ANNUAL REPORT

The Danish Health and Medicines Authority's annual pharmacovigilance report 2012

Sundhedsstyrelsen

Contents

2012 – continued improvement of the safety of medicinal products

The overall aim of the Danish Health and Medicines Authority's (DHMA's) pharmacovigilance work is *continued improvement* of the safety of medicinal products. The specific activity may be, e.g., making changes to product information or package leaflets, issuing warnings on the use of a medicinal product in a particular population or information for doctors or the general population. However, safety of medicinal products also involves creating transparency with respect to adverse reactions reported and easy access to package leaflets and product information.

Pharmacovigilance work has been strengthened in recent years, primarily via targeted action plans and a wide collaboration with all parties based on discussions in and recommendations from the Danish Council for Adverse Drug Reactions. In 2012, the DHMA initiated a change in the Council for Adverse Drug Reactions. Through an amendment to the Danish Medicines Act, the DHMA established the Danish Pharmacovigilance Council which replaces the Council for Adverse Drug Reactions. Like its predecessor, the new Council will advise the DHMA on handling issues regarding pharmacovigilance and adverse reactions.

Under the heading *continued improvement*, the DHMA focused on communication and transparency , analyses of adverse reaction data and international collaboration.

Communication about the safety of medicinal products is now better structured. The DHMA issues the monthly newsletter Danish Pharmacovigilance Update, in which we describe new findings and studies and focus on adverse reactions reported to the Danish database. Doctors, pharmacists and the industry are frequent readers.

If we need to issue information on a short notice, the information is published on the DHMA's website or as direct communication to the relevant players, including, e.g., publication on Promedicin.dk (Danish website). Furthermore, once a year, the DHMA prepares an annual report covering all of its activities.

For several years, it has been on our agenda to find a way to extend the focus on *continued improvement* to transparency with respect to adverse reactions reported. This is a rather difficult task, since there is a lot of data, and they are to be presented anonymously and in such a way that makes sense. In continuation of the pharmacovigilance action plan, the DHMA implemented its new IT system Sentinel which made it possible to place all Danish adverse reaction data from 1968 and up until now on the website.

In the summer of 2012, new and improved EU legislation on pharmacovigilance entered into force. As a result, the European work on adverse reactions is now organised in a new and more efficient way. A committee was established to discuss issues on pharmacovigilance and safety of medicinal products according to firm procedures. The European work on adverse reactions is another field of *continued improvement*. The committee has two Danish members.

Collaboration is a precondition for creating *continued improvement* in the DHMA's work on safety of medicinal products. Therefore, the DHMA has entered into collaboration with Aalborg Hospital Science and Innovation Center in Aalborg, the Statens Serum Institut, National Institute for Health Data and Disease Control, the Danish National Agency for Patients' Rights and Complaints and others.

It is very important to *continue improving* the reports from Danish hospitals. In 2012, the Capital Region of Denmark and Region Zealand decided to establish a special function to handle adverse reaction reporting – a so-called Adverse Drug Reaction Manager. The decision was based on a previous, experimental establishment of such a function that resulted in a quantitative and qualitative improvement. The initiative deserves high praise and recognition.

Development in the number of adverse reaction reports from 2009 to 2012

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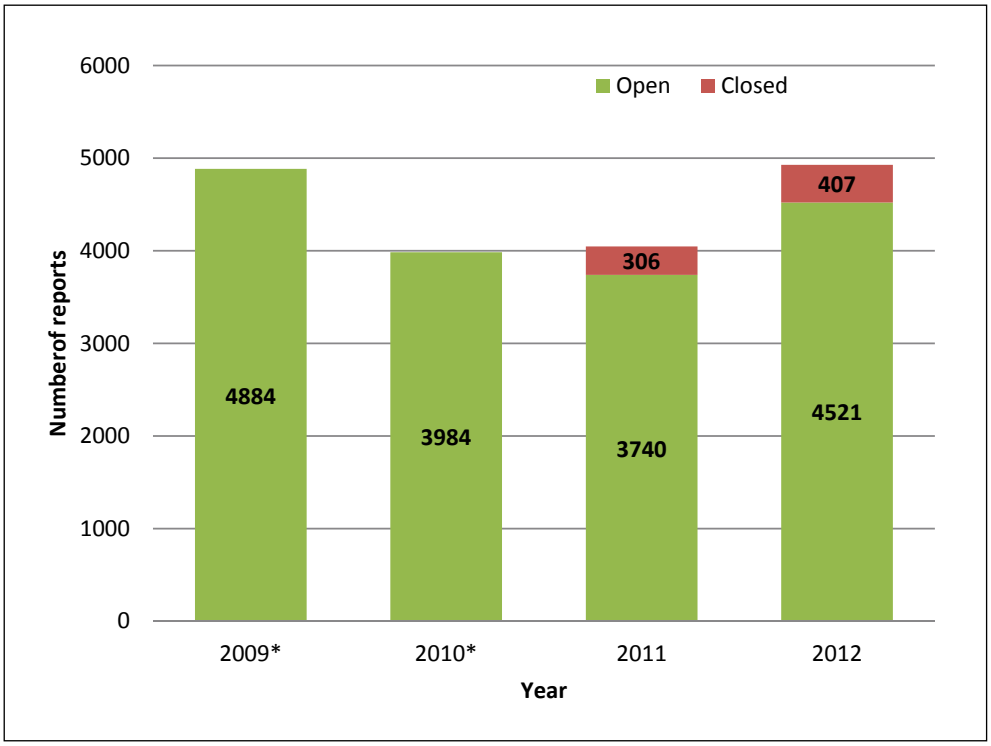

Figure A. Development in the number of adverse reaction reports from 2009 to 2012.
** The numbers of duplicate reports in 2009 and 2010 have not been determined. Therefore, only the green columns are comparable.*

In 2012, the DHMA received a total of 4,521 adverse reaction reports. Of these reports, approx. 47% were classified as serious.

Due to the new legislation from 2012, the number of adverse reaction reports increased compared to the previous two years, primarily because more reports from consumers were filed by companies. The large number of adverse reaction reports in 2009 was due to unusually many reports concerning Pandemrix®, Gardasil® and Eltroxin®, which characterised the pharmacovigilance work that year.

The DHMA will continue to focus on the importance of adverse reaction reporting in order to improve the pharmacovigilance and safety of medicinal products on a continuous basis.

The number of adverse reaction reports in 2012 by reporter type

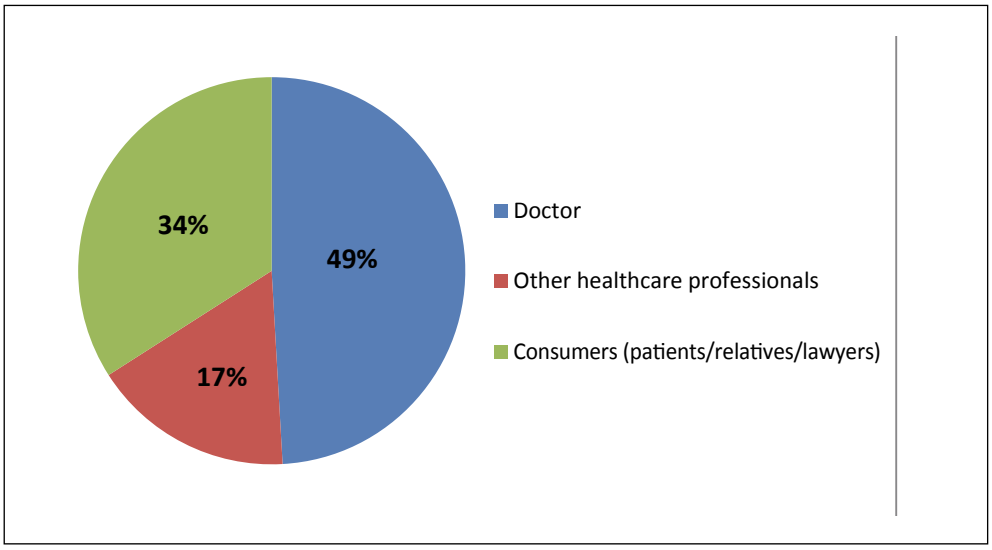

Figure B. The number of adverse reaction reports in 2012 by reporter type. ***

In 2012, as in 2011, doctors filed the most adverse reaction reports with the DHMA. Doctors accounted for 49% of the reports, while consumers or their representatives accounted for 34% of the adverse reaction reports. The remaining 17% of the reports came from other healthcare professionals.

This distribution differs from that seen in 2011, since the DHMA received more reports from consumers or their representatives and fewer from doctors in 2012. In 2011, 61% of the reports came from doctors and 25% from patients and their relatives. The total number of reports from doctors was 2,452 in 2012 as opposed to 2,724 in 2011. The development is primarily a result of the fact that more adverse reaction reports from consumers are being filed by companies concerning consumers (read more about this development on pages *20-21*) and an increase in the number of patient insurance cases.

The percentage of serious adverse reaction reports decreased to 46% in 2012 as opposed to 60% in 2011. An explanation for this increase in reports from consumers in 2012 may be

* We have chosen to include reports from lawyers along with reports from medicine users, since reports in this category are received from the Danish Patient Insurance Association – thereby being cases representing a medicine user.

** Among the reports received, there are several so-called duplicates – a duplicate in the sense that the same report was received from different reporters. Such reports are taken as one, therefore only counting as one report, but both reporters are included in the statement of types of reporters.

*** Unexpected adverse reactions are adverse reactions not included in the summary of product characteristics for the medicinal product in question.

that the reports typically were non-serious. Of the reports from consumers, 71% were non-serious, whereas the corresponding figure was 45% for the reports from doctors.

According to the Danish medicines legislation, doctors have an obligation to report all serious adverse reactions as well as suspected unexpected adverse reactions*** from all medicinal products. Furthermore, doctors have an obligation to report all suspected adverse reactions observed within the first two years following placement of a new medicinal product on the market.

Other healthcare professionals, medicine users and their relatives do not have an obligation to report adverse reactions to the DHMA, but they have an opportunity to do so.

You can report adverse reactions from medicinal products at *report a side effect or incident*

Top 5 of the most frequently reported active substances and consumption figures in 2012

Since 3 August 2012, the holder of the marketing authorisation for a medicinal product has been obliged to report all suspected adverse reactions observed in Denmark to the DHMA. Prior to that date, the marketing authorisation holder only had to report suspected serious adverse reactions. That makes it difficult to compare the 2012 top 5 lists of the most frequently reported active substances and vaccines to the top 5 lists published in previous annual reports.

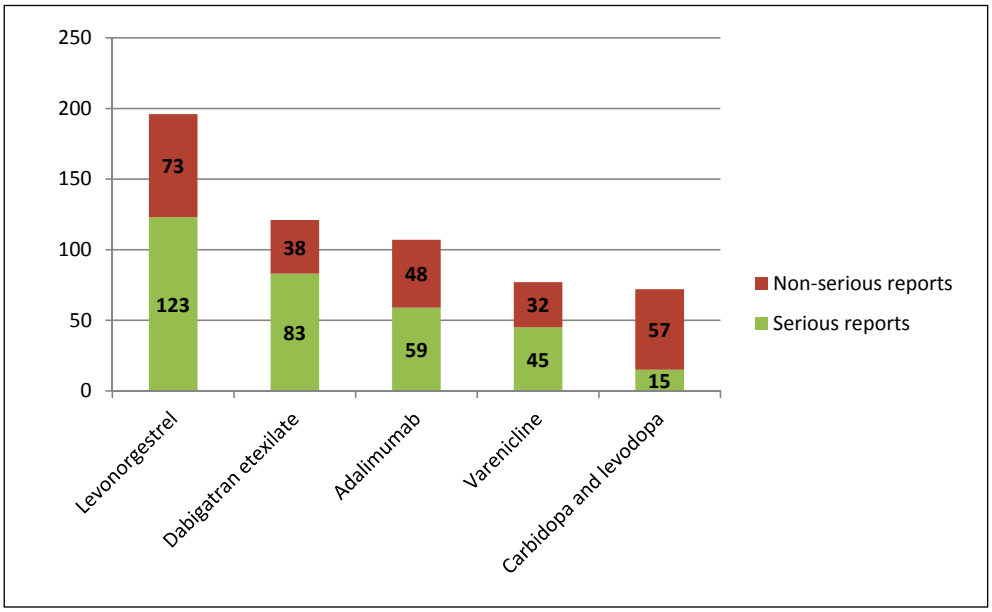

Figure C. Top 5 of the most frequently reported active substances with adverse reactions in 2012.

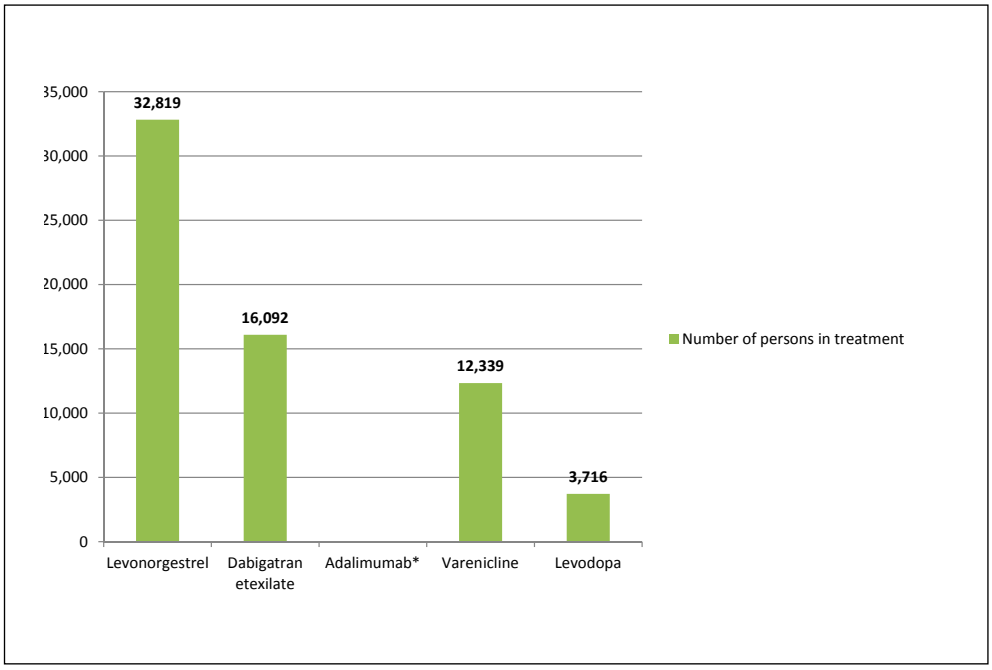

Figure D. Number of persons in treatment with active substances on the top 5 of the most frequently reported in 2012.[1] [2]

The five active substances for which the most adverse reactions were reported in 2012, are shown in Figure C. The number of adverse reaction reports for active substances should always be seen in the light of the consumption of the medicinal product as shown in Figure D.

The consumption figures are from the Danish Register of Medicinal Product Statistics of the State Serum Institute. The number of persons in treatment was calculated as the number of persons having redeemed at least one prescription for the active substance in question in 2012. Adalimumab (marked with an * in Figure D) is primarily given to patients in hospitals or purchased for use in the practice of specialists. Therefore, the exact number of patients in treatment with this type of medicinal product is unknown.

Levonorgestrel (Mirena® and NorLevo®)

The highest number of reports in 2012 concerned the active substance levonorgestrel, for which the DHMA received a total of 196 reports. Of these reports, 123 were categorised as serious.

Levonorgestrel is a gestagen hormone used either alone or in combination with oestrogen in different types of contraceptives. The statement herein only covers medicinal products containing levonorgestrel as the only active substance, and therefore does not include

1 Levodopa comprises Duodopa, Levodopa/carbidopa 'Teva', Sinemet 12.5/50, Sinemet Depot and Sinemet Depot Mite.

2 Here, levonorgestrel does not comprise NorLevo, as this is an over-the-counter drug.

contraceptive pills. All reports but one concerned the medicinal product with the trade name Mirena®. The remaining report concerned NorLevo®.

Mirena® is a hormone IUD inserted into the uterus as contraception. The product has been marketed since 1993 and thus is not a new medicinal product. NorLevo® is a tablet for acute contraception to be used within 72 hours after unprotected intercourse or after contraceptive failure. NorLevo® has been marketed since 2001.

The majority of the reports in 2012 concerned known adverse reactions. Among the adverse reactions most frequently reported were, e.g., vaginal bleeding and IUD rejection/dislocation.

Many of the reports have been forwarded to the DHMA by the company marketing Mirena®. To a certain extent, the reporting is stimulated, since the reports have been submitted from doctors to the company via a 'warranty scheme', under which the company covered part of the expense for an IUD up until 15 August 2012, in case it was decided to remove it based on a medical assessment.

Since July 2012, the marketing authorisation holder has followed the European Medicines Agency's instructions to classify bleedings as serious adverse reactions. These were previously classified as non-serious. This may explain why the percentage of serious adverse reactions for this active substance is still high, now that the marketing authorisation holder must also report non-serious adverse reactions to the DHMA.

Dabigatran etexilate (Pradaxa®)

The second highest number of reports in 2012, a total of 121, concerned dabigatran etexilate. Of these reports, 83 were categorised as serious.

Dabigatran etexilate is used for the prevention of blood clots in adult patients following elective total hip or knee replacement surgery (reconstructive surgery) and for the prevention of blood clots in adult patients with non-valvular atrial fibrillation.

Dabigatran etexilate was marketed for the former indication in 2008 and for the latter indication in August 2011. The number of users and the number of adverse reaction reports increased from 2011 to 2012.

The reports mainly concerned gastrointestinal symptoms, particularly bleedings. Gastrointestinal bleeding is a known adverse reaction.

Patients receiving dabigatran etexilate or other types of anticoagulants have an increased risk of bleeding as compared to patients not receiving anticoagulants. When prescribing anticoagulant therapy, the doctor should specifically consider the patient's age and overall bleeding risk.
Elderly patients have an increased risk of bleeding, per se.

On pages *33-34* of this annual report, the DHMA describes issues related to the use of dabigatran etexilate with a particular focus on the new indication, the number of users and adverse reaction reports. The issues are also mentioned in the newsletters *Danish Pharmacovigilance Update, March 2012*, and *Danish Pharmacovigilance Update, September 2012*.

Adalimumab (Humira®)

In 2012, the DHMA received a total of 107 reports concerning the biological drug adalimumab. Of these reports, 59 were categorised as serious.

Adalimumab is used for the treatment of various immunoinflammatory diseases, e.g., rheumatoid arthritis, Crohn's disease and psoriasis, if other medicines have shown lack of efficacy.

The adverse reactions most frequently reported comprised, i.a., known adverse reactions such as administration site reactions (rash, redness, pain and itching). In the field of biological medicines, the DHMA collaborates with a number of clinical databases, i.e., DANBIO, Dermbio and DCCD, in which adverse reactions are recorded.

Varenicline (Champix®)

In 2012, the DHMA received 77 reports concerning varenicline. Of these reports, 45 were recorded as serious.

Champix® is indicated for smoking cessation in adults and was marketed in 2006.

The adverse reactions most frequently reported were, i.a., psychiatric adverse reactions such as depression. The summary of product characteristics mentions post-marketing reports of changes in behaviour or thinking, including depression.

Levodopa and carbidopa (Duodopa®, Sinemet®)

A total of 72 reports concerning Duodopa® and Sinemet® were received in 2012. Of these reports, 15 were recorded as serious. Only one report concerned Sinemet®. The products are used for the treatment of Parkinson's disease and Parkinson's syndrome.

Sinemet® is taken as tablets, and Duodopa® is a gel suspension for continuous administration via a tube. Duodopa® is used for the treatment of advanced levodopa-responsive Parkinson's disease when other drugs have not given satisfactory results.

The adverse reactions most frequently reported concerned tube-related issues in particular, e.g., occlusion and dislocation. These issues are described in the summary of product characteristics for Duodopa®.

Top 5 of the most frequently reported vaccines and consumption figures in 2012

The five most frequently reported vaccines in 2012 are shown in Figure E. In general, there are much fewer vaccines in the market compared to conventional medicines, but on the other hand, many people are vaccinated in connection with immunisation programmes.

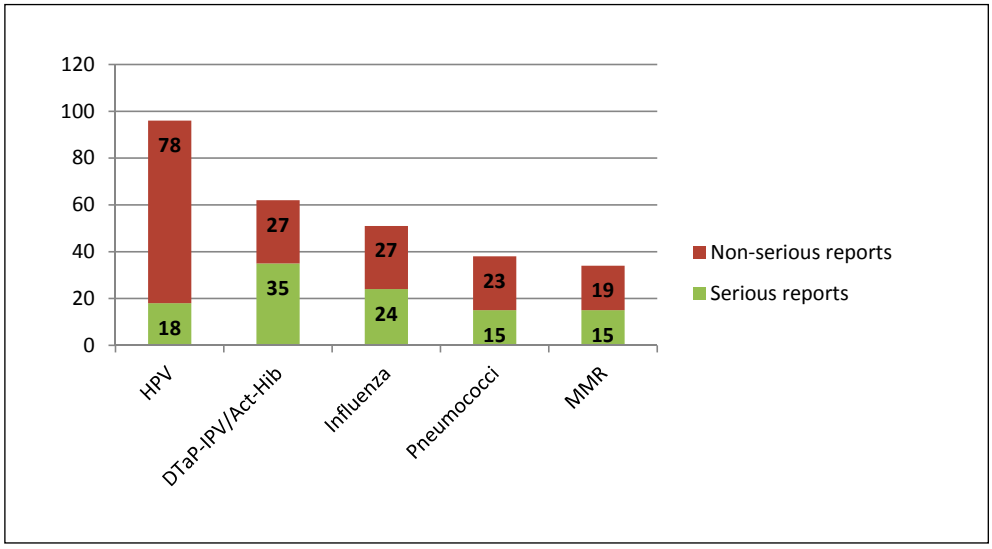

Figure E. Top 5 of the most frequently reported vaccines with adverse reactions in 2012.

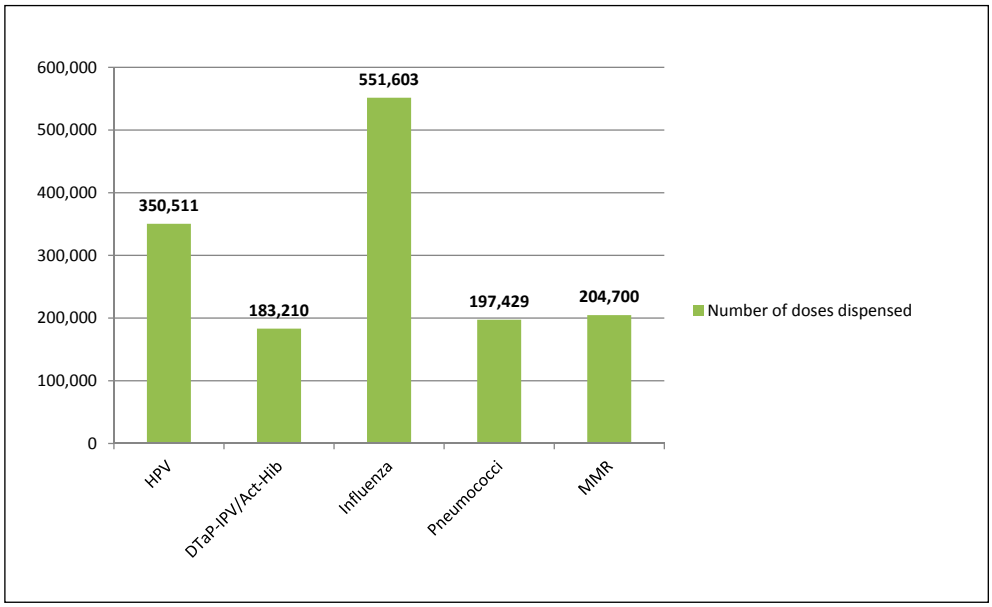

Figure F. Number of doses dispensed of vaccines on the top 5 of the most frequently reported in 2012.

The number of vaccinees/number of doses dispensed

The figures in Figure F are extracted from the Danish Register of Medicinal Product Statistics. The figures show the number of doses dispensed. Several vaccines are given a number of times to the same person, such as in the childhood immunisation programme, and vaccines dispensed in 2012 were not necessarily used in that year.

Vaccines included in the childhood immunisation programme

Among the vaccines for which the most adverse reactions were reported, are the vaccines included in the childhood immunisation programme. The vaccines concerned are the HPV vaccine (Gardasil®), the diphtheria-tetanus-pertussis-polio-Hib (meningitis) vaccine (DTaP-IPV/Act-Hib), the vaccine against measles, mumps and rubella (MMR) and the pneumococcal vaccine (Prevanar). The HPV vaccine had the highest number of reports of all the vaccines.

The majority of the adverse reactions reported were known and comprised, i.a., general malaise, including dizziness, headache and fever, urticaria and injection site reactions such as itching, redness and granuloma formation.

With the Danish Finance Act of 2012, funds were allocated to offer vaccination against cervical cancer (HPV vaccination) to all women born in 1985-1992 during 2012 and 2013. The free vaccination with HPV vaccine must be given during the period 27 August 2012 up until the end of 2013. This may explain why the number of HPV vaccines dispensed and the number of adverse reaction reports have increased as compared to 2011.

As of 1 April and the rest of 2012, vaccination against measles, mumps and rubella (MMR) was available free of charge in Denmark for young adults who had not had measles and had not previously been vaccinated against measles. The offer was targeted at persons over the age of 18 born in 1974 or later.

The Danish Health and Medicines Authority's (DHMA's) vaccination panel, which consists of representatives from various DHMA units and the Statens Serum Institut, National Institute for Health Data and Disease Control, met quarterly in 2012 to assess the suspected adverse reactions reported for vaccines (primarily vaccines in the childhood immunisation programme).

The assessments of the adverse reactions reported are described in the newsletters *Danish Pharmacovigilance Update, June 2012*, and *Danish Pharmacovigilance Update, October 2012*. The overall conclusion is that the Danish childhood immunisation programme continues to be safe.

Influenza vaccines (seasonal influenza and Pandemrix®)

When assessing the number of reports by vaccine, the 51 reports concerning influenza vaccines was the third highest number of reports received by the DHMA.

The majority of the reports concerned vaccination against seasonal influenza. The adverse reactions most frequently reported are known and concerned, i.a., influenza-like symptoms including joint pain, fever and fatigue as well as administration site reactions such as swelling, redness and pain.

Again in 2012, the DHMA received reports concerning the influenza A H1N1 vaccine Pandemrix®. The vaccine was not used in Denmark in 2011 and 2012, and the reports all concerned vaccinations given in 2009. The potential adverse reactions occurred in 2009-2010.

Adverse reaction reports from Danish hospitals by region from 2010 to 2012

In 2012, the DHMA received a total of 1,064 adverse reaction reports from the regional hospitals and psychiatry. Reports from private hospitals, clinics and municipal psychiatry are not included in this number. For 2011 and 2012, a distinction was made between direct and indirect reports. The direct reports came from hospitals/psychiatry, whereas the indirect reports were received via a pharmaceutical company.

Out of the 1,064 adverse reaction reports in 2012, 884 (84%) came directly from the regions, and the DHMA was able to identify 175 as reports from the pharmaceutical companies. Compared to 2011, the number of direct reports decreased by 11% (in 2011, the DHMA received 999 adverse reaction reports from hospitals). See Figure G.

The total number of reports should be seen in the light of the large consumption of medicinal products in hospitals – including the large consumption of new medicinal products, the suspected adverse reactions from which doctors are obliged to report. Considering this, there is still some way to go before the number of reports reaches a professionally optimal level.

Initiatives to increase the reporting of adverse reactions from hospitals
Several regions are working on increasing the focus on adverse reaction reporting. In the Capital Region of Denmark, e.g., assistance from an Adverse Drug Reaction Manager has led to considerable success in adverse reaction reporting. Read the contribution to the annual report from the Capital Region of Denmark on page *16*. The DHMA is always looking for ways to increase the awareness of adverse reactions and reporting from hospitals. For instance via campaigns and information efforts. In 2012, the DHMA completed a pre-analysis to serve as the basis for a nationwide psychiatry campaign targeted at hospital psychiatry among others.

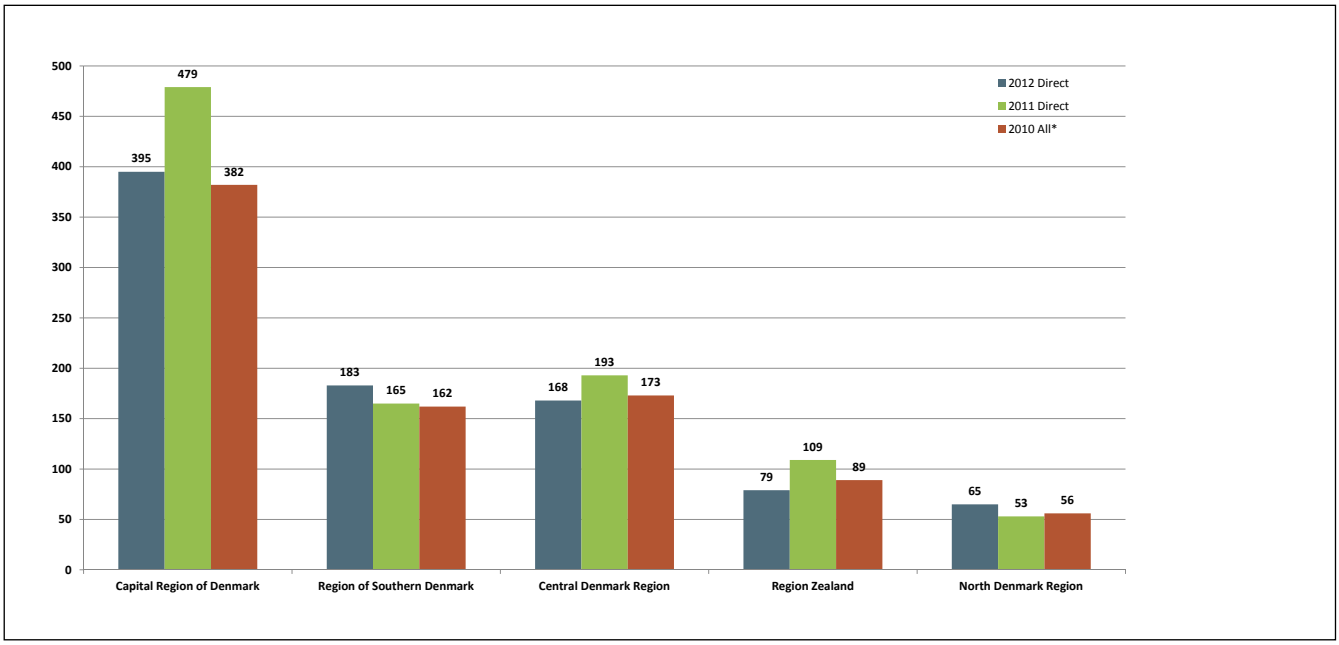

Figure G. Adverse reaction reports from Danish hospitals in 2012 by region.

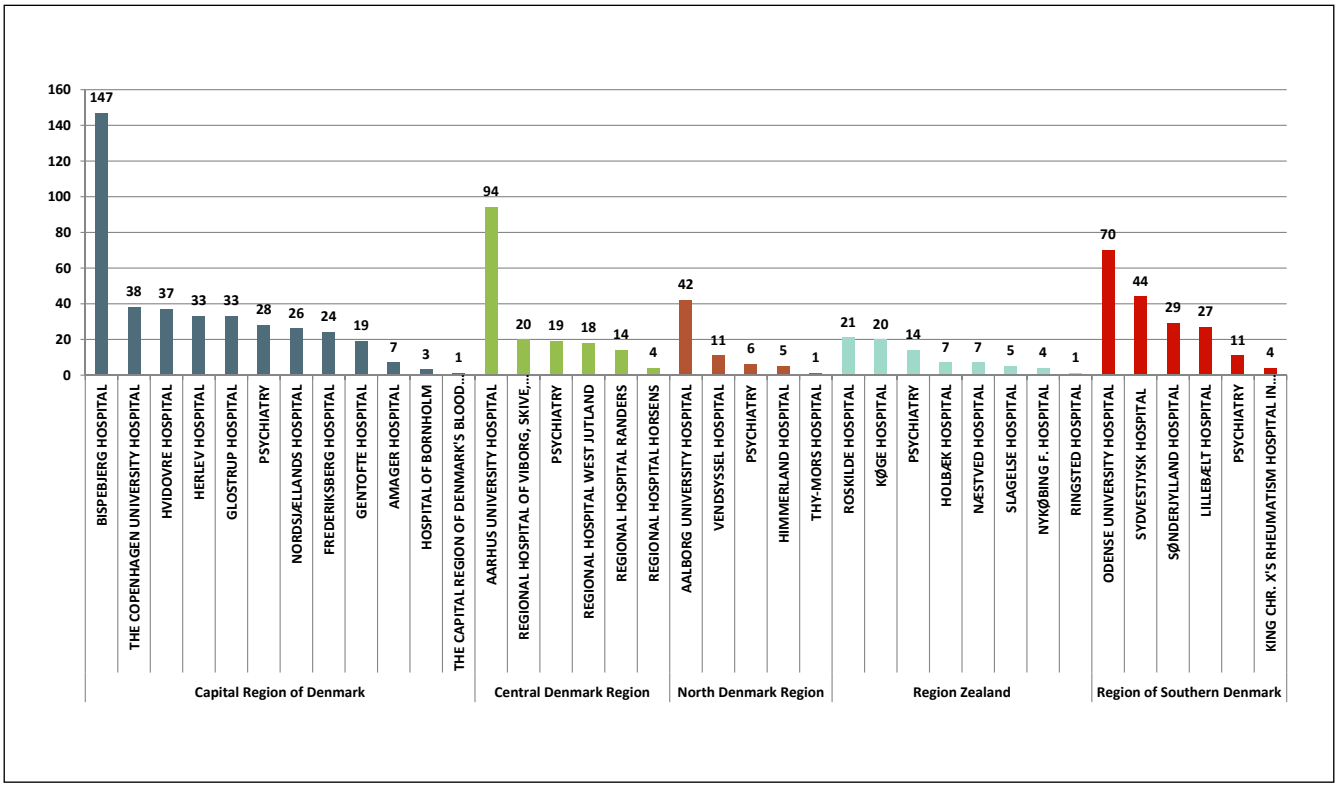

Figure H.

* In 2010, there was no distinction made between direct and indirect reports, which makes it difficult to compare 2010 to the other years.

Adverse Drug Reaction Manager assists the Capital Region of Denmark with adverse reaction reporting

Contribution from the medicinal products committee in the Capital Region of Denmark

Based on the national action plan in the pharmacovigilance area, Bispebjerg Hospital introduced an Adverse Drug Reaction Manager (ADR Manager) in their Department of Clinical Pharmacology in 2011.

The ADR Manager function was handled by doctors in the Department of Clinical Pharmacology, and during the 1-year project period, the ADR Manager handled adverse reaction reporting for five medical departments. These departments have been informed regularly about the project and the opportunity to report adverse reactions via the ADR Manager. The aim of the project was to facilitate the doctors' work with often lengthy adverse reaction reporting and thereby to step up the number of reports to the DHMA.

In practice, the doctors in the five departments could contact the ADR Manager by telephone or fax, giving information about the patient's civil registration number, medicinal product and adverse reaction. Afterwards, the ADR Manager reported the adverse reaction on the DHMA's website using electronic information retrieved from OPUS, LABKA II, web1000 and EPM. That way the doctors' time consumption was reduced from 30 to 3 minutes per report. Furthermore, the number of adverse reactions reported from Bispebjerg Hospital was increased fivefold – a change interpreted as being directly effected by the service provided to the clinical doctors by the ADR Manager.

The ADR Manager function will now be implemented throughout the Capital Region of Denmark.

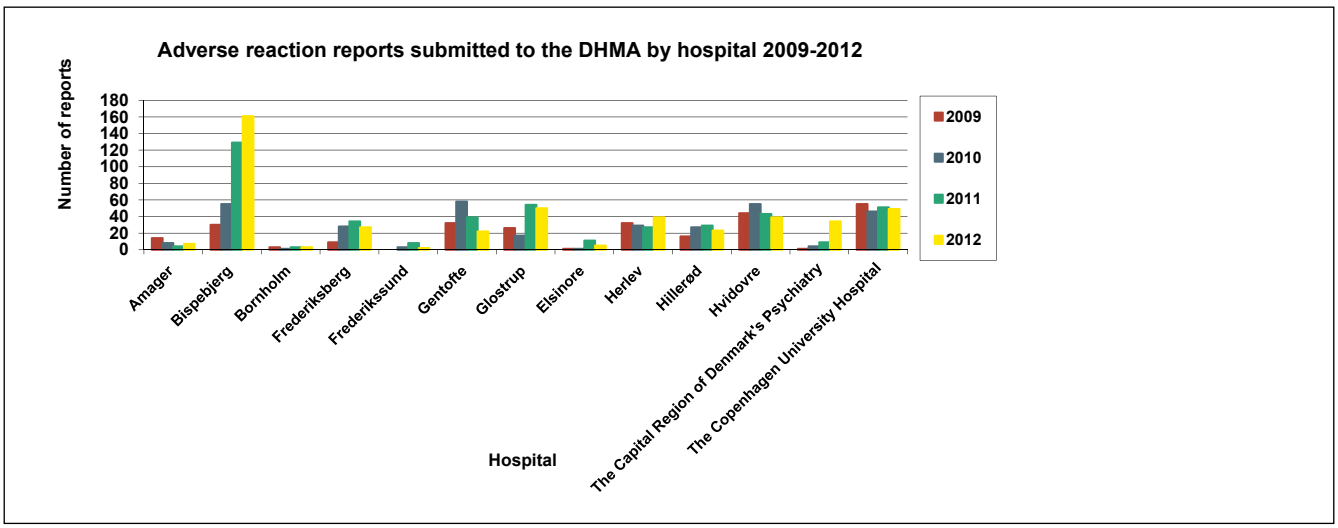

Figure I.

Medicines subject to stricter reporting requirements, and adverse reaction reports in 2012

When a new medicine is granted a marketing authorisation, it is necessary to monitor the safety profile for this new product as closely as possible. Therefore, all new medicines are subject to so-called stricter reporting requirements. This means that doctors and dentists, in accordance with Danish pharmaceutical legislation, have an obligation to report all suspected adverse reactions observed within the first two years following placement of a new medicine on the market. Subsequently, doctors and dentists are only obliged to report all serious and/or unexpected adverse reactions.

The DHMA is responsible for updating the list of medicines subject to stricter reporting requirements. The list is updated monthly and is available on the DHMA's website.

In 2012, 109 medicines were subject to stricter reporting requirements. Not all 109 medicines were on the list during the whole year. For instance, if a medicine was marketed in March 2010, it was subject to stricter reporting requirements until March 2012, i.e., not throughout 2012.

Medicines subject to stricter reporting requirements, and adverse reactions reported in 2012

For 68 out of the 109 medicines subject to stricter reporting requirements in 2012, the DHMA did not receive any adverse reaction reports. There may be several explanations to this.

When a new medicine is marketed it is not necessarily used. And when an adverse reaction is observed, it may not be reported to the DHMA. Also, the lack of reports may be due to inadequate knowledge about which medicines are subject to stricter reporting requirements.

Effect of the stricter reporting requirements

Of the 109 medicines subject to stricter reporting requirements, the DHMA has chosen to present further data for 11. Figure J shows the development in the consumption of these 11 medicines. The consumption shows an increasing trend, to different degrees, for all products except for the antidiabetic drug Bydureon. Table 1 below shows the number of adverse reaction reports by product.

Consumption of selected medicines subject to stricter reporting requirements

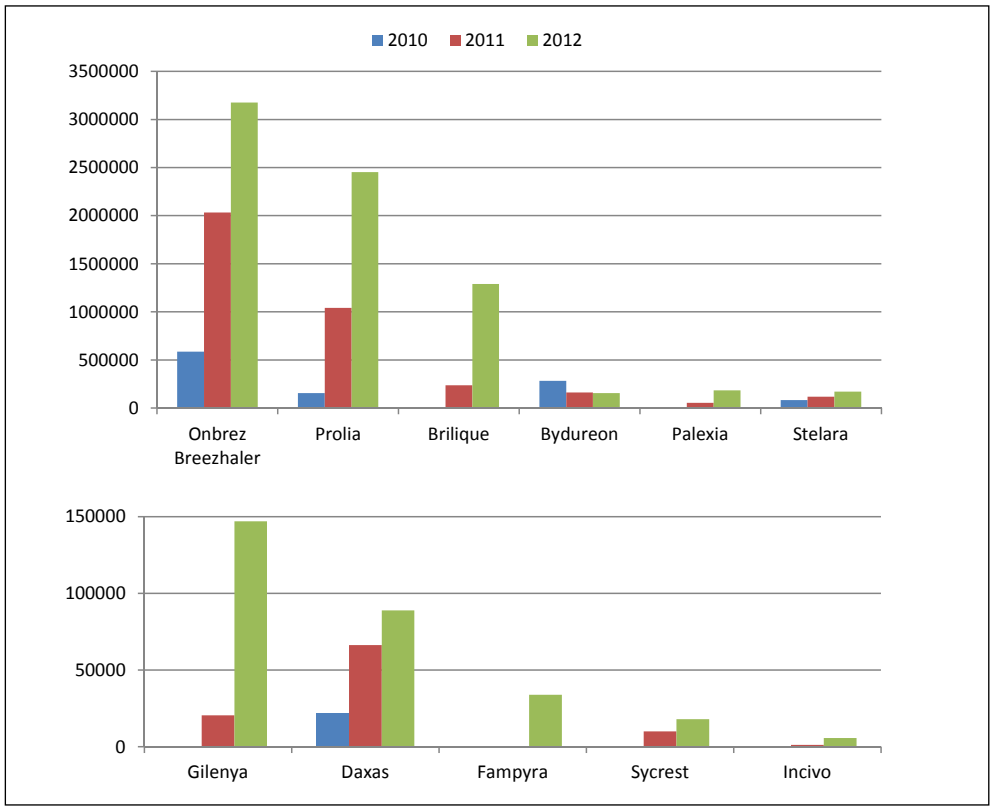

Figure J. This figure shows the development in the consumption of 11 medicines subject to stricter reporting requirements in 2010, 2011 and 2012. The consumption is stated in Defined Daily Doses (DDD) The consumption differs a lot between the 11 medicines. Therefore, they were split in groups of five and six and presented in two graphs with different scales.

The adverse reactions reported in association with these 11 medicines indicate that the stricter reporting requirements make a difference. There is a significant predominance of mild adverse reactions. These 11 medicines are characterised in being used for seriously ill people.

Trade name	Company	Marketing date	Indication	Adverse reaction reports*
Onbrez	Novartis	22-02-2010	COPD**	33
Prolia	Amgen	28-06-2010	Osteoporosis	79
Brilique	AstraZeneca	24-01-2011	Prevention of thrombosis	34
Bydureon	Eli Lilli	17-10-2011	Type 2 diabetes	16
Palexia Depot	Grünenthal	27-12-2010	Chronic pain	44
Stelara	Janssen-Cilag	17-05-2010	Psoriasis	16
Gilenya	Novartis	02-05-2011	Sclerosis	38
Daxas	Nycomed	20-09-2010	COPD**	30
Fampyra	Biogen Idec	03-10-2011	Sclerosis	5
Sycrest	N.V. Organon	04-04-2011	Mania	10
Incivo	Janssen-Cilag	31-10-2011	Chronic hepatitis C	10

*Table 1. The table presents the number of *adverse reaction reports received from the marketing date through 2012. **COPD – Chronic obstructive pulmonary disease. The above figures in themselves do not give rise to communication between the DHMA and the company.*

The DHMA is using the stricter reporting requirements as a pharmacovigilance tool. During our evaluation of signals concerning recently marketed medicines, we pay special attention to new and previously unknown adverse reactions. On the DHMA's website, it is possible to see the list of medicines subject to stricter reporting requirements. Furthermore, medicines subject to stricter reporting requirements are especially marked on *www.promedicin.dk*.

See the complete *List of medicines with stricter reporting requirements for doctors, dentists and veterinarians to report adverse reactions (in Danish only)*.

Common European procedure coming up

The new European legislation on safety of medicines includes a demand for common European stricter reporting requirements, called Additional Monitoring. It has not yet been decided when this common procedure is to be implemented, and, currently, it is not known how it will affect the Danish stricter reporting requirements. However, the DHMA expects this to be sorted out before the end of 2013.

New EU legislation concerning monitoring safety of medicinal products

In July 2012, new EU pharmacovigilance legislation entered into force. The Danish Health and Medicines Authority, DHMA, was, among other things due to the Danish EU Presidency, closely involved in the implementation of the new legislation.

Strengthened patient safety

The new legislation aims to strengthen patient safety by improving the present system used for monitoring safety of medicinal products in Europe.

Overall, the legislation is to ensure:

- Highly scientifically and internationally anchored decisions based on a risk-based approach
- A high level of transparency and information to the general public and patient involvement
- Rational processes and collaboration in order to use the resources in the best possible way and prevent duplicated work

The new strengthened pharmacovigilance is supported by, i.a., the PRAC, the new EU Pharmacovigilance Risk Assessment Committee.

The new legislation considerably strengthens the collaboration between the EU countries, thus ensuring that resources and experience are used in the best possible way through work sharing in a number of key areas. The new Pharmacovigilance Risk Assessment Committee serves as a common forum to ensure a uniform high quality and a risk-based approach to the work.

Definition of adverse reactions expanded

The new legislation introduced an expanded definition of adverse reactions to focus on potential harmful effects of medicinal products also in case of off-label use, e.g., abuse, overdose or medication errors.

Furthermore, future reports of suspected adverse reactions occurring in the EU will be stored in a common database in order to improve the utilisation of the collective knowledge of risks of medicinal products.

In various fields, the new legislation ensures that all EU countries obtain the same high standard with respect to transparency and patient involvement that has long been the practice in Denmark. For instance, consumers in all EU countries now have the right to report suspected adverse reactions from medicinal products, and the product information for medicinal products will be publicly available. In Denmark, it has been possible for consumers to report suspected adverse reactions since 2003.

We are already seeing an effect of the amended legislation

As shown on *page 5*, more companies reported consumer adverse reactions in 2012 as compared to previous years. This development may be interpreted as being directly effected by the amended legislation.

The graph below presents the development in adverse reaction reports. Adverse reactions reported directly to the DHMA are plotted on the blue curve. Adverse reactions reported via a pharmaceutical company are plotted on the red curve.

Danish adverse reaction reporting influenced by EU legislation

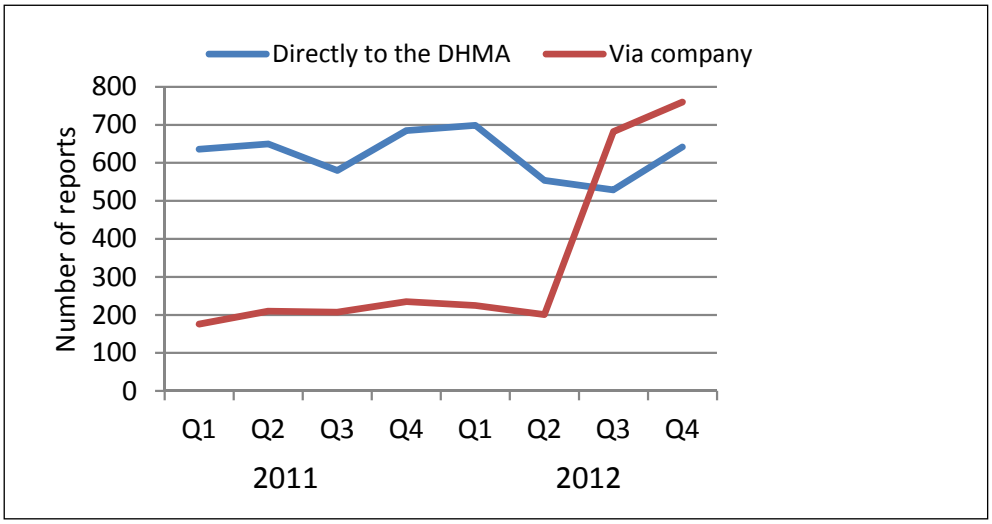

Figure K. Development in the number of adverse reactions reported by quarter in 2011 and 2012.

The increase in the number of adverse reaction reports received via a company coincided with the entering into force of the new legislation. This shows that companies adjusted their reporting according to the new definition of adverse reactions. The DHMA will be able to analyse this development in 2013, when data for a whole year with the new definition of adverse reactions become available.

Past as well as future adverse reaction reports received by the DHMA form part of the basis on which the safety of a medicinal product is assessed.

The obligation of doctors to report suspected adverse reactions from medicinal products is more or less unchanged, with the exception that the reporting obligation does not apply to suspected adverse reactions resulting from medication errors. Doctors and dentists may, but do not have to, report this type of adverse reactions to the DHMA. Information on the obligation to report is available on *the DHMA's website*.

Read more about the new definition of adverse reactions in *Danish Pharmacovigilance Update, September 2012*.

The Danish Health and Medicines Authority's work on adverse reaction signals in 2012

In 2012, the DHMA implemented new methods for detecting and monitoring new adverse reaction signals for medicinal products. A signal refers to reported information on a new potential causal relationship between an event (most often an adverse reaction) and a medicinal product. A signal can also be a new aspect of a known correlation. Additionally, the DHMA also focuses on correct use of medicinal products in clinical practice. For instance whether a type of medicinal product is prescribed to the right patients and whether known precautions for the use of medicinal products are observed to avoid patient inconvenience and adverse reactions. Adverse reaction reports also contribute significantly to this work.

What are the sources of adverse reaction signals?
Adverse reaction signals may derive from various sources such as adverse reaction reports, Periodic Safety Update Reports (PSURs), monitoring programmes, literature, clinical and epidemiological studies, other authorities or the media. Signal assessment is a complex and lengthy process. Therefore, the signals are prioritised based on a clinical assessment and potential public health implications. A few signals enable immediate action. However, it is often necessary to await further information or initiate other types of analyses, e.g., registry studies, to disconfirm or confirm a potential adverse reaction signal after a while prior to taking the matter any further. The DHMA also conducts cross-cutting analyses of adverse reaction data and monitoring programmes aimed at detecting new adverse reaction signals for, e.g., specific medicinal products or in groups of patients.

Upon detection of a new potentially clinically relevant adverse reaction signal, the next step is to validate and confirm the signal. This means that easily accessible information about the signal is examined to ensure that the evidence available is sufficient to confirm the signal. If so, the signal is subjected to further analysis followed by a thorough assessment before deciding whether to take action. This comprehensive work includes studying adverse reaction reports as well as information from the literature, studies and other relevant data.

Danish and international signals
A signal may be of relevance in Denmark only, which is the case when, e.g., the signal refers to a specific Danish treatment practice, or it may be of a more international nature. If the latter is the case, the DHMA will communicate information about the signal via the EU system. The DHMA will always communicate information about important signals on the DHMA's website or in the newsletter *Danish Pharmacovigilance Update*. A potential signal may also be well-known and closed with no further action, or the DHMA may choose to await more (new) knowledge prior to deciding how to move forward.

Just like the DHMA forwards information about signals to other countries, we also receive information about signals from other countries on which we need to act. This way, the DHMA participates in the international work on pharmagovigilance at a global level.

Monitoring signals in the Danish adverse drug reaction database and EudraVigilance, the European pharmacovigilance database
The work of the DHMA includes regular monitoring of data from adverse reaction reports in the Danish adverse drug reaction database as well as the EudraVigilance database and analysing data to detect new adverse reaction signals. This work is based on a

combination of advanced technology, statistical analysis methods and manual monitoring as part of the everyday processing of adverse reaction reports.

In 2012, the DHMA implemented a new IT system which enables advanced statistical processing of the Danish adverse reaction data. The system can compare large amounts of data and facilitate identification of medicinal products with unexpected risk profiles. For instance a medicinal product for which an adverse reaction occurs more frequently than for other medicinal products. Furthermore, the DHMA monitors all reports of very serious adverse reactions (as defined by the European Medicines Agency (EMA)), reports concerning foetuses and children and reports of fatal cases. Every week, the system prepares a list of potential new signals based on all these criteria, and all the listed signals are screened weekly. The system screens up to 300 potential Danish adverse reaction signals weekly. A signal may appear on the list several times and will be screened every time.

Due to the new pharmacovigilance legislation which entered into force in 2012, Denmark, and thus the DHMA, is also responsible for monitoring the European pharmacovigilance database Eudravigilance for adverse reaction signals for a number of active substances contained in certain nationally approved medicinal products. Other EU member states monitor other active substances. Collectively, the monitoring covers most of the nationally approved active substances in Europe. Currently, Denmark is responsible for monitoring 111 substances. In case other member states detect signals for these active substances, the DHMA have an obligation to assess these signals too. Every month, the EMA prepares a list of potential signals for all active substances. The criteria for this list are comparable with the criteria used for the Danish adverse reaction data.

Signals in 2012

In 2012, the DHMA detected and monitored various adverse reaction signals. Some of them are mentioned in the list below.

Medicine	Signal	Action / Communication
Dabigatran	Serious gastrointestinal tract bleeding associated with too high doses of dabigatran (Pradaxa) in patients over 80 years of age.	Monitoring programme. Article in Danish Pharmacovigilance Update. News announced on www.lmst.dk
Finasteride	Potential risk of abnormalities in male foetuses, if pregnant women are exposed to finasteride which can be absorbed through the skin. Signal based on reports from pharmacies pointing out that finasteride 5 mg tablets are sometimes prescribed 1/4 or 1/5 of a tablet daily.	Article in Danish Pharmacovigilance Update.
Fluoxetine and sertraline.	Growth inhibition in children in treatment with the SSRIs fluoxetine and sertraline.	Article in Danish Pharmacovigilance Update.
Loperamide	Risk of death associated with abuse of loperamide.	The signal was closed following detailed analysis.

Metformin	Rare, but serious risk of lactic acidosis in diabetics treated with metformin for type 2 diabetes.	Article in Danish Pharmacovigilance Update.
Monoamino oxidase inhibitors	Serious adverse reactions (fainting and unconsciousness) in case of concomitant use of MAOI and other antidepressants.	Article in Danish Pharmacovigilance Update.
Nitrofurantoin	Known, but rare pulmonary adverse reactions. Nitrofurantoin is not approved for prophylactic use. The pulmonary adverse reactions may occur more frequently in case of prophylactic use.	Article in Danish Pharmacovigilance Update. Planned analysis of the prescription pattern in Denmark.
Promethazine	Concern about increased use of promethazine for the indication insomnia and risk of increased incidence of adverse reactions.	Prescription and over the counter sales monitoring.
Roflumilast	Increased risk of psychiatric adverse reactions in COPD patients with a mental disorder. Particular focus on suicidal behaviour and self-harm.	Analysis of drug consumption. Article in Danish Pharmacovigilance Update. Planned registry study.
SSRIs	Possible correlation between the use of SSRIs and the development of autism.	Epidemiological study (awaits publication).
SSRIs	Possible increased incidence of malformations in newborns exposed to antidepressants (SSRIs) during pregnancy.	Registry study. News announced on *the DHMA's website*.

Publication of adverse reaction data from the Danish adverse drug reaction database

As part of the action plan for a strengthened pharmacovigilance 2011-2013, the DHMA will process adverse reaction data reported in order to publish general overviews (Drug Analysis Prints, DAPs) of adverse reaction data in anonymised form. Such DAPs were published in June and July 2012.

What are the contents of the DAPs?

The DAPs collate information about adverse reactions reported in anonymised form broken down by active substances.

Each DAP contains a list of suspected adverse reactions reported in Denmark for a particular active substance. The list specifies the different types of suspected adverse reactions reported to the DHMA and the number of suspected adverse reactions.

The adverse reactions are grouped by System Organ Class. This means that, e.g., suspected adverse reactions related to ear disorders are grouped together. Here is a more detailed breakdown of the reports, e.g., details of inner ear symptoms and tinnitus.

The Drug Analysis Prints are saved in a PDF format which is downloadable from *the DHMA's website*. Also, the website specifies the reservations related to the use of the DAPs.

DAPs for vaccines

Adverse reaction reports related to vaccines are not available online. The current technical solution does not allow generation of a credible overview of the number and distribution of adverse reaction reports related to vaccines. But you are welcome to request individually generated DAPs for vaccines from the DHMA.

What are the DAPs used for?

The DAPs primarily provide the reader with an overview of the suspected adverse reactions reported to the DHMA. The DAPs serve as updated reference documents internally in the DHMA and as part of our communication.

The information in the DAPs may help to identify potential safety issues with a medicinal product. For instance, it may be useful to a doctor, who suspects an adverse reaction, to be able to see whether there are previous reports submitted to the DHMA of a similar adverse reaction.

DAPs in 2012

In 2012, pages on the DHMA's website related to DAPs were shown just below 7,000 times. The number of downloads of the DAPs was not recorded. Over the year, the DHMA received just below ten inquiries related to the DAPs. Since the publication in the middle of 2012, the DAPs have been updated monthly. This updating frequency will be continued in 2013. The number of published DAPs as of 2 January is 1,729. This is the number of active substances

for which the DHMA has received adverse reaction reports. Of the total number of DAPs, 724 have been updated since the initial publication. Thus, the DAPs are dynamic and change with the DHMA's receipt of reports of adverse reactions from the use of medicinal products in Denmark.

Adverse reaction reports from consumers or their representatives in Denmark

Since 2003, it has been possible for medicine users and relatives to report adverse reactions to the DHMA. The DHMA has reviewed the adverse reaction reports received during the years 2003-2011 to clarify how reports from medicine users differ from reports from healthcare professionals and specify how such differences contribute to improving patient safety.

During the period in question, 18.6% of the reports were received from medicine users and relatives, and in the last four years studied, the reports from medicine users and relatives represented more than 20% of the total number of reports received by the DHMA.

Differences between reports from medicine users/relatives and healthcare professionals

The most frequent product groups in the adverse reaction reports differed between the reporter groups. It was thyroid therapy for medicine users, vaccines for doctors, immunosuppressants for other healthcare professionals and drugs for obstructive airway diseases for pharmacists.

In some cases, medicine users reported adverse reactions not reported by healthcare professionals. For instance, medicine users reported a change in the sense of taste in association with the use of products containing the active substance simvastatin. It is important to keep in mind that a correlation between an adverse reaction and a medicinal product does not necessarily exist just because of recording a report in the DHMA's adverse reaction database.

The conclusion of the analysis is clear. Medicine users and their relatives play a key role in making medicine safer and more effective. The analysis shows that the contribution to the total number of adverse reaction reports from reports submitted by medicine users and relatives is significant, quantitatively as well as qualitatively. In general, the reports from medicine users provide important, well-documented information contributing to increased patient safety.

Medicine users report long after the occurrence of the adverse reaction

However, the analysis also shows that medicine users took relatively long to submit their adverse reaction reports. It may be due to the fact that a medicine user is not aware that the condition in question may be caused by an adverse reaction, or he/she may be unaware of the possibility to report adverse reactions. The delayed reporting may delay the DHMA's analyses and may be problematic, because the factual circumstances of the adverse reaction are easier to remember right after the onset of it.

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

See *Adverse drug reactions reported by consumers in Denmark – compared with reports from healthcare professionals*.

Campaigns 2012 – focus on adverse reaction reporting

In 2012, the DHMA launched an adverse reaction campaign targeted at healthcare professionals in the nursing sector. The DHMA also launched a campaign targeted at medicine users, including follow-up targeted at nursing staff. Furthermore, a pre-analysis was initiated to prepare for a campaign in the field of psychiatric adverse reactions. Common to all these campaigns is the fact that they focus on adverse reaction reporting to the DHMA, and they all form part of the Minister's action plan for improved pharmacovigilance.

Respond to adverse reactions – and help making medicine more safe for everyone. – A nationwide campaign targeted at municipal nursing staff

The campaign in brief

In the spring and summer of 2012, the DHMA conducted a nationwide campaign targeted at nursing staff in all Danish municipalities. The purpose of the campaign was to prepare the municipal nursing staff to better respond to adverse reactions and report them to the DHMA.

The campaign was evaluated through a series of telephone interviews with managers and employees of various care facilities during the period August-October 2012.

The result – increased attention, strengthened dialogue and more awareness in the field of adverse reactions

The campaign involved various material including flyers for social and healthcare helpers, folders for nurses and social and healthcare assistants and training material for use in department meetings. Generally, the material was well received and initiated dialogue and discussion about the everyday handling of adverse reactions.

The evaluation shows that it is important to focus on the existing line of authority at each individual care facility and nursing home in association with adverse reaction reporting. Very few social and healthcare helpers and assistants feel well equipped to report adverse reactions themselves. They inform a nurse about their observations, and the nurse contacts a doctor.

The campaign primarily resulted in increased attention, strengthened dialogue and more awareness in the field of adverse reactions. It played a part in placing adverse reactions on the agenda and provided the nursing staff with a discussion input concerning roles and lines of authority.

During the spring of 2013, the DHMA will follow up with yet another initiative targeted at nursing staff in Danish municipalities. This initiative forms part of a nationwide campaign under the name 'Not everyone reacts the same way'. With respect to nursing staff, it will be based on the experience from 'Respond to adverse reactions – and help making medicine more safe for everyone'.

Not everyone reacts the same way – an information campaign targeted at medicine users, specific groups of patients and healthcare professionals in the care sector

The campaign in brief
In 2012, the DHMA started preparing for a future campaign to be launched during the spring of 2013. It is a follow-on to recent years' information efforts in the pharmacovigilance area and targets some of the same groups: medicine users, specific groups of patients and healthcare professionals in the nursing sector. The campaign will be aimed at making the target groups aware of adverse reactions and the possibility to report them to the DHMA.

The message – we react differently to medicine
The campaign will be conducted via retail shops and the municipalities, and the material will include posters, badges, folders and film for information screens in pharmacies and for training purposes in care facilities and nursing homes.

The campaign's key message is that the diversity of individuals is reflected in their response to medicine. Some individuals experience adverse reactions while others do not. Therefore, the experience of each individual is important to the DHMA's monitoring of the safety of medicinal products.

Read more about the campaign *Ikke alle reagerer ens – når du melder en bivirkning, hjælper du os alle sammen* (Not everyone reacts the same way – you help all of us when you report an adverse reaction, in Danish only).

Information campaign in the psychiatric field

In the autumn of 2012, the DHMA started preparations to bring adverse reactions into focus in the psychiatric field from which the number of adverse reaction reports received by the DHMA is low. This initiative includes a pre-analysis, a pilot project in North Denmark Region and a nationwide campaign to be launched during the course of 2013.

The campaign target groups are relatives, medicine users, patient organisations and hospital and social psychiatry staff.

Based on the results of the pre-analysis, further work on the campaign will focus on placing adverse reactions on the agenda in general, strengthening the existing staff lines of authority and increasing the number of reports from the psychiatric field.

Focus areas in 2012

The DHMA had several major focus areas within medical treatment and safety in 2012.

Focus on consumption and safety of contraceptive pills

Contraceptive pills are an effective and important form of contraception in Denmark and provide a great advantage to each individual woman and to society as a whole.

The risk of blood clots from the use of contraceptive pills has been known for a long time, but still causes concern and gives rise to considerations about the optimal use of this form of contraception.

In the beginning of the year, the DHMA reviewed the most important literature on contraceptive pills and the risk of blood clots as well as the most recent data on consumption and adverse reactions reported in Denmark.

The review confirmed that the risk of blood clots in each individual user of contraceptive pills is generally low and that the older types of contraceptive pills – the so-called 1st and 2nd generation pills – are associated with the lowest risk.

However, the analysis of the consumption showed that Danish women most frequently used contraceptive pills of the 3rd generation type, and that this was also the type most frequently prescribed by doctors to new users of contraceptive pills.

The product information currently available in the contraceptive pill packages, already includes the latest knowledge of the safety of the medicine.

The report gave rise to emphasising recommendations to doctors to prescribe 2nd generation contraceptive pills as first choice, to the extent possible, and to examine for risk factors for blood clots in women prior to starting contraceptive pills and regularly during treatment.

Read *P-piller – Forbrug og risiko for blodpropper* (Contraceptive pills – Consumption and the risk of blood clots, in Danish only).

The DHMA followed up on the report in September 2012.

The September statement of the consumption showed that doctors and patients had followed the recommendations: The consumption of 2nd generation contraceptive pills had increased significantly since the beginning of 2012. At the same time, the consumption of the new types of contraceptive pills with the highest risk of blood clots had decreased correspondingly (3rd and 4th generation).

This is a positive trend. However, it continues to be important that doctors pay attention to prevention and early detection of blood clots.

Read *Forbrug af p-piller og risiko for blodpropper (opdatering)*.Consumption of contraceptive pills and the risk of blood clots (update - in Danish only)

Long-term treatment with bisphosphonates

In January 2012, the DHMA published a report on long-term treatment of osteoporosis patients with bisphosphonates. In the report, the DHMA reviewed treatment patterns and evidence of suspected adverse reactions from long-term treatment with bisphosphonates.

The main conclusions of the report were that an increasing number of osteoporosis patients are started on bisphosphonates and that often the patients remain in treatment for many years.

The knowledge of long-term treatment with bisphosphonates in osteoporosis patients is very limited. However, in recent years, reports suggestive of long-term adverse reactions have been received.

Until further clarification has been obtained about the long-term effect of treatment, it is important to stay attentive to symptoms in patients receiving bisphosphonates that could be suggestive of long-term adverse reactions. In addition, it is important to assess the possibility for pausing or stopping treatment in certain patients with a low risk of fractures.

Read *Long-term treatment of osteoporosis patients with bisphosphonates* .

Consumption and adverse reactions from the use of statins

In October 2012, the DHMA published a review of consumption patterns for and safety of statins.

The report showed that the consumption of medicines for the treatment of elevated cholesterol levels has increased in recent years and that statins now rank among the largest-selling medicines in Denmark.

The number of adverse reactions reported for statins has increased with consumption. In some cases, the adverse reactions are serious, but they are well-known and described in the product information.

Based on the review, the DHMA concluded that high doses of statins should be offered only to high-risk patients and that doctors should stay attentive to the risk of interactions with other medicines.

In general, it should be assessed whether the expected benefits of the statins outweigh the risk of adverse reactions for each individual patient prior to initiating treatment– especially when considering primary preventive treatment.

Read *Viden om forbrug og bivirkninger ved behandling med statiner*.(Knowledge of consumption and adverse reactions from the use of statins, in Danish only).

Monitoring adverse drug reactions in children with autoimmune diseases receiving biological treatment.

Recent years has seen a substantial increase in the approval and use of biological medicines in children.

At the end of 2012, the DHMA published a report that focused on identifying a suitable way of collecting adverse reactions in the small group of children treated with biological medicines. This group includes children with severe arthritis and connective tissue diseases, chronic inflammatory bowel disease (Crohn's disease) and the skin disease psoriasis.

Only a few reports concerning children treated with biological medicines

The DHMA's adverse reaction database contains only a few suspected adverse reactions concerning children treated with biological medicines. This is not problematic in itself and may reflect that the medicines are safe and well-tolerated.

However, a small questionnaire survey associated with the report revealed a few examples of adverse reactions that had not been reported by parents and relatives. The reason could be that they did not regard them as serious adverse reactions. However, the reason could also be that many people are not aware of their possibility to report adverse reactions to the DHMA themselves.

The report showed that parents and relatives of children treated with biological medicines had outstanding knowledge of and insight into the children's disease. Often, they were also more focused on adverse reactions from medicines used in their children than doctors, because they experienced the adverse reactions in everyday life.

Collaboration with other databases on reporting

Apart from the DHMA's adverse reaction database, a number of clinical databases have been established, e.g., DANBIO, Dermbio and DCCD, in which adverse reactions are recorded.

According to the report, the exchange of experience between the databases functions well, and some of the information is forwarded to the DHMA's adverse reaction database automatically. Based on the report, the DHMA will investigate whether it is possible to further facilitate the access to data on adverse reactions.

Read *Overvågning af bivirkninger hos børn med autoimmune sygdomme i biologisk behandling* (Monitoring adverse drug reactions in children with autoimmune diseases receiving biological treatment, in Danish only).

Proactive monitoring of anticoagulants – a collaboration with medical experts from Aalborg Hospital Science and Innovation Center in Aalborg

In 2011, the DHMA initiated a collaboration partnership with North Denmark Region, Aalborg Hospital Science and Innovation Center in Aalborg with respect to proactive monitoring of a group of anticoagulants marketed during 2011 and 2012 for the new indication of preventing blood clots in patients with atrial fibrillation.

Background for the collaboration
The background for the proactive collaboration was to enable identification of new potential hazards associated with the use of the drugs as early as possible after marketing and to study known and new causal relationships between the medicine and adverse reactions. When new medicinal products are marketed, or medicinal products are approved for a new indication, the DHMA may receive more reports of serious adverse reactions than expected due to the fact that the population using such a product is not necessarily similar to the population participating in the preceding clinical studies.

The DHMA considered it to be extremely important to monitor this group of drugs, since anticoagulant treatment is one of the most risky medical treatments. Overtreatment may increase the risk of bleeding, while undertreatment may increase the risk of blood clots. Furthermore, the new treatment could replace the older well-known warfarin treatment which, in 2011, was used by approx. 87,000 persons in Denmark including 7.5% of persons in the 65+ age group.

Results of the collaboration in 2012
A total of three anticoagulants were approved for the new indication of preventing blood clots in patients with atrial fibrillation. Pradaxa® (dabigatran etexilate) was the first of these three to be marketed for the new indication in August 2011. The second drug to be marketed for the same new indication was Xarelto® (rivaroxaban) in February 2012 and finally, at the end of the year, Eliquis® (apixaban) in December 2012.

The collaboration included monitoring the development in the consumption based on prescriptions redeemed at pharmacies and recorded in the Danish Register of Medicinal Product Statistics. We reviewed adverse reactions reported to the DHMA. The data were communicated in status reports published on the DHMA's website, and we initiated analyses and a comparison study.

In August 2012, a year after marketing Pradaxa®, this drug had approx. 9,000 users, more users than each of the other two drugs. In the same period, the DHMA received 106 adverse reaction reports concerning use of Pradaxa® for atrial fibrillation. Of these, 71 were categorised as serious, and there were eight fatal cases. Two out of three serious reports concerned bleeding, and seven of the fatal cases were related to the bleeding event. Early in the monitoring period, we discovered that the deaths in particular concerned patients of high age – over 79 years of age. That intensified our focus on this population, and easy access to data from the Danish Register of Medicinal Product Statistics allowed studying the prescription for this patient population in detail.

Four months after marketing Pradaxa® for the new indication, 10% of elderly patients over 79 years of age had been prescribed Pradaxa capsules with too high doses as compared to the dose recommended according to the summary of product characteristics for this drug. Via the DHMA's website and promedicin.dk, we recommended doctors to follow the dose recommendation and to consider the patient's age. A follow-up analysis showed that the percentage of elderly patients over 79 years of age who were prescribed too high doses decreased significantly during 2012.

In addition to the intensified focus on elderly patients, the collaboration also enabled monitoring the adverse reaction profiles of the drugs on an ongoing basis, and pooling data from several national health registers enabled comparing serious adverse reactions requiring hospitalisation and the preventive effect of the drugs on blood clots to the use of warfarin. The first data showed that the products are comparable in terms of efficacy and adverse reactions, and the results of this study are expected to be published in 2013 in a scientific journal.

Further collaboration in 2013

The collaboration continues in 2013, and we will monitor any changes in the consumption of the three anticoagulants and adverse reactions reported. So far, it has not been possible to include Eliquis® in the monitoring, since it has only recently been marketed. Therefore, the collaboration on the three drugs will be continued, and in 2013 we will study the patient population receiving the drugs in detail.

Daxas® and increased risk of psychiatric adverse reactions

In 2011, the DHMA performed an initial consumption analysis for the drug Daxas® (roflumilast)[1] which was followed up by an updated and extended analysis in 2012. Among other things, an analysis of drug consumption may elucidate the prescription of a drug for a group of patients and give an insight into aspects of the relation between recommended use and use in clinical practice. This was one of the objectives of the Daxas® analysis. The analysis was performed exclusively on Danish data from the Danish Register of Medicinal Product Statistics and the Danish adverse drug reaction database.

Adverse reactions and risk management plan

Daxas® is subject to a so-called risk management plan describing a number of activities in addition to the usual monitoring of the drug safety to be implemented to ensure safe and efficient use of the drug. The reason for the risk management plan requirement is that clinical studies have shown very serious adverse reactions that require additional monitoring. Daxas® is associated with increased risk of psychiatric adverse reactions such as anxiety, insomnia, nervousness and depression. Rare cases of suicide and suicidal thoughts have been observed in clinical studies and subsequently in adverse reaction reports. The most common adverse reactions are decreased appetite, weight loss, nausea, abdominal pain, diarrhoea, insomnia and headache.

Since the approval of Daxas® in 2010, the DHMA has received 32 adverse reaction reports comprising a total of 68 adverse reactions – including one fatal report. The majority of the reports (71%) concern adverse reactions related to the gastrointestinal tract, weight loss or decreased appetite. The second most reported adverse reactions are psychiatric adverse reactions (25%) and adverse reactions related to the nervous system (25%). Even though the adverse reactions reported are the ones expected to occur most frequently, the DHMA takes the psychiatric adverse reactions particularly seriously. Examples of psychiatric adverse reactions are anxiety, depression/depressive symptoms, insomnia, nightmares, suicide attempts and suicide.

During the first six months after marketing, the DHMA received two serious reports of suicide and suicide attempt, respectively, in two patients relatively shortly after their initiation of treatment with Daxas®. These very serious risks are known, and the DHMA cannot rule out a correlation between the events and Daxas®. The drug is not recommended in patients with a history of depression with suicidal thoughts. As part of the risk management plan, each prescribing doctor receives a package of, i.a., training material aimed at informing the doctor about use, adverse reactions and precautions associated with the use of Daxas®.

1 Daxas® is approved for the treatment of severe and very severe chronic obstructive pulmonary disease (COPD).

New knowledge of suicidal thoughts and suicidal behaviour
At the end of 2012, the European Medicines Agency concluded, based on adverse reaction reports, that a possible correlation between the medicine and suicidal thoughts or suicidal behaviour cannot be ruled out, and that suicidal thoughts may occur within weeks or months even in patients without a history of depression.
A history of mental health problems such as anxiety, panic attacks, anorexia and alcoholism may be a risk factor with respect to adverse reactions related to suicidal thoughts.

Analysis of drug consumption

The first analysis of Daxas® was completed in October 2011 and included the first 563 Daxas® patients. The second analysis was completed at the end of October 2012 and included all 959 patients who had been started on a treatment after marketing the product in September 2010 and had redeemed at least one prescription during the period studied. During this period, the patients redeemed a total of 3,767 prescriptions for Daxas®, and the analysis was based on these prescriptions.

The average age at the time of the first redemption was 70 years, and the majority (87%) of the patients were over 60 years of age. The majority (53%) of the patients were women in all age groups up to 79 years. In the 80+ age group, the numbers of women and men were almost equal. Of the 32 adverse reaction reports concerning Daxas® received by the DHMA, the majority concern patients over 60 years of age, and for this group the number of reports received is equally distributed between women and men. Overall, there is a slight predominance of adverse reaction reports concerning women. According to the summary of product characteristics for Daxas®, the pharmacokinetics of the product varies between groups of, i.a., elderly patients and women. However, this does not give cause for increased risk and a need to adjust the dose in these groups.

The first analysis particularly concentrated on investigating whether contraindications and precautions associated with the use of Daxas® were respected. The analysis offered a clear signal that a large part of the patients definitely suffered from mental disorders, since a large number of them were also undergoing treatment for depression, despite the special precautions during treatment of this particular group of patients. The analysis said nothing about the risk profile in patients treated with antidepressants. Also, it could not indicate whether the doctor knew about the increased risk of psychiatric adverse reactions in these patients.

Based on the findings of the analysis and due to receipt, at the time, of two adverse reaction reports concerning suicide and suicide attempts and a number of reports concerning other psychiatric adverse reactions, the DHMA informed the doctors about the signal in *Danish Pharmacovigilance Update, December 2011*. In addition to the signal mentioned, the analysis resulted in the overall conclusion that the prescribing doctors respected the other contraindications and precautions specified, to the extent analysis was enabled by looking at concomitant treatment with other medicines.

The first analysis showed that 29% of the patients had been treated with antidepressants for up to six months prior to initiation of treatment with Daxas®, and 26% either continued using antidepressants or started using such medicines following redemption of their first prescription for Daxas®. Thus, a large part (77%) of the patients undergoing prior treatment for depression continued that treatment following start-up of treatment with Daxas®. Based on the findings and the signal from the first analysis, the DHMA decided to focus the second analysis on the psychiatric adverse reactions. The first analysis was delimited to looking at antidepressants – a single marker for the diagnosis of depression. The second analysis was extended to cover use of antipsychotics and the smoking cessation products Champix® and Zyban® that are both known to cause psychiatric adverse reactions including suicidal thoughts and suicidal behaviour. Additionally, the analysis was extended to include treatment with other medicines within 2 years prior to the first redemption of a prescription for Daxas®. The follow-up period after start-up of Daxas® was longest (2 years and 2 months) for the first Daxas® patients and was gradually reduced down to no follow-up period for patients who did not receive Daxas® until October 2012. Thus, this analysis prioritised the period prior to start-up of Daxas® and treatment with other medicines during that period.

The special precautions associated with prescription of Daxas® also concern concomitant treatment with other medicines that may cause psychiatric adverse reactions that may or may not be increased by Daxas®. The findings of the analysis with respect to the smoking cessation products did not give rise to a signal, since only a few patients received either Champix® (6%) or Zyban® (2%) prior to start-up of Daxas®, while only nine patients received Champix® and no patients received Zyban® after start-up of Daxas®.

The analysis of prior treatment with antipsychotics showed that less than 3% of the patients received that type of medicine prior to start-up of Daxas®. Thus, it does not seem that a signal similar to the one for antidepressants exists for antipsychotics alone. When looking at antipsychotics and antidepressants taken together, the most recent analysis showed that 32% of the patients redeemed a prescription for these types of medicine within 6 months prior to the first redemption of a prescription for Daxas® as compared with 29% in the first analysis. When looking further back, the numbers rose to 35% and 38% for the periods 1 year and 2 years, respectively, prior to the first redemption of a prescription for Daxas®.

This means that the most recent analysis confirms the findings and the signal from the first analysis, and the DHMA will continue to encourage doctors to stay attentive to psychiatric symptoms in these patients and to carefully assess benefits and risks of treatment with Daxas® in patients with a history of mental disorders.

The most frequently reported groups of adverse reactions	Number of reports/ adverse reactions	Adverse reactions (number)
Adverse reactions related to the gastrointestinal tract, weight loss and decreased appetite	23/31	Abdominal discomfort (1), Abdominal pain (2), Abdominal pain upper (2), Diarrhoea (5), Dyspepsia (1), Dysphagia (1), Flatulence (1), Gastrointestinal disorder (1), Haematemesis (1), Nausea (8), Rectal haemorrhage (1), Swollen tongue (2), Weight decreased (2), Decreased appetite (3)
Psychiatric adverse reactions	9/16	Agitation (1), Anxiety (2), Completed suicide (1), Depressed mood (1), Depression (2), Depressive symptom (2), Insomnia (2), Mania (1), Mood swings (1), Nightmare (1), Restlessness (1), Suicide attempt (1)
Adverse reactions related to the nervous system	9/13	Depressed level of consciousness (1), Dizziness (3), Dysarthria (1), Headache (5), Tremor (3)

Table 2. The most frequently reported adverse reactions concerning Daxas®.

International collaboration in the pharmacovigilance area in 2012

2012 witnessed significant changes in the international collaboration on assessing and monitoring adverse reactions (pharmacovigilance). In July, a new comprehensive European legislation entered into force (*see pages 20-21*). The new regulatory framework strengthens the international collaboration in the pharmacovigilance area and is considered the most extensive change in the European history of drugs since the establishment of the European Medicines Agency (EMA) in 1995.

New European adverse reaction committee

In accordance with the new legislation, a new European adverse reaction committee, the Pharmacovigilance Risk Assessment Committee (PRAC), was established, and the first meeting took place in Brussels in July. The PRAC replaced the European Pharmacovigilance Working Party.

The PRAC has two members from each EU member state. Primarily, the Committee is responsible for monitoring safety of medicinal products *following* marketing. The PRAC meets for four days every month (except for August). Agendas and minutes of the meetings are publicly available on the EMA's website.

The DHMA heads a number of tasks in the PRAC. The DHMA (including the former Danish Medicines Agency) has given the European collaboration a high priority for many years. The DHMA, on behalf of the EU, has been in charge of assessing quality, efficacy and safety of a wide range of new medicinal products prior to granting the marketing authorisation. Following marketing, the DHMA has the overall responsibility for continued assessment of the safety of these medicinal products and for presenting the cases in the PRAC.

Changes under the new legislation

The new legislation provides improved procedures, clear division of responsibilities, consistent work sharing and better prioritisation of the tasks. All of this together ensures a better use of resources.

Examples of other changes include

- New definition of adverse reactions
- Strengthening of the work in the field of new signals
- Introduction of integrated benefit/risk assessment
- Increased focus on adverse reactions from new medicinal products
- Improved communication
- Involvement of doctors and patients

The new definition of adverse reactions not only covers adverse reactions from the use of medicinal products for the approved indications, but also adverse reactions associated with, i.a., abuse and medication errors.

Detection of new, as yet unacknowledged adverse reactions when searching for signals in the adverse reaction database, is a very important part of the pharmacovigilance work. The legislation lays down clear rules for the future work on signals, including responsibilities of authorities and the pharmaceutical industry.

So far, pharmacovigilance has been limited to assessing the risk of medicinal products. With the new legislation, pharmacovigilance also covers assessing the efficacy of medicinal products – in situations requiring an assessment of the benefit/risk balance of a medicinal product.

For instance, this is the case when assessing the Periodic Safety Update Reports to be submitted regularly to the authorities by the marketing authorisation holder. Future updates must include a section in which the manufacturer presents an analysis of the benefit/risk balance – based on what is known about the efficacy of the medicinal product and the latest knowledge of the adverse reactions associated with the product.

Our knowledge of adverse reactions from new medicinal products originates from the clinical trials on which the granting of a marketing authorisation is based. Following marketing, it is important that doctors and patients pay special attention to adverse reactions from the new medicinal product – since rare serious adverse reactions most often are not detected in the course of the clinical trials. To this end, the new legislation introduced a special labelling for new medicinal products (a black triangle + a text) to point out to doctors and patients that the medicinal product in question is new, and that they should/may report any adverse reactions to the DHMA.

Increased transparency with the new legislation

Overall, the new legislation prepares the way for increased transparency and more and better information on adverse reactions from medicinal products. Websites and web portals will gradually be expanded and improved. The EMA may arrange public consultations for specific adverse reaction cases and is to coordinate future issuing of information on adverse reactions in the EU. This ensures that all EU consumers receive the same important information in due time.

When the pharmacovigilance system was established in the 1960s and onwards, doctors and patients were not included in the network. Today, they are and will be even more so in the future. Doctors and patients will be represented in the PRAC, and patients may report adverse reactions to the authorities on their own. This was made possible in Denmark in 2003. In future, all patients in the EU will have this opportunity.

The PRAC has come off to a good start

Following the establishment in July 2012, the PRAC, during the first six months, assessed a very large number of signals, Periodic Safety Update Reports, risk management plans and epidemiological research protocols. In parallel, many resources were allocated to implementing the new legislation and developing new forms of collaboration.

Furthermore, the PRAC decided to once again review the safety of, e.g., analgesics (codeine, diclofenac), contraceptive pills and acne products. This work is expected to be completed during 2013.

The DHMA has the overall responsibility for reviewing the safety of diclofenac. Several Danish studies (Gislason et al. 2006, 2008; Fosbøl et al. 2006, 2009; Scherning Olsen et al. 2011) will be included in the review. The review of contraceptive pills focuses on the risk of blood clots. This review will also include several Danish studies (Lidegaard et al. 2011, 2012).

Pharmacovigilance in 2013

In 2013, the DHMA will complete the work initiated by the Pharmacovigilance Action Plan II. This action plan put focus on improving IT, strengthening collaboration, increasing professional knowledge, utilising adverse reaction data and increasing new knowledge of such data. Based on this plan, we launched a number of initiatives. At present, we are putting a lot of efforts into establishing an adverse reaction web service to provide doctors – whether in a practice or in a hospital – with the opportunity to report adverse reactions directly using all available master data, so that the form 'fills in itself' to the maximum extent possible. This service will further facilitate reporting. We expect to have the service up running in the autumn of 2013.

International collaboration is of great importance
The international collaboration on pharmacovigilance in the European Medicines Agency plays a major role in the daily activities of the DHMA. With the establishment of PRAC resulting from the implementation of the new legislation in the summer of 2012, this Committee has become the central forum for discussing safety issues related to medicinal products. The Committee includes two members from Denmark, and the professional assessments tie up a lot of the DHMA's resources. The DHMA has noted that the other EU countries are also making additional efforts, and we will continue to inform about the results of this work in Danish Pharmacovigilance Update in 2013.

Focus on adverse reaction reporting
In 2013, once again the DHMA will highlight the importance of adverse reaction reporting. The main target groups will be consumers, patient organisations and nursing staff. The message to be communicated will focus on the facts that people are different and react differently to medicine and that some people will experience adverse reactions. We will emphasise that every person's experience is of importance to the pharmacovigilance work and that a person reporting an adverse reaction to the DHMA will be helping other medicine users. Anyone may report an adverse reaction, and persons experiencing adverse reactions may contact their doctor, who will assess whether the treatment should be changed.

Another focus area in 2013 will be the use of psychotropics. In this context, we will monitor the compliance with advice and recommendations from the DHMA concerning this type of medicinal products based on registry analyses. It will be done in a way to ensure that each region maintains focus on using these medicinal products correctly.

The number of adverse reactions reported from the psychiatric field is extremely small. Therefore, in 2013, the DHMA will take action in order to receive a more true and fair number of reports from this important field. We intend to inform about the possibility/ obligation to and importance of reporting adverse reactions in the psychiatric field. We expect to extend the efforts to cover the whole nation after completing a campaign pilot project conducted in collaboration with North Denmark Region.

The Danish Pharmacovigilance Council – the first assignments
The work in the new Danish Pharmacovigilance Council will start for real in 2013. One of the Council's first assignments will be to prepare a draft for the Pharmacovigilance Action Plan III including proposals related to continued improvement of the work of the DHMA. The DHMA looks very much forward to the collaboration and to implementing the wishes of the Council related to improvement and renewal.