, whereas the corresponding figure for reports from doctors is 48%. For other healthcare professionals, this percentage is 72.

The difference may be caused by the fact that doctors are also required to report non-serious ADRs for some products (ref. 1), and other healthcare professionals may not have found it necessary to report non-serious ADRs. For consumers and pharmacists, the seriousness of ADRs most likely has not influenced the decision to report.

Since 1 July 2010, the DHMA has tried to obtain a medical confirmation of the most serious ADRs reported by consumers (see above). During the period 1 July 2010 through 31 December 2012, the attempt was only successful for 18% of the reports. Lack of confirmation can be explained by the following: Either it was not possible to obtain a reply from the doctor asked, or the doctor found that the consumer's symptoms were not caused by the product administered.

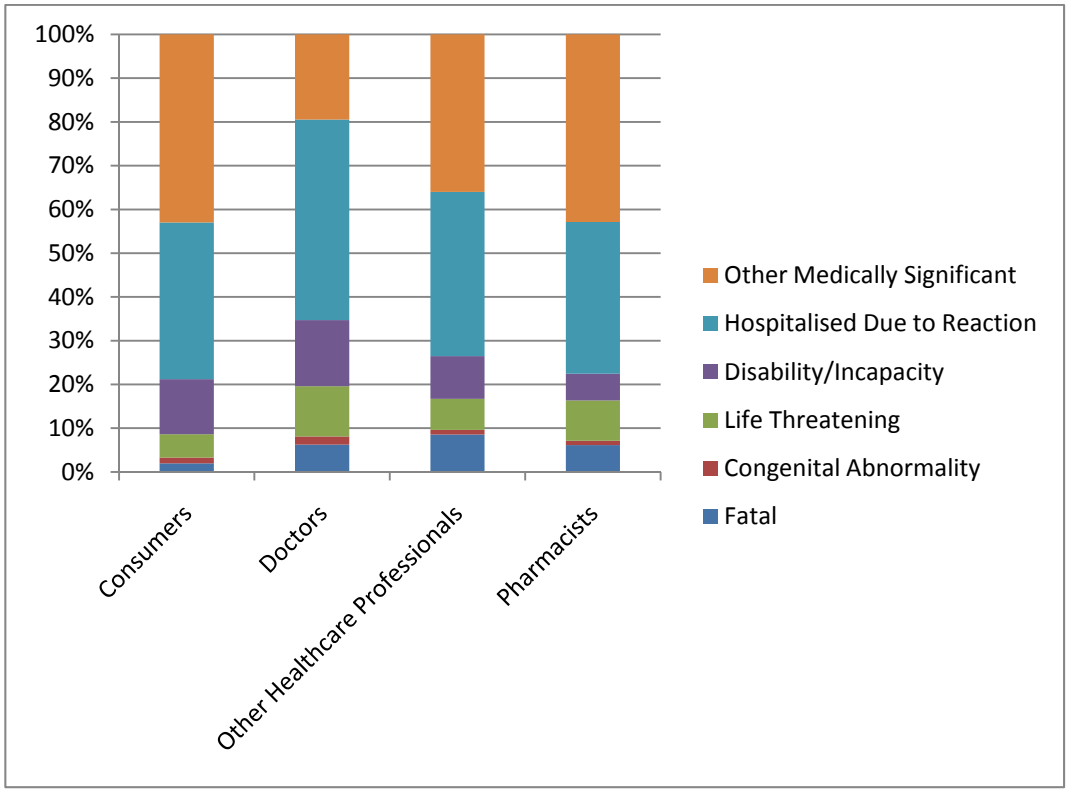
Figure 7. Proportion of serious reports per year sorted by reporter type.



The above figure shows how the proportion of serious reports has changed over the years for the different reporter types. In 2009, when the number of ADRs from consumers peaked, there was a concurrent decrease in the proportion of serious ADRs. The number of reports concerning Eltroxin® increased drastically that year and comprised 47% of the total number of reports from consumers in 2009, but 93% of these reports were non-serious.

Through all the years studied, the group of other healthcare professionals submitted the highest proportion of serious reports.

Figure 8. Percentage distribution of seriousness criteria, by reporter type.



As shown by the above figure, consumers used the seriousness criterion 'disability' almost as often as doctors. The reason may be that, in such situations, they were continuously reminded of their condition and the cause of it, and then decided to report the ADR.

When a consumer is not able to report, a representative can do it. However, the psychological state of the representative who just lost a loved one can explain the low proportion of reports with the seriousness criterion fatal for this group. Doctors have a duty to report ADRs if they believe there is a correlation between a product and the death of a consumer.

The seriousness criteria 'congenital anomaly', 'life-threatening', 'disability' and 'required hospitalisation or prolonged hospitalisation' were used relatively more often by doctors than any of the other groups, and the percentage of reports with the seriousness criterion 'medically significant' is lowest for this group.

Other healthcare professionals, pharmacists and doctors used the seriousness criterion 'fatal' most often. However, the figures for pharmacists are low and they refer only to reports concerning six consumers who died.

7.10 Outcome of the ADR

When reporting an ADR, the outcome is recorded as:

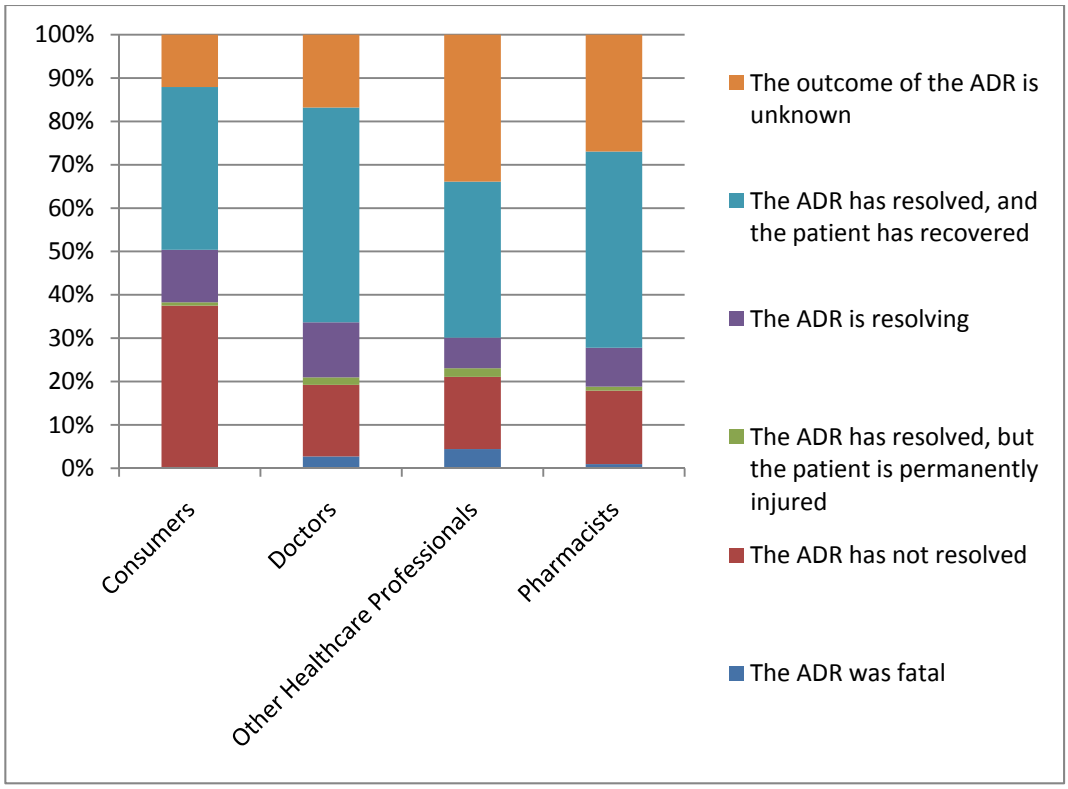
- The ADR has resolved, and the patient has recovered
- The ADR has not resolved

- The ADR has resolved, but the patient is permanently injured
- The ADR is resolving
- The ADR was fatal
- The outcome of the ADR is unknown

Through all the years studied, the ADR reporting form for healthcare professionals has included tick boxes for the above.

As mentioned above, the ADR reporting form for consumers changed over the years 2003-2011. Previously, it was possible for consumers to tick off any of the above-mentioned ADR outcomes. On the present form, they can only tick off whether an ADR reported has not resolved, has resolved, or whether it is resolving. Other ADR outcomes are ticked off upon receipt by the DHMA based on the text written in each consumer report.

Figure 9. Percentage distribution of the ADR outcome by reporter type



As shown by the above figure, all four groups most frequently reported ADRs which have resolved and had no consequence. Furthermore, this figure shows that ADRs resulting in death for the consumer most frequently were reported by other healthcare professionals and doctors.

For consumers, ADRs of the type 'has not resolved' are the second-most frequently reported ADRs. This is understandable, since the consumers, at the time of reporting that type of ADR, were experiencing the ADR and continuously reminded of their situation – and therefore decided to report the ADR. However, the different groups may also interp-

ret concepts such as 'being healthy' differently. A doctor may be of the opinion that a patient is healthy if, e.g., values for blood tests have normalised, whereas the consumer may still be tired and consider that an ongoing ADR.

The frequencies of ADRs of the types 'has not resolved', 'is resolving' or 'the outcome is unknown' are seen almost as often as in reports from doctors.

For other healthcare professionals and pharmacists, ADRs of the type 'the outcome is unknown' are the second-most frequently reported ADRs. This can be explained by the fact that these groups do not monitor patients closely after onset of ADRs.

8 Comparison with other countries

In the past, it was not possible for consumers to report ADRs in all countries. However, in July 2012, a new legislation entered into force throughout the EU, according to which all member states must have a reporting system for ADRs reported by consumers.

In the Netherlands and UK, as in Denmark, it has been possible for consumers to report ADRs for many years, and these two countries have analysed the reports received from consumers.

8.1 The UK

In 2011, a study of ADR reports was published in the UK (ref. 5).

In the study which covered a two year period (1 October 2005 – 30 September 2007), all reports were analysed. During this period, 19.8% of the ADRs were reported by consumers and 80.2% by healthcare professionals.

In the reports from consumers as well as from healthcare professionals, more ADRs concerned women than men. In the consumer reports, 63% of ADRs concerned a woman. The corresponding figure for reports from healthcare professionals was 57%.

In the consumer reports, the median age was around 54 years. In the reports from healthcare professionals, it was 53 years. For both reporter types, the median age of male consumers was higher than for female consumers in the reports analysed.

The consumer reports comprised a significantly higher number of ADRs (median 3) per report than the reports from healthcare professionals (median 2).

The three System Organ Classes (SOCs) most frequently involved in ADR reports submitted by consumers were 'nervous system disorders', 'general disorders and administration site conditions' and 'gastrointestinal disorders'. For healthcare professionals, the SOCs most frequently involved were 'skin disorders', 'general disorders and administration site conditions' and 'nervous system disorders'.

The most frequent ADRs reported by consumers were nausea, headache and dizziness. For healthcare professionals, they were nausea, headache and vomiting.

The top three product groups reported by consumers were nervous system products followed by cardiovascular products and systemic anti-infective products. The corresponding list for healthcare professionals included the same three products groups, but in the

following order of decreasing frequency: nervous system products, systemic anti-infective products and, finally, cardiovascular products.

For both reporter groups, 58.8% of reports were classified as serious. However, the seriousness criteria for which an ADR required hospitalisation, was life-threatening or resulted in death were more frequently ticked off in the reports from healthcare professionals than from consumers. Approx. 45% of consumer reports described that a reported ADR or the outcome thereof had an impact on common everyday activities.

More healthcare professionals than consumer representatives reported an ADR that resulted in the consumer's death. The reports from healthcare professionals described more frequently that the consumer had recovered. Conversely, far more consumers reported that they had not recovered.

8.2 The Netherlands

The Dutch study (ref. 6) covers the three-year period April 2004 through April 2007.

Consumers and healthcare professionals submitted 19% and 81%, respectively, of the total number of reports.

Here too, reports from both groups mainly concerned female consumers (63% for consumers and 61% for healthcare professionals).

The reports from consumers comprised 2.1 ADR on average. For reports from healthcare professionals, the corresponding figure was 1.6.

The median age was 48 years in the consumer reports and 49 years in the reports from healthcare professionals. There are no gender specific figures.

The three SOCs most frequently involved in ADR reports submitted by consumers were 'nervous system disorders', 'psychiatric disorders' and 'gastrointestinal disorders'. The corresponding list for other healthcare professionals included the same three SOCs. However, the list for pharmacists included the SOC 'skin disorders' rather than 'psychiatric disorders'.

The most frequent ADRs reported by consumers were myalgia (muscle pain), fatigue and headache. For healthcare professionals, they were headache, rash and dizziness.

The types of drugs most frequently reported by consumers were statins, selective serotonin reuptake inhibitors and beta-blockers in the listed order. Healthcare professionals are divided into GPs, specialists and pharmacists. The most frequently reported product groups were statins, beta-blockers and anticoagulants for GPs, benzodiazepines, proton pump inhibitors and statins for specialists and statins, benzodiazepines and anticoagulants for pharmacists.

In the reports from consumers, 19.5% of ADRs were classified as serious, and the corresponding figure in the reports from healthcare professionals was 21% - in other words, fairly equal figures. However, the seriousness criteria for which an ADR required hospitalisation, prolonged hospitalisation or resulted in death were more frequently ticked off in the reports from healthcare professionals than from consumers. Consumers, on the other hand, reported more frequently than healthcare professionals that an ADR caused disability or was life-threatening.

With respect to ADR outcomes, more consumers than healthcare professionals described in their ADR reports that the ADR had not resolved.

9 Summary

The number of reports from consumers has seen an increase from 2003, the year they were given the opportunity to report, and up until 2009, after which a slight decrease has been noted. In the last four years studied, the consumer reports represented more than 20% of the total number of reports received by the Danish Health and Medicines Authority.

The review found similarities as well as differences between reports from consumers, doctors, other healthcare professionals and pharmacists.

As regards the personal characteristics such as gender and age, all reporter types submitted more reports concerning women than men. The reports from pharmacists differ markedly with respect to the average age of the consumer.

The number of ADRs per report is 3.7 for the consumer reports received, whereas the corresponding number is between 2.1 and 2.4 for the other reporter types. The reason could be that consumers mainly reported disorders, whereas the other reporter types reported disorders grouped in diagnoses.

The five most frequent System Organ Classes (SOCs) involved in ADR reports are almost identical across the four types, but consumers most frequently reported ADRs within the SOC 'nervous system disorders', and doctors, other healthcare professionals and pharmacists most frequently reported ADRs within the SOC 'general disorders'.

The ADRs most frequently reported are headache and fatigue in consumer reports, nausea and fever in reports from doctors, nerve injury and injection site pain in reports from other healthcare professionals and lack of product effectiveness and dizziness in reports from pharmacists. The ADRs nausea, headache and dizziness appear in the list of the five ADRs most frequently reported by consumers as well as in the corresponding list for doctors.

The number of substances per report is between 1.05 and 1.21. The consumer reports comprise a low number (1.06), and 95.5% of their reports comprise one substance only.

The most frequently reported product groups found in the ADR reports differed between the reporter types. It was thyroid therapy for consumers, vaccines for doctors, immunosuppressants for other healthcare professionals and drugs for obstructive airway diseases for pharmacists.

An analysis of the substances reported showed that five in ten substances are identical in the lists of the ten most frequently reported substances by consumers and doctors, respectively. For these five substances, presence of ADRs reported only by consumers, was shown.

The percentage of reports classified as serious varied between the reporter types. Consumers reported the lowest percentage of serious reports. Also, there was a difference in the use of the seriousness criteria. Consumers used the criteria death and life-threatening less frequently than the other reporter groups. Whether these data are comparable is open

to discussion, because the ADR reporting form for consumers changed during the period studied.

All reporter types most frequently reported ADRs with the outcome that the ADR has resolved, and the consumer has recovered. For consumers, ADRs which has not resolved are the second-most frequently reported ADRs. This is understandable, since the consumers, at the time of reporting that type of ADR, were experiencing the reaction and were thus continuously reminded of their situation – and therefore decided to report the ADR. However, the different reporter types may also have interpreted concepts such as 'being healthy' differently.

A review of the existing literature from the Netherlands and UK showed that there are certain similarities to the Danish consumer reports.

10 Conclusion

Based on nine years of handling consumer reports, the Danish Health and Medicines Authority (DHMA) has found that the contribution from this reporter type to the total number of ADR reports is significant, quantitatively as well as qualitatively. In general, the consumer reports provide valuable, well-documented information.

There are many similarities between reports from consumers and healthcare professionals, respectively – but also differences. Consumer reports are not an alternative to reports from healthcare professionals – but they complement each other. There is no doubt that reports from consumers contribute significantly to a reliable safety monitoring of medicines.

This report concerns an analysis of the ADR reports received in the DHMA's database during the period 2003-2011. Hence, this description reveals the complete picture – as it is not a random sample from the database, and there is no data uncertainty. Accordingly, statistics only includes variables for which data are not comprised by all the reports, i.e., gender and age of the consumer.

In Denmark, electronic signal generation has been renewed in recent years. The contribution of spontaneous reports from consumers will be monitored on an ongoing basis.

Following this analysis, the DHMA initiated an electronic questionnaire survey in order to establish what motivates consumers to report ADRs. The results are to be used in helping the DHMA find out where and how to take action in order to ensure that more consumers will report future suspected ADRs of the medicine they take. The results of the survey will be available in the middle of 2013.

11 Reference list

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12 List of Annexes

Annex I: ATC codes used in Table 9.

Annex II: The ten most frequently reported substances, by reporter type.

Annex III: ADRs reported for simvastatin, levothyroxine sodium, influenza, purified antigen, citalopram and Papillomavirus, by reporter type.

Annex I: ATC codes used in Table 9

A02: Drugs for acid-related disorders

A10: Drugs used in diabetes

C09: Agents acting on the renin-angiotensin system

C10: Lipid modifying agents

G03: Sex hormones and modulators of the genital system

H03: Thyroid therapy

J01: Antibacterials for systemic use

J07: Vaccines

L01: Antineoplastic agents

L04: Immunosuppressants

M01: Antiinflammatory and antirheumatic products

N01: Anaesthetics

N02: Analgesics

N03: Antiepileptics

N05: Psycholeptics

N06: Psychoanaleptics

R03: Drugs for obstructive airway diseases

R06: Antihistamines for systemic use

Annex II: The ten most frequently reported substances, by reporter type

Tables A-D show, for each reporter type, the ten most frequently reported substances. The number of reports comprising the substance is shown as well.

A. Consumers

Substance	No. of reports comprising the substance at least once (%)
Levothyroxine sodium	985 (21.3)
Simvastatin	173 (3.7)
Influenza, purified antigen	121 (2.6)
Drospirenone and oestrogen	108 (2.3)
Citalopram	90 (1.9)
Human papillomavirus (types 6, 11, 16, 18)	64 (1.4)
Tramadol	58 (1.3)
Venlafaxine	55 (1.2)
Lamotrigine	55 (1.2)
Isotretinoin	52 (1.1)

B. Doctors

Substance	No. of reports comprising the substance at least once (%)
Influenza, purified antigen	726 (4.1)
Simvastatin	436 (2.5)
Diphtheria-Haemophilus influenzae B-pertussis-poliomyelitis-tetanus	407 (2.3)
Human papillomavirus (types 6, 11, 16, 18)	397 (2.2)
Infliximab	394 (2.2)
Adalimumab	393 (2.2)
Etanercept	322 (1.8)
Measles, comb. w. mumps and rubella, live attenuated	269 (1.5)
Citalopram	241 (1.4)
Levothyroxine sodium	232 (1.3)

C. Other healthcare professionals

Substances	**No. of reports comprising the substance at least once (%)**
liximab	125 (5.7)
Articaine, combinations	83 (3.8)
Anthrax vaccines	75 (3.4)
Grass pollen	50 (2.3)
Etanercept	43 (2.0)
Diphtheria-Haemophilus influenzae B-pertussis-poliomyelitis-tetanus	38 (1.7)
Influenza, purified antigen	31 (1.4)
Rituximab	30 (1.4)
Lidocaine, combinations	27 (1.2)
Quetiapine	27 (1.2)

D. Pharmacists

Substances	**No. of reports comprising the substance at least once (%)**
Budesonide	10 (2.9)
Insulin aspart	9 (2.6)
Losartan and diuretics	8 (2.3)
Dextromethorphan	8 (2.3)
Simvastatin	8 (2.3)
Citalopram	7 (2.0)
Formoterol and other products for obstructive pulmonary disease	7 (2.0)
Nicotine	6 (1.7)
Atorvastatin	5 (1.5)
Omeprazole	5 (1.5)

Annex III: ADRs reported for simvastatin, levothyroxine sodium, influenza, purified antigen, citalopram and papillomavirus, by reporter type

Tables A-E show the ADRs for the substances: simvastatin, levothyroxine sodium, influenza, purified antigen, citalopram and papillomavirus for which the difference in the reporting frequency between doctors and consumers was 1% or more.

The tables show the occurrence of the ADRs as a percentage of all ADRs reported for the substance sorted by reporter type.

Table A. Simvastatin

Simvastatin				
ADR	**Consumers**	**Doctors**	**Other health-care professionals**	**Pharmacists**
Rhabdomyolysis	0	3.3	8.7	0
Muscle spasms	4.2	1.5	0	5.0
Extremity pain	3.3	1.6	0	5.0
Increased concentration of creatinine phosphokinase	0.2	1.6	4.4	0
Impaired memory	1.5	0.4	0	0
Insomnia	1.8	0.5	0	0
Joint pain	5.2	3.8	0	0
Nausea	1.7	2.9	0	0
Urticaria	0	1.2	4.4	0
Sleeping problems	1.7	0.5	0	0
Muscle pain	8.8	10.1	8.7	0
Fatigue	4.0	2.9	4.4	0
Memory loss	1.7	0.3	0	0

Table B. Levothyroxine sodium

Levothyroxine sodium				
ADR	**Consumers**	**Doctors**	**Other healthcare professionals**	**Pharmacists**
Weight gain	3.5	1.5	5.6	0
Headache	7.0	5.4	1.4	9.1
General malaise	1.2	2.6	1.4	0

Table C. Influenza, purified antigen

Influenza, purified antigen				
ADR	**Consumers**	**Doctors**	**Other healthcare professionals**	**Pharmacists**
Urticaria	0.2	2.5	0	0
Extremity pain	4.2	1.9	3.5	0
Nausea	4.6	2.4	10.5	0
Headache	6.3	4.2	6.1	0
Injection site pain	3.6	2.2	3.5	14.3
Fatigue	4.9	3.6	1.8	0
Myalgia	2.3	3.6	3.5	0
Rash	0.4	1.6	1.8	0
Influenza-like symptoms	2.7	1.5	0	14.3
Redness at the injection site	0.6	1.7	0.9	0

Table D. Citalopram

Citalopram				
ADR	**Consumers**	**Doctors**	**Other healthcare professionals**	**Pharmacists**
Suicidal thoughts	2.1	0.3	0	0
Hyponatraemia	0	1.7	0	0
Headache	4.6	3.1	7.7	7.1
Therapeutic response unexpected with substitution	0.4	1.9	0	7.1
Weight gain	1.8	0.3	0	0
Change in the sense of taste	1.4	0	0	0
Nausea	5.0	3.6	2.6	7.1
Fatigue	2.5	1.2	0	0
Confusion	0	1.2	0	0
Insomnia	1.8	0.7	2.6	0
Influenza-like condition	1.4	0.3	2.6	0
Arrhythmias	1.4	0.3	0	0
Paraesthesias	1.4	0.3	0	0
Somnolence	1.1	0	0	0
Urticaria	0	1.0	0	0

Table E. Papillomavirus

Papillomavirus				
ADR	**Consumers**	**Doctors**	**Other healthcare profes-sionals**	**Pharmacists**
Itchy rash	4.4	1.8	0	0
Urticaria	3.7	5.3	4.4	0
Patchy baldness	1.5	0	0	0
Dry skin	1.5	0	0	0
Food allergy	1.5	0	0	0
Muscle spasms	1.5	0.1	0	0
Dizziness	5.2	3.8	4.4	0
Swelling at the in-jection site	0.7	2.0	0	0
Headache	5.9	4.7	8.7	0
Lymph gland tu-mour	0	1.1	0	0
Pain	0	1.1	0	0
Extremity pain	2.2	1.2	0	0