# ANNUAL REPORT

# Danish Health and Medicines Authority's annual pharmacovigilance report 2013

Sundhedsstyrelsen
Danish Health and Medicines Authority

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# Preface

2013 marked a decade of adverse drug reaction (ADR) reporting by patients and relatives in Denmark. Denmark was one of the first countries to give patients and relatives the opportunity to report adverse reactions themselves. In the last few years, the reports from patients and relatives have accounted for about one third of all reports, and the 10-year anniversary made it relevant for us to look at how these reports contribute to overall monitoring. An analysis concluded that the reports from patients and relatives contribute significantly to pharmacovigilance (the monitoring of adverse reactions), both when it comes to quantity and quality, which means they successfully supplement the reports from doctors and other healthcare professionals.

**Pharmacovigilance work influenced by many cases**

2013 was a busy year for pharmacovigilance. A number of cases attracted a lot of media attention, which rubbed off on the ADR reporting statistics. Especially the HPV vaccine against cervical cancer was in focus and made up a large proportion of the reports in 2013. In August, reports of a relatively new diagnosis, known as POTS[1], prompted us to request the European Medicines Agency to investigate POTS as a newly identified possible adverse reaction to the HPV vaccine. Since then, the safety and the clearly predominant positive effects of the HPV vaccine have been firmly established in Danish and international studies. The HPV vaccine case successfully demonstrated how the pharmacovigilance activities work, and not least how important and beneficial the ADR reports from doctors and other healthcare professionals are, together with the reports submitted by patients and their relatives (read more about the monitoring activities regarding the HPV vaccine on *page 24*).

**User involvement and openness in our work with adverse reactions**

In step with the growing interest in our pharmacovigilance activities, openness has become an important factor in ensuring utmost security and safety for medicine users. In 2013, we therefore strengthened efforts to maintain and do more in this area, e.g. by continuing to publish all ADR reports in a depersonalised and structured form on our website, and by sending out important safety information, not only to doctors and other healthcare professionals directly, but also to the general public and the patients. In our electronic newsletter *Danish Pharmacovigilance Update* – now in its fifth year – we continually report safety information from the European collaboration and from our own analysis of the reports.

The work with and not least the collaboration on pharmacovigilance are becoming stronger every day, driven e.g. by very favourable interactions with the Danish Pharmacovigilance Council. By following up on action plans, the Council has helped set the direction for the pharmacovigilance activities of the Danish Health and Medicines Authority, DHMA, and has put focus on the areas that needed to be reinforced overall.

In the last two action plans, the Council has highlighted the need for expanded IT competencies, strengthened ADR analysis and communication, and not least collaboration with medicine users and research institutions. The Council has further emphasised that it is important to keep launching campaigns to make health professionals and patients aware that the reporting of adverse reactions is important to strengthen security and, in particular, the safety of using medicines, but also that users should still be involved in the monitoring work and invited to dialogue.

*Henrik G. Jensen, Head of the Pharmacovigilance & Medical Devices Division*

**1** Postural Orthostatic Tachycardia Syndrome.

# Development in the number of ADR reports from 2012-2013

In 2013, the DHMA received altogether 6681 adverse drug reaction (ADR) reports[1], which is an increase of 35 % compared to 2012.

### Large increase in the number of reports

Over the past 10 years, the number of reports has increased gradually (figure 1), and there are several explanations. In 2003, the possibility of reporting adverse reactions to the DHMA was opened to patients and their relatives, and in the past few years, their reports account for one third of all reports. It has become easier to report adverse reactions through better and more supportive IT functionality, and over the years, both doctors and patients have become more keen to report adverse reactions as a result of for example campaigns launched at various target groups, which have raised awareness on reporting adverse reactions to the DHMA.

In the last decade, certain types of medicines also yielded many ADR reports, e.g. antidepressants (SSRIs), the medicine for treatment of low metabolism Eltroxin®, the influenza vaccine Pandemrix®, and the HPV vaccine against cervical cancer Gardasil®. Both the reports for Eltroxin® and Pandemrix® made the total number of reports increase in 2009 when considerably more adverse reactions were reported compared to earlier years.

In addition, the first action plan in the pharmacovigilance area (Action plan I for strengthened pharmacovigilance 2009-2011) was launched this year by the Danish Ministry of Health and Prevention, introducing measures that spurred ADR reporting. Finally, the latest increase in the number of reports can be explained by new pharmacovigilance legislation enacted in 2012 in both Denmark and the EU.

### HPV vaccine against cervical cancer behind large number of reports in 2013

The HPV vaccine attracted a lot of media attention in the summer of 2013, which generated a large number of ADR reports. We received a total of 511 reports related to the HPV vaccine, which surpassed what had been submitted altogether for the vaccine since it was introduced in the childhood immunisation programme in January 2009. You can read more about our work with monitoring adverse reactions of the HPV vaccine on *page 24*.

1 The 6681 ADR reports also include reports submitted to the DHMA more than once, so-called duplicates. Duplicates may occur when, for example, both the doctor and the patient report the adverse reaction. In 2013, there were 461 duplicates, up from 407 in 2012.

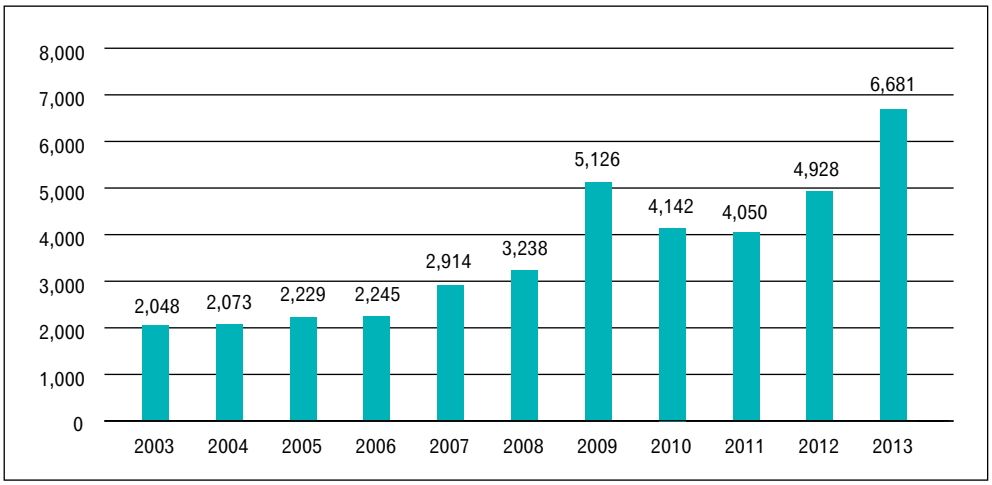
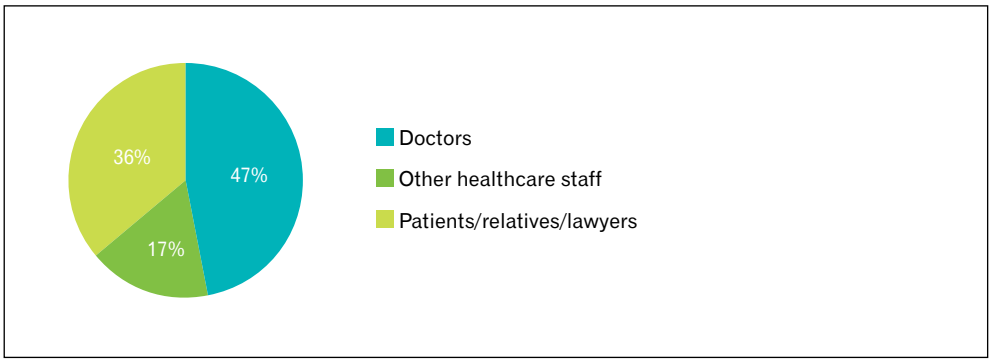



*Figure 1. Development in the number of ADR reports submitted to the DHMA from 2003-2013*
*Please be aware that when the DHMA receives additional information, this may alter the information in the adverse reactions database, implying that there may be variations between previously published figures and the figures reported here.*

## ADR reports by reporter type in 2013




The proportion of reports from doctors, other healthcare professionals and patients/relatives breaks down in much the same way as in 2012. Doctors once again submitted most reports to the DHMA at 47 % in 2013 (49 % in 2012), whereas patients and their relatives took second place at 36 %, which is a slight increase on 2012 when they accounted for 34 % of the reports. The last 17 % of the reports in 2013 were submitted by healthcare professionals – e.g. nurses, pharmacists, midwives and radiologists.

It is no surprise that doctors account for the largest share of reports; Unlike the other groups, they have an obligation to report adverse reactions to the DHMA. Reporting is optional for other healthcare professionals, patients and relatives.

The reporting of adverse reactions is a crucial source to knowledge about medicines after market entry, and it is so to speak the backbone of pharmacovigilance activities. This is why the DHMA puts continuous efforts into informing and encouraging, not only doctors and other healthcare professionals, but also patients and their relatives to report adverse reactions.

In 2013, we teamed up with pharmacies across Denmark in a campaign aimed at patients and relatives with the headline “Not everyone reacts the same” (Danish title: “Ikke alle reagerer ens”). Read more about the campaign on *page 23*.

**Doctors are bound to report specific adverse reactions to the Danish Health and Medicines Authority**

It follows from the Danish executive order no. 826 of 1 August 2012 that doctors are obliged to report all suspected serious adverse reactions as well as all suspected unexpected adverse reactions of medicines. Furthermore, doctors have an obligation to report all suspected adverse reactions of a medicine during its first two years on the market.

The list of new medicines subject to doctors' stricter reporting duty can be found on the DHMA website: *Medicines with stricter reporting requirements for doctors, dentists and veterinarians*.

# Top 5 most frequently reported active substances and number of users in 2013

The top 5 active substances generating the most ADR reports to the DHMA in 2013 appear from figure 1. Any reflection on the number of ADR reports should always be made in light of how many users there are, which is shown in figure 2. There may be many reasons why an active substance ranks among the top 5 most frequently reported substances. The five active substances behind the most ADR reports in 2013 partly reflect reporting stimulated by a questionnaire survey and partly reporting boosted by increased consumption of two of the active substances. It goes for all five active substances that the adverse reactions are known and described in the product information for each product. The reports submitted for the five active substances are described in detail on the next pages.

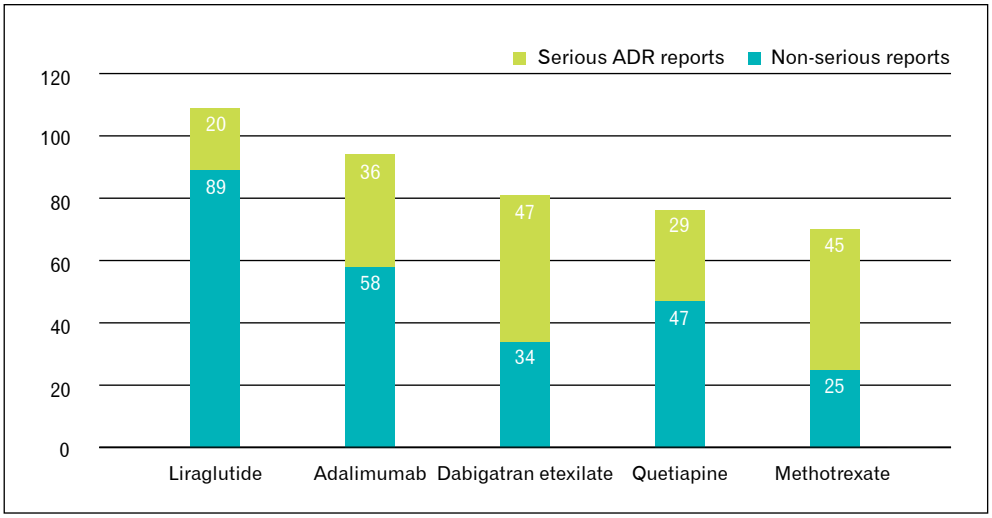



*Figure 1: Top 5 active substances generating the most ADR reports to the DHMA in 2013*

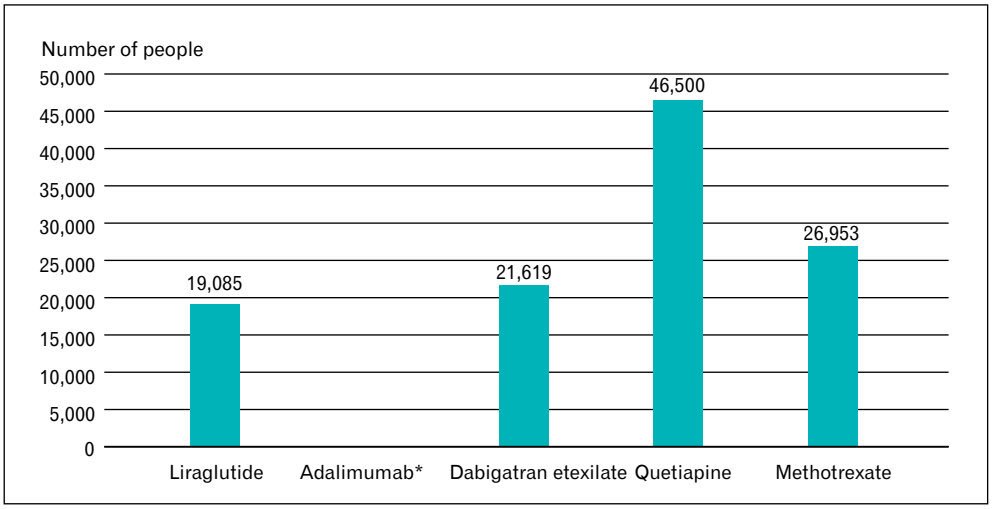



*Figure 2. Number of people who redeemed at least one prescription for the concerned medicine in 2013[2]. Adalimumab (marked by an *) is chiefly dispensed to patients in hospital or purchased for use in a specialist practice, and we therefore do not know the exact number of patients treated with this type of medicine.*

## Liraglutide (Victoza®)

In 2013, most of the reports we received concerned the active substance liraglutide, which is approved for combination treatment of type 2 diabetes. We received a total of 109 ADR reports for liraglutide, of which 20 were classified as serious. 76 % of the reports were submitted by patients on liraglutide, or by a relative.

The many liraglutide reports can be explained by stimulated reporting as a result of 600 completed questionnaires, which the medicine's marketing authorisation holder received in the beginning of 2013 as part of market research activities. The questionnaire had been handed out by pharmacies across Denmark to patients who redeemed a prescription for this type of medicine. Adverse reactions were subsequently identified on the basis of the questionnaires and reported to the DHMA.

The number of liraglutide users rose from 17,807 in 2012 to 19,085 in 2013, while the number of reports increased from 47 in 2012 to 109 in 2013. The increase primarily concerned non-serious reports.

The most frequently reported adverse reactions were symptoms from the gastrointestinal tract such as nausea, stomach ache, vomiting and diarrhoea. Reduced appetite and weight loss were also reported as suspected adverse reactions. All are well-known adverse reactions that appear from the medicine's summary of product characteristics.

2 The consumption figures are from the Register of Medicinal Product Statistics, Statens Serum Institut, National Institute for Health Data and Disease Control (SSI).

Infection and pancreatic cancer were also reported as suspected adverse reactions of liraglutide treatment. Inflammation of the pancreas is a known adverse reaction of liraglutide described in the medicine's product information.

In 2013, the European Medicines Agency, EMA, reviewed existing data on a possible link between liraglutide (and other GLP-1 analogues) and the risk of pancreatic cancer.

Data from clinical trials do not indicate an increased risk, however, the number of adverse reactions has been too small to draw a final conclusion. The EMA is watching this area closely, and in 2011 two independent studies on the risk profiles of diabetic treatment were initiated – and more specifically the risk profiles in relation to the pancreas. The first results are expected in 2014.

**Adalimumab (Humira®)**

In 2013, we received altogether 94 reports involving adalimumab, which is a biological medicine for the treatment of a number of different immune-mediated inflammatory disorders when other medicine has been inadequate, for example for the treatment of rheumatoid arthritis, chronic intestinal disease (Crohn's disease) and psoriasis. 58 of the reports were classified as serious.

The number of serious reports did not increase from 2012 to 2013.

Among the most frequently reported adverse reactions in 2013 were known ADRs such as reactions at the injection site, e.g. rash, redness, pain and itching as well as infections such as influenza and symptoms from the gastrointestinal tract such as nausea.

As part of the monitoring of biological medicines, collaboration takes place with a number of clinical databases, DANBIO, Dermbio and DCCD, which register adverse reactions among other things.

**Dabigatran etexilate (Pradaxa®)**

We received a total of 81 reports in 2013 concerning the blood-thinning medicine dabigatran etexilate authorised for the prevention of blood clots in adults with heart rhythm abnormalities (non-valvular atrial fibrillation). 47 of them were classified as serious.

The number of users rose from 16,092 in 2012 to 21,619 in 2013, while the number of reports fell from 119 in 2012 to 81 in 2013, reflecting primarily a fall in the number of suspected serious reports.

The reports especially described symptoms from the gastrointestinal tract, in particular bleeding and pain. Gastrointestinal bleeding is a known adverse reaction of dabigatran etexilate described in the medicine's product information. The use of dabigatran etexilate

and other types of blood-thinning medicine is associated with an increased risk of bleeding. Prescribers should therefore pay special attention to the patient's age and overall risk of bleeding. Older patients are at greater risk of bleeding.

**Quetiapine (Seroquel®, Seroquel Prolong®, Quetiapine 'TEVA'® etc.)**
76 ADR reports in 2013 concerned quetiapine, which is authorised for the treatment of schizophrenia, bipolar disorders as well as add-on therapy in the treatment of major depressive episodes in patients with unipolar depression. 29 of the reports were classified as serious. The number of ADR reports in 2012 was 46. Particularly the number of serious reports increased in 2013.

Also the number of users rose from 39,352 in 2012 to 46,500 in 2013. This sharp rise in users can be explained by a corresponding drop in consumption of the other antipsychotics. It is a development that we are watching closely.

The reports predominantly concerned symptoms from the gastrointestinal tract, e.g. constipation and common symptoms of fatigue, which are well-known adverse reactions described in the medicine's summary of product characteristics.

**Methotrexate (Metex®, Emthexate®, Methotrexate® etc.)**
70 ADR reports concerned methotrexate in 2013. Methotrexate is authorised for the treatment of certain types of cancer, severe psoriasis and rheumatoid arthritis. 45 of the reports were classified as serious. The number of reports in 2013 was the same as in 2012, and the number of users has been stable the last two years.

The reports predominantly concerned symptoms from the gastrointestinal tract, e.g. stomach ache, and symptoms from the respiratory passages, e.g. pneumonia, which are known adverse reactions described in the medicine's summary of product characteristics.

# Top 5 most frequently reported vaccines and consumption figures in 2013

The five vaccines behind the most reported adverse reactions in 2013 are shown in figure 1. Although there are generally much fewer vaccines on the market than conventional medicines, quite many people are vaccinated as part of immunisation programmes.

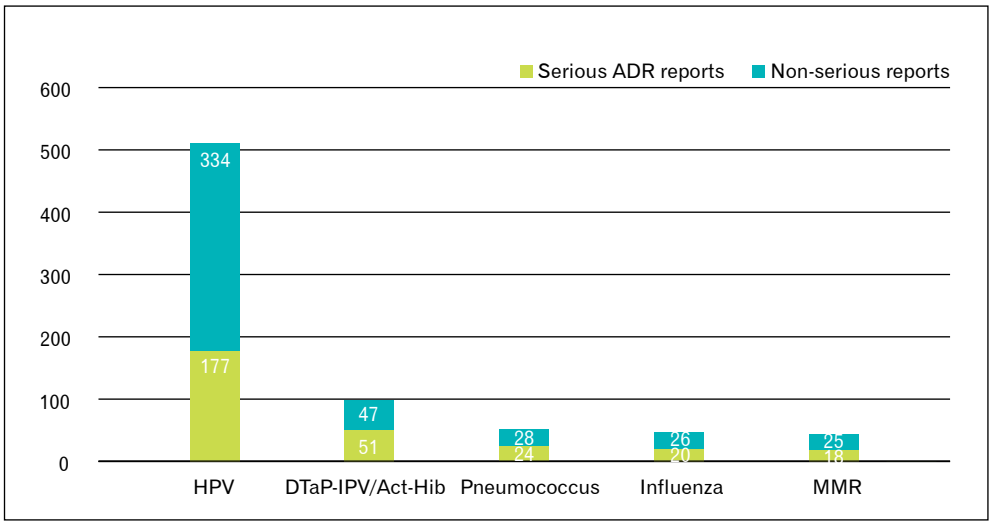



*Figure 1. Top 5 most frequently reported vaccines and the number of adverse reactions reported in 2013*

### Number of vaccinated people/doses dispensed

The numbers in figure 2[1] show how many vaccine doses have been dispensed (the influenza vaccine shows sales figures), which is not the same as the number of vaccinated people. Many vaccines are given several times to the same person, e.g. the childhood immunisation programme, and not all vaccines dispensed in 2013 may necessarily have been used in that year.

1 The consumption figures are drawn from the Register of Medicinal Product Statistics, Statens Serum Institut, National Institute for Health Data and Disease Control (SSI).

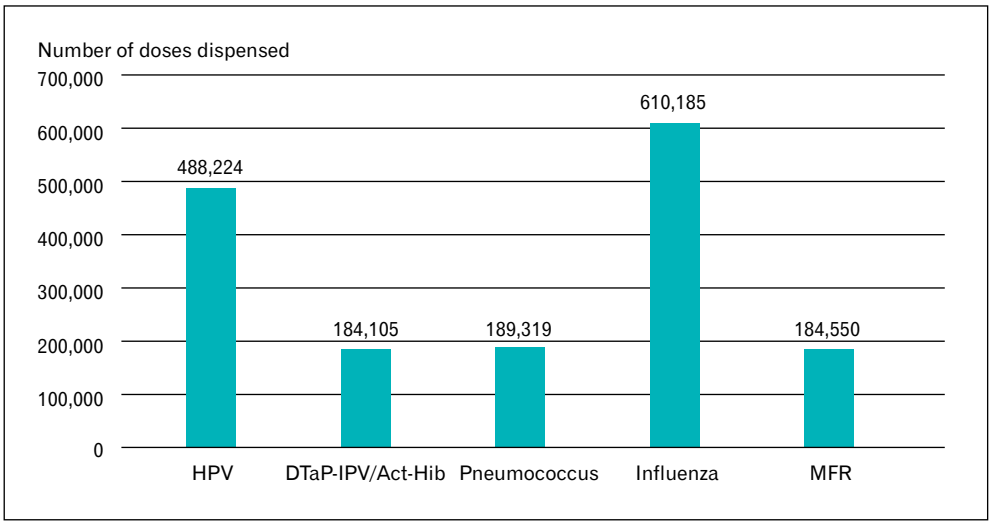



*Figure 2. Number of doses dispensed of the top 5 most frequently reported vaccines in 2013.*

## Most reports concern vaccines in the Danish childhood immunisation programme

Several of the vaccines on the top 5 list in 2013 were vaccines in the Danish childhood immunisation programme: the cervical cancer vaccine (the HPV vaccines Gardasil®/Silgard® and Cervarix®), the vaccine against diphtheria, tetanus, pertussis, polio and infections caused by haemophilus influenza type B (DTaP-IPV/Act-Hib), the vaccine against pneumococcus (Prevenar®/Prevenar 13® and Pneumovax), and the vaccine against measles, mumps and rubella (the MMR vaccine, predominantly Priorix® and M-M-Rvaxpro).

We received most reports for the HPV vaccine in 2013, more specifically 511 reports. The number of reports should be considered in light of how many people were vaccinated. Figure 2 shows that approx. 488,000 vaccine doses were dispensed in 2013. The vaccine is given in three doses to offer full protection against HPV, which means that approx. 162,000 people were vaccinated against HPV in 2013. We describe the monitoring of adverse reactions from the HPV vaccine separately on *page 24*.

The volume and nature of reported adverse reactions from the childhood vaccines DTaP-IPV/Act-Hib, the MMR vaccine and the pneumococcal vaccine correspond to what has previously been reported to us, i.e. primarily known and well-described adverse reactions such as local reactions at the injection site, fever and general discomfort. Among the serious reports related to DTaP-IPV/Act-Hib there were several cases of granuloma and aluminium allergy, among which a number of cases where the pneumococcal vaccine had been given at the same time. But there were also cases of granuloma among the non-serious reports. Most of the serious cases were reported via the Danish Patient Compensation Association (previously the Danish Patient Insurance Association). Most likely, the relatively high number of reports of granuloma was caused by increased focus on the condition, and not because there are more incidents of granuloma than before. In addition, a number of cases of whooping cough

(pertussis) were reported in people already vaccinated. This is expected as the vaccine does not offer full protection. The remaining vaccines in the childhood immunisation programme in top 5 in 2013 did not show any clear pattern for the reports classified as serious.

Every three months, a meeting is held by a vaccination panel with representatives from different divisions in the DHMA and the Statens Serum Institut, National Institute for Health Data and Disease Control (SSI). All suspected adverse reactions reported for vaccines in the childhood immunisation programme are assessed at these meetings. The assessments and conclusions from these meetings are described and published routinely in our electronic newsletter *Danish Pharmacovigilance Update*.

### Influenza vaccines (primarily Fluarix® and Vaxigrip®)

In 2013, we received 46 reports concerning seasonal influenza vaccines.

Considering that a total of 610,185 influenza vaccine doses were sold in 2013, the number of ADR reports is low. They mostly addressed known, non-serious adverse reactions such as influenza-like symptoms, including joint pain, fever and fatigue as well as reactions at the injection site such as swelling, redness and pain.

# ADR reports from Danish hospitals by region, 2013

In 2013, the DHMA received 1189 ADR reports in total from the Danish hospitals[1], covering also reports from mental health centres in the five regions.

Overall, the number of reports from the hospitals increased markedly in 2013 compared to the preceding two years, and there were particularly many from the Capital Region of Denmark in 2013 (figure 1).

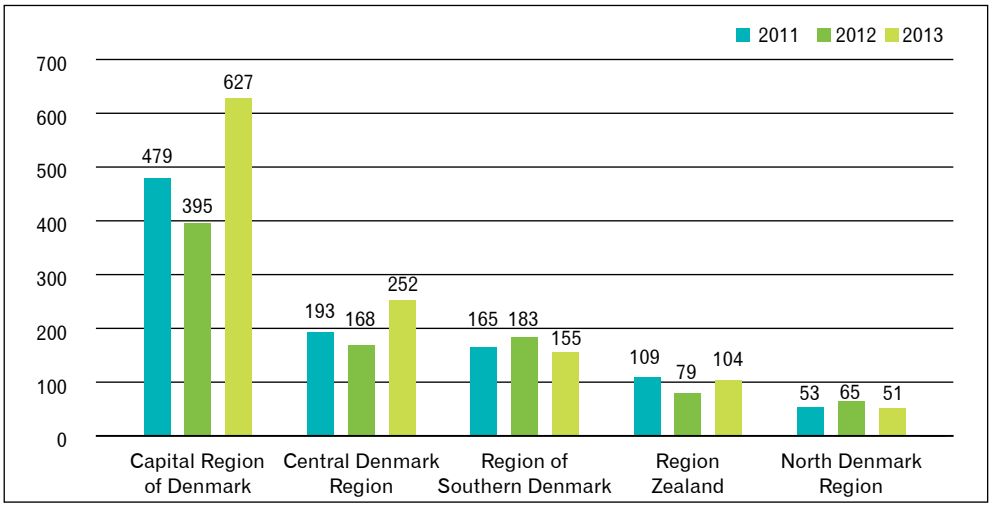



*Figure 1. ADR reports from Danish hospitals in 2011-2013 by region. The chart is not adjusted for the population size of the respective five regions.*

### Adverse drug reaction manager role a huge success

The major increase in the number of reports from particularly the Capital Region of Denmark has largely happened because in 2013 the Region started using an adverse drug reaction (ADR) manager who has helped doctors with ADR reporting. As can be seen from figure 2, a little over half of the reports (345 of 627) comes from Bispebjerg Hospital. At first, the ADR manager role started as a 12-month project where only the doctors at Bispebjerg Hospital could use the ADR manager, but now, the role has been expanded so that all hospital doctors throughout the region can draw on the manager (Read the Capital Region of Denmark's contribution to the annual report on *page 15*).

The 345 reports we received from Bispebjerg Hospital in 2013 cover both reports from the ADR manager and reports submitted directly by departments at Bispebjerg Hospital[2].

1 Only reports received directly from the hospitals are included in this report.

2 As of 1 June 2013, it appears from the reports on behalf of which hospital/department they are submitted. In the next annual report, it will therefore be possible to detail where the reports come from.

In 2013, we established more formal collaboration with the ADR manager in the Capital Region of Denmark. As part of this collaboration, we supply monthly lists of the ADR reports we have received from the ADR manager. The Capital Region of Denmark then uses these lists to evaluate the ADR manager role.

Roskilde Hospital introduced a similar ADR manager role on 1 February 2014. The ADR manager will handle the reporting of all adverse reactions on behalf of all hospitals in Region Zealand.

### Collaboration with the Copenhagen University Hospital's Drug Committee

Compared to previous years, we also received considerably more reports in 2013 from the Copenhagen University Hospital – up from 38 reports in 2012 to 95 reports in 2013 (figure 2). The Copenhagen University Hospital's Drug Committee has intensified efforts to boost the number of reports in 2013, which is the reason why the number of reports from this end has increased.

### Increase in the number of reports from three regions

Apart from the significant increase in the number of reports from the Capital Region of Denmark, we also received nearly 100 reports more in 2013 than in 2012 from the Central Denmark Region (see the distribution of reports in figure 3). This may be due to the Region's increased focus on ADR reporting (Read the Central Denmark Region's contribution to the annual report on *page 19*). In 2013, we also saw an increase in the number of reports from Region Zealand from 79 reports in 2012 to 104 in 2013 (see the distribution of reports in figure 5), and we expect this trend to continue after the Region has introduced an ADR manager inspired by the Capital Region of Denmark (Read Region Zealand's contribution to the annual report on *page 20*). Compared to 2012, we received fewer reports in 2013 from both the Region of Southern Denmark and the North Denmark Region (see the distribution of reports in figures 4 and 6). Across all five regions, it is a general trend that there are particularly few reports from mental health centres in 2013, which is a continuing trend from previous years.

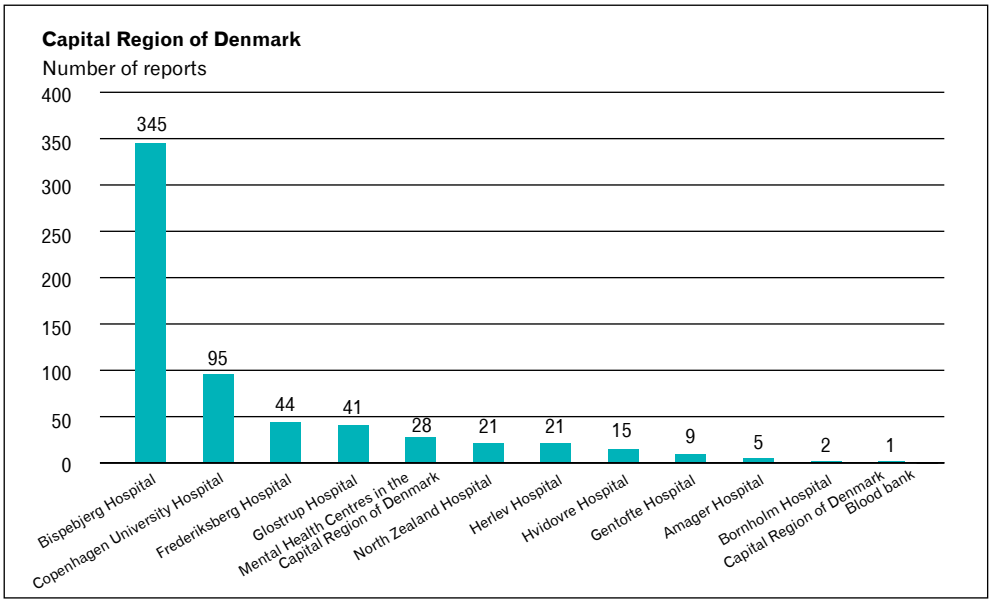



*Figure 2. ADR reports received in 2013 from the Capital Region of Denmark distributed among hospitals.*

In the beginning of 2014 we therefore launched an ADR campaign aimed at hospital and community mental health centres, which we hope will raise doctors' awareness on adverse reactions in psychiatry.

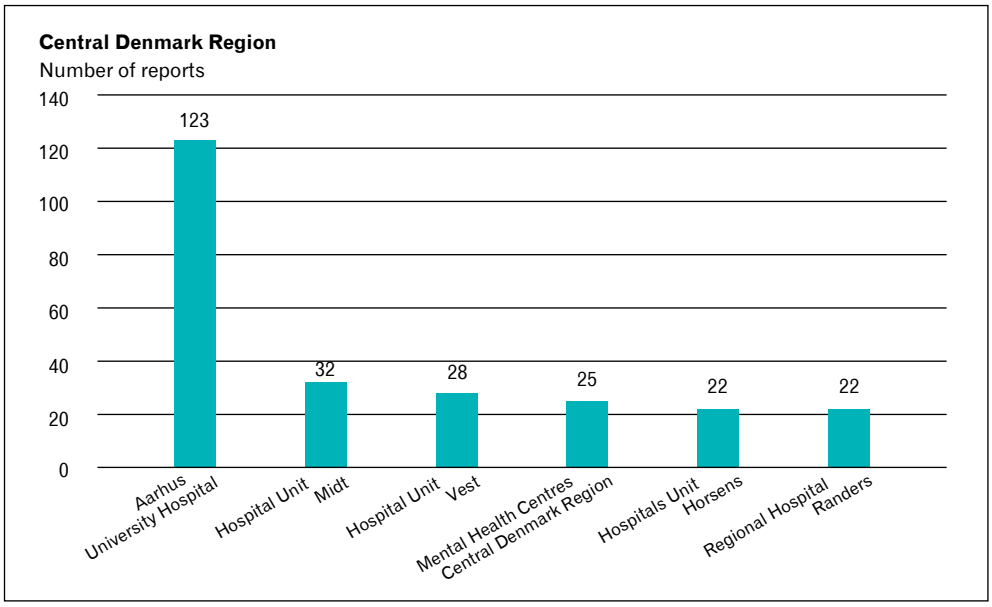



*Figure 3. ADR reports received in 2013 from the Central Denmark Region distributed among hospitals.*

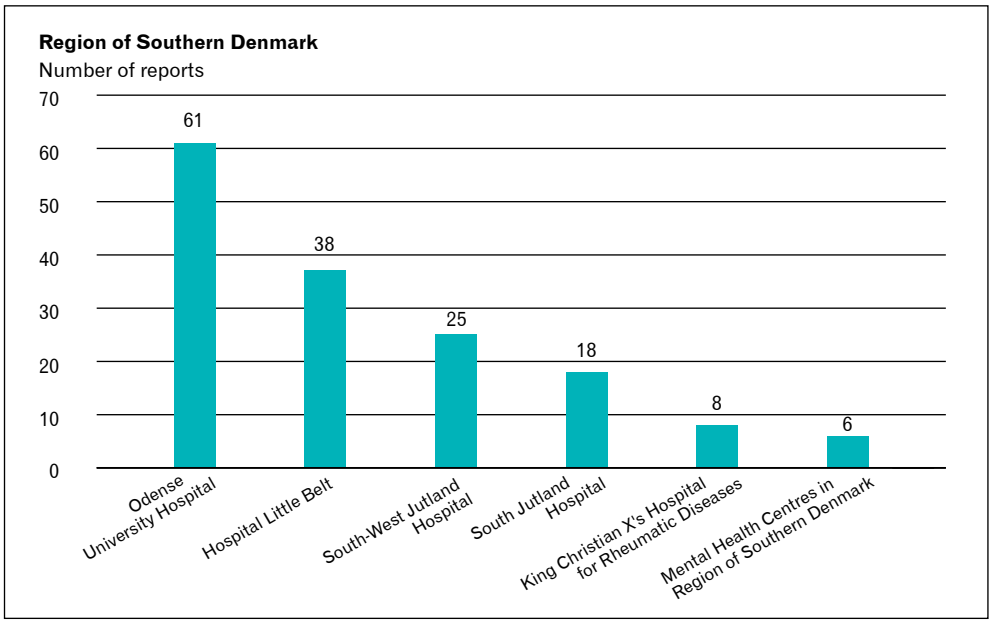



*Figure 4. ADR reports received in 2013 from the Region of Southern Denmark distributed among hospitals.*

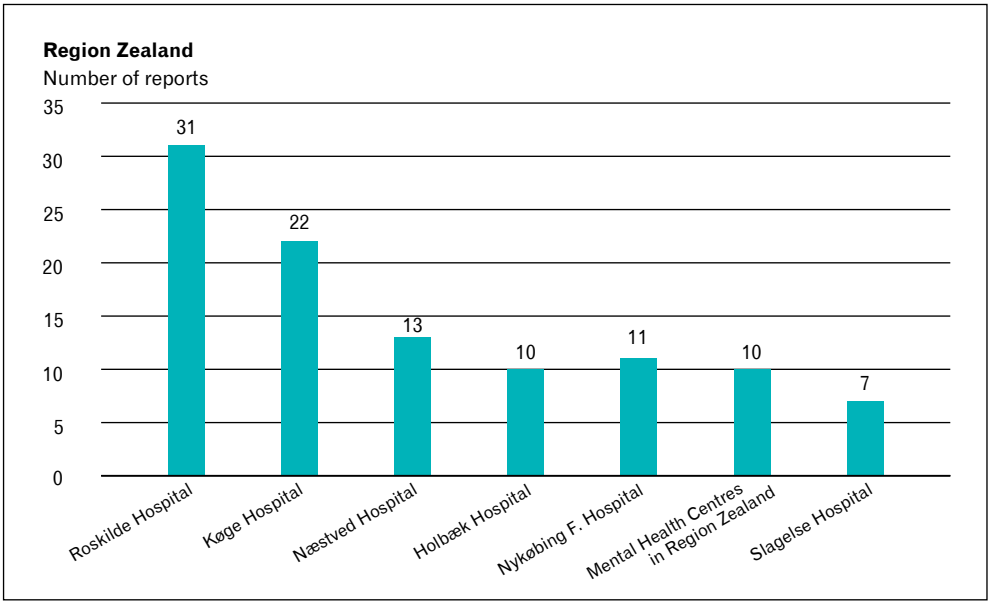



*Figure 5. ADR reports received in 2013 from the Region Zealand distributed among hospitals.*

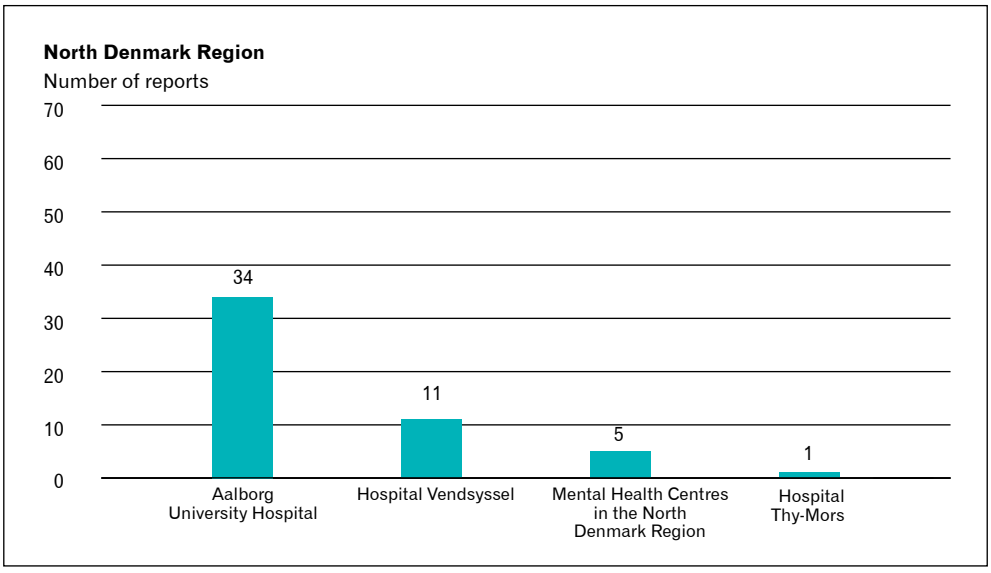



*Figure 6. ADR reports received in 2013 from the North Denmark Region distributed among hospitals.*

## The Capital Region of Denmark's ADR manager role – contribution by the Capital Region of Denmark

*By Espen Jimenez Solem, MD PhD, ADR Manager in the Capital Region of Denmark*

The ADR manager role is handled by the Department of Clinical Pharmacology at Bispebjerg Hospital, and since January 2013 the role has assisted doctors in the Capital Region of Denmark with reporting adverse reactions to the DHMA. The role reduces the time that the clinician spends on the reports (from about 30 to 3 minutes), and at the same time, the clinician opens dialogue with a doctor in the Department of Clinical Pharmacology.

### Number of reports from the ADR manager in the Capital Region of Denmark

In 2013, the ADR manager reported 337 adverse reactions to the DHMA, i.e. 54 % of all reports from the hospitals in the Capital Region of Denmark. In 2013, the total number of reports from the Capital Region of Denmark increased by 35 %. In 2013, an increasing number of the reports from the Region was handled by the ADR manager, and consequently the reports submitted by the ADR manager accounted for 80 % of the total number of reports in December 2013 (see figure 1).

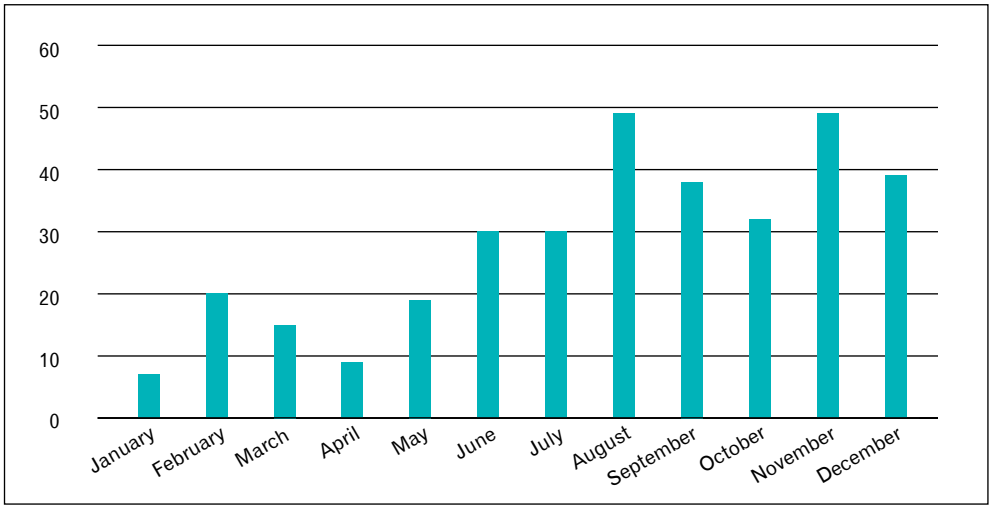



*Figure 1. Number of reports from the Capital Region of Denmark's ADR manager in 2013.*

### The ADR manager role

If the clinician suspects that an adverse reaction is subject to reporting, he or she can contact the ADR manager by email or telephone and simply provide the patient's civil registration number, medicine and adverse reaction. The ADR manager will then forward the clinician's suspicion to the DHMA after reviewing the patient's medical history, other medicines and supplementary examinations.

The initial goal was a fivefold increase in the number of ADR reports in the Capital Region of Denmark. This goal has proven difficult to achieve, and throughout 2013 we have therefore stepped up measures to further increase the number of reports. The local drug committees and deputy chief executives of all the Region's hospitals are informed of the number of reports and receive brief success stories every month. In addition, presentations are made at the morning conferences in the hospital departments. Finally, knowledge about the ADR manager is integrated in our post- and pre-graduate training in clinical pharmacology.

We expect the number of reports submitted via the ADR manager to increase further in 2014 as awareness about the role becomes more widespread.

## The Central Denmark Region's ADR reporting measures – contribution by the Central Denmark Region

*By Ann Dalgaard Johnsen, Regional Pharmaceutical Representative in the Central Denmark Region*

The Regional Drug Committee in the Central Denmark Region focuses heavily on raising awareness about ADR reporting. Therefore, the Committee works closely with the DHMA's Pharmacovigilance & Medical Devices Division to become the first Region to integrate the DHMA's new web service for direct reporting of adverse reactions in the Region's electronic patient record system (EPJ).

All hospital units in the Central Denmark Region work from the regional guidelines "Observation and reporting of adverse reactions" (Danish title: "Observation og indberetning af bivirkninger af lægemidler". Basically, the guidelines refer to observation, documentation and reporting, which comprise the following elements:

- Nursing staff is responsible for observing adverse reactions and forwarding observations to the treating doctor and/or doctor on call.
- Doctors are responsible for assessing whether treatment with the medicine in question is to be continued, changed or stopped, and whether adverse reactions need to be treated.
- Doctors are obliged to report all adverse reactions of a medicine in the first two years of marketing, all adverse reactions of medicines subject to stricter reporting requirements and magistral medicines as well as all serious and unexpected adverse reactions regardless of how long the medicine involved has been marketed.
- Adverse reactions of medicines must be documented in the EPJ system of the Central Denmark Region.
- Reporting of adverse reactions must be done to the DHMA.

Since 1 September 2013, the hospital unit in Horsens has been running a project with a junior doctor in specialist training in Clinical Pharmacology who handles the ADR manager role in the medical department.

The ADR manager works closely with the pharmacists who carry out daily medicines reconciliation in several departments. When the pharmacists carry out medicines reconciliation, they pay special attention to possible adverse reactions, and these are reported to the DHMA in collaboration with the ADR manager.

There is ongoing focus on the reporting of adverse reactions by the hospital pharmacy, which instructs all new staff members on the duty to report adverse reactions when they start. The hospital pharmacy also sends out newsletters with focus on adverse reactions. The latest one was issued in December 2013.

Furthermore, the hospital pharmacy reflects on the patients' medical treatment – including adverse reactions – and may in collaboration with the treating doctor take part in the assessment of adverse reactions and adjustment of medical treatment.

## Pharmacovigilance measures in Region Zealand – contribution by Region Zealand

*By Senior Physician Stig Ejdrup Andersen and Pharmacist Marianne Sindahl Larsen*
*Clinical Pharmacological Unit, Region Zealand*

The pharmacovigilance measures in Region Zealand revolve around the Clinical Pharmacological Unit, which was established in August 2013 based on wishes to strengthen work on rational pharmacotherapy and pharmaceutical safety.

One of the key priorities of the new unit was to introduce an ADR manager role using the Capital Region of Denmark as a role model. The role is filled by a pharmacist with back-up from a senior physician.

Apart from assisting the physicians with reporting adverse reactions, the ADR manager is to further the importance of ADR reports, strengthen dialogue on adverse reactions with the clinicians, ensure high-quality reports to make them more useful to the DHMA and should generally promote knowledge about pharmaceutical safety in the Region. The Clinical Pharmacological Unit also offers advice on the handling of specific adverse reactions and carry out thorough literature searches if additional information is needed.

After the role was introduced in February 2014, great efforts have been put into spreading knowledge about the role. Visits have been paid to the hospitals in the Region at staff meetings, and the major medical departments have also been offered visits. During these visits, we have spoken about the practical tasks of ADR reporting and talked about adverse reactions in general, including the importance of ADR reports. Several of these meetings promoted sound discussions about the handling and the definition of adverse reactions, including the problems that the professionals meet in practice when they have to deal with adverse reactions.

To help our colleagues in their daily work to remember ADR reporting, we have made pocket cards with contact details and descriptions of which adverse reactions must be reported. We have handed out these cards and post-it pads with contact details at all meetings.

In the first eight weeks, 26 adverse reactions were reported to the role, which corresponds to one third of all reports from the Region in 2012.

Together with the ADR manager in the Capital Region of Denmark and the DHMA, a network group has been formed, which is to meet a couple of times a year to discuss various problems and issues that each and everyone experience as part of ADR reporting. We also envisage that the Unit is to participate in projects and efforts in the pharmacovigilance area in the longer term.

The task ahead is to maintain awareness and interest. One way of achieving this is to provide feedback to the hospitals regularly, not only on reporting patterns, but also by sending out professional statements based on incoming reports.

# Closing of Pharmacovigilance action plan II

In 2013, we completed Pharmacovigilance action plan II (Action plan II for strengthened pharmacovigilance 2011-2013), which was launched by the Danish Ministry of Health and Prevention in June 2011. The main purpose of the action plan was to continue strengthening the monitoring of adverse reactions and thus to improve patient safety and security of taking medicines.

## Main results from Action plan II

In 2013, it was ten years since Danish medicine users and their relatives got the opportunity to report adverse reactions themselves to the DHMA. This landmark caused us to analyse the first nine years' experience with reports submitted by medicine users and their relatives. The analysis showed that the medicine users and their relatives contribute significantly, both in quantity and quality, to the overall reporting of adverse reactions, and their reports are generally thorough and well-documented. Action plan II highlighted the need for closer collaboration with patient organisations when important safety information is to be communicated. As part of this collaboration, we prepared needs-based articles and reports on adverse reactions in connection with specific treatments in cooperation with different patient associations.

### Initiatives to raise awareness on ADR reporting

Under the action plan, we organised two campaigns to raise awareness on the reporting of adverse reactions and likewise to boost the reporting frequency. In 2012, we launched a campaign at the municipalities' eldercare nursing staff, and in 2013 we targeted medicine users via the pharmacies (read more about the campaign on *page 23*). In the second half of 2013, the DHMA developed and planned a nationwide campaign aimed at doctors, patients and relatives within mental healthcare.

### Roll-out of the ADR manager role in more regions

Under Action plan II, an ADR manager role was introduced in several Danish regions. On completion of the action plan, two regions had committed to establishing this special role (Read more about the regional ADR managers on *pages 14-21*). The remaining three regions have informed us that they are working on alternative models.

### Establishment of advanced analysis tools to investigate reported adverse reactions

To improve our work with the monitoring of adverse reactions, we introduced an analysis tool capable of delivering advanced analyses of reported adverse reactions and identifying possible patterns in complex data. A publication form has been developed, which means that there is openness about all adverse reactions reported to the DHMA from 1968 and onwards. The lists of all reported adverse reactions have been made available at the DHMA website *Drug Analysis Prints: reported adverse reactions*.

The pharmacovigilance action plans have strengthened our work with medicines safety and adverse reactions. Action plan I laid down the fundamental elements needed to carry out technically adequate monitoring of medicines. Action plan II developed the DHMA's professional competencies so that we are now capable of making complicated data analysis. In parallel, Action plan II has improved our communication and collaboration with all actors involved and has not least strengthened their network.

# Campaigns 2013

## "Not everyone reacts the same" – initiative targeting medicine users and relatives

In spring 2013, we launched the campaign "Not everyone reacts the same" (Danish title: "Ikke alle reagerer ens"), informing the Danes that they can report adverse reactions of medicine via *www.meldenbivirkning.dk*.

The aim was to increase the number of reports from medicine users and their relatives, so strengthening the monitoring of medicine – ultimately making it more safe to use medicine.

The campaign was launched in April 2013 in health centres, pharmacies and Matas stores around the country in collaboration with a number of patient associations.

You can read more information about the campaign in Danish at the DHMA website: *Ikke alle reagerer ens*.

## "Respond to adverse reactions and help make medicine safer for all" – additional campaign material for the municipalities' eldercare nursing staff

In the beginning of 2013, we produced three short films, which zoomed in on the signals, procedures and insecurities that could play a decisive role in detecting and reporting adverse reactions.

The films were intended to be used by the nursing staff in educational settings to decode inappropriateness in a number of unclear everyday situations. The films were developed in supplement to the campaign material that was launched in 2012.

**Film themes**
The three short films each tell the story of a resident/user who has experienced adverse reactions from a medicine. The films also show three different scenarios that evolve in the discovery of an adverse reaction, e.g. reporting and notification of a doctor, notification of a doctor and reporting. Finally, the films show some of the most common insecurities involving the discovery of an adverse reaction: Insecurity as to whether known and non-serious adverse reactions must be reported, problems with finding/understanding the package leaflet or doubts about whether it is or is not an adverse reaction.

Links to the films were sent to the municipalities' nursing staff in the spring of 2013.

The films are in Danish and can be watched at the DHMA website *Reagér på bivirkninger – og hjælp med at gøre medicin mere sikker for alle* (Respond to adverse reactions and help make medicine safer for all).

# Focus areas 2013

## The HPV vaccine against cervical cancer

During the summer and autumn of 2013, there was great awareness on adverse reactions from the HPV vaccine. Not surprisingly, the heightened awareness had a knock-on effect on the overall reporting rate for the HPV vaccine in 2013 when the number of both serious and non-serious adverse reactions rose sharply compared to the previous years (figure 1). We therefore put stronger focus on the HPV vaccine 2013.

Since the HPV vaccine became part of the Danish childhood immunisation programme in 2009, the DHMA has continually monitored and evaluated the reports of suspected adverse reactions from the HPV vaccine along with the other vaccines in the childhood immunisation programme. As the awareness on the HPV vaccine grew stronger in 2013, we chose to review and assess this vaccine separately. We published the results of the first comprehensive review of adverse reactions to the HPV vaccine in *Danish Pharmacovigilance Update, 27 June 2013*.

### The HPV vaccine is part of the Danish childhood immunisation programme

The HPV vaccine was included in the Danish childhood immunisation programme on 1 January 2009. All 12-year-old girls have since been offered the vaccine at no cost. However, doctors started vaccinating girls born in 1993, 1994 and 1995 as part of a catch-up programme that ran until the year-end 2009. On 27 August 2012, free HPV vaccination was introduced to all young women born between 1985 and 1992. This offer ended on 31 December 2013 with the introduction of altered age limits for receiving the HPV vaccination vaccine in the Danish childhood immunisation programme free of charge, implying that the vaccination can now be given up until the age of 18 (instead of the prevous age limit of 15). In addition, a temporary offer for free HPV vaccination has been adopted for women born between 1993-1997. It expires at the end of 2015.

### Brief outline of the results from the review of adverse reactions reported for the HPV vaccine

We reviewed and evaluated all adverse reactions reported since the introduction of the HPV vaccine on 1 January 2009 until 31 December 2012. The review showed that the adverse reactions reported in Denmark compared to international experience and that nothing suggested increased occurrence or deviations of serious adverse reactions compared to previous descriptions.

A later review of adverse reaction data from the period 1 January 2013 to 9 September 2013 revealed a sharp increase in the number of serious adverse reactions within a relatively short period of time. In this nine-month period alone, we received 80 reports of suspected serious adverse reactions from the HPV vaccine, which was far more than what was reported in the first four years after the vaccine was introduced. Four of the serious ADR reports described the diagnosis POTS (Postural Orthostatic Tachycardia Syndrome), while several other reports described symptoms suggestive of this diagnosis.

The increase in submitted reports and the reports suggestive of POTS prompted us to request the European Medicines Agency, EMA, to investigate POTS as a newly identified possible adverse reaction to the HPV vaccine.

It is still unclear whether there is a causal relationship between POTS and the HPV vaccine, or if the cases reflect pure coincidences between the vaccine and a disorder which typically has the same onset age as the age of the vaccinees. Likewise, the exact incidence and prevalence of POTS is unknown, which makes it difficult to asses if there is an increased incidence rate of POTS in people vaccinated with the HPV vaccine.

At the DHMA, we are keeping constant watch on any new cases of POTS that are reported, and we routinely discuss the problem with experts in the area. The latest reports from 7 March 2014 show that a total of 26 cases of POTS have been reported in Denmark.

The assessment of POTS as a possible new adverse reaction to the HPV vaccine is still ongoing in European settings. We will report the results from the investigation as soon as the review has been finalised.

The vaccine's positive effects have now been established in Danish and international studies. For this reason, the DHMA assesses that the vaccine still fulfils its purpose of being an significant element in the prevention of the serious disease of cervical cancer. The benefits of the vaccine continue to outweigh any possible risks.

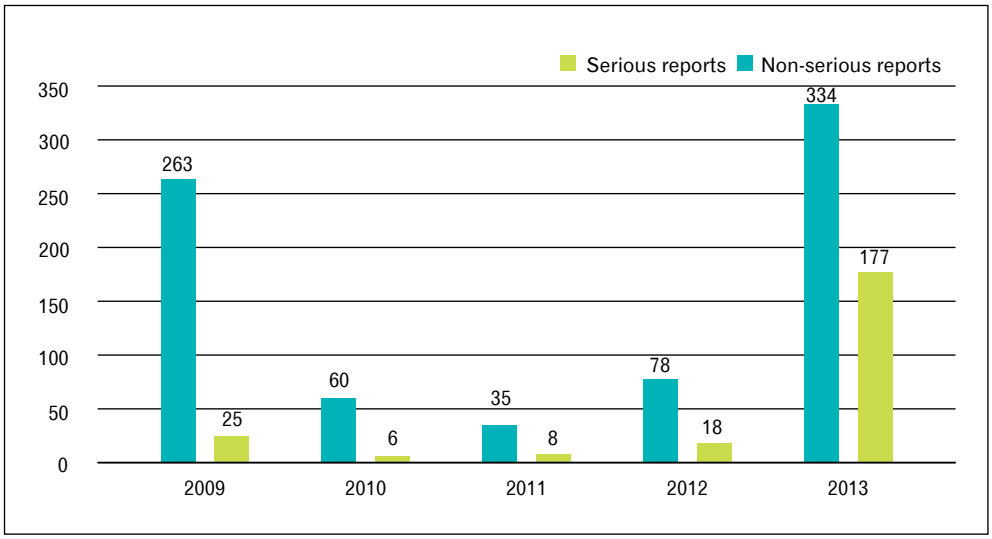



*Figure 1. Development in the number of reports submitted for the HPV vaccine, broken down by serious/ non-serious reports from 1 January 2009 – 31 December 2013.*

**The POTS diagnosis**

POTS is a diagnosis of exclusion confirmed by a so-called tilt table test, where the heart rate changes fast. What causes POTS remains unclear, but the condition has been described as occurring after, for example, rapid growth in the teenage years, after infectious diseases or after severe trauma such as a road accident, etc. The key symptoms of POTS are increased heart rate when standing up after lying down.

## Monitoring of medicines for induction of labour

The number of births initiated medically or mechanically rose from 17.3 % in 2008 to 25.1 % in 2012, and in 2013 the Danish Ministry of Health requested that the DHMA prepare and implement a plan to monitor medicines for induction of labour.

The main purpose of the plan is to increase the quality, safety and security of labour-inducing medicines, including among other things:

- to contribute to ensuring quality of the medicine used,
- to ensure monitoring of labour-inducing drugs,
- to contribute to ensuring that adverse reactions are reported, and
- to ensure that reports are followed-up as needed.

A number of initiatives have been launched as part of this plan, e.g. a future analysis of all reported adverse reactions and adverse drug events of medicines used to induce labour. This analysis will be made in cooperation between the Danish Society of Obstetrics and Gynaecology, the Danish Association of Midwives, the Danish National Agency for Patients' Rights and Complaints and the DHMA.

In addition, monitoring and analysis will be implemented for the use of magistral preparations of misoprostol and the misoprostol-containing medicine Angustar®, just as the hospital pharmacies' production will be inspected.

The obligation to report adverse reactions has been tightened for labour-inducing medicines, and we have offered to inform locally about the reporting of adverse reactions to all professional groups concerned. These information activities have started.

Finally, the plan establishes new rules, which means that from now on it is no longer an option but an obligation for midwives to report adverse reactions as part of their activities in line with the reporting duty that only applies to doctors today.

A combined status report will be prepared before the summer holidays in 2014.

# Consumption and adverse reactions from immunomodulatory biological medicines in Denmark

Another focus area in 2013 was biological medicines used for the treatment of arthritis, gastrointestinal or skin disorders. We reviewed Danish consumption figures and ADR reporting statistics as well as the newest publications in the area.

Our review was described in a report published on the DHMA website on 13 June 2013.

## Brief outline of the outcome of the review

There is a continuous rise in the consumption of biological medicines for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology. The biggest consumption increase is in rheumatology, where especially the medicines adalimumab, etanercept and infliximab are used.

The number of reported adverse reactions that concerned the biological medicines in question generally follows consumption. Consequently, the most adverse reactions were reported for the biological medicines that are consumed the most.

The most frequently reported adverse reactions involved well-known symptoms described in the medicines' summaries of product characteristics, e.g. headache, nausea and infections.

Internationally, there have also been reports of more rare adverse reactions, which – given the present knowledge in the area – cannot be ruled out as possible adverse reactions to the medicines, e.g. development of lymphoma or other cancer diseases. In the summaries of product characteristics, these are often described as occurring rarely. These types of adverse reactions have also been reported in Denmark.

## Conclusion

The risk profile of the current biological medicines has been assessed to be acceptable, especially in light of the medicines' beneficial effects. Especially the risk of infection is increased when using these medicines, and special attention is to be paid to atypical infections. No data have shown any certain advantages of any of the medicines over others in respect of the risk of infection.

When treatment is to be initiated, patients should be selected carefully – which would include attempts to identify patients at special risk of e.g. cardiovascular disease as well as relevant screening for latent tuberculosis and chronic hepatitis B. This can reduce the risk of adverse reactions.

Read the report on biological medicines (in Danish only) *Focus report on consumption and adverse reactions of immunomodulatory biological medicines (Danish title: Fokusrapport om forbrug og bivirkninger af immunmodulerende biologiske lægemidler)*

# Strong pain-relieving medicine (NSAID) – a report on consumption, reported adverse reactions and adverse drug events in Denmark

In August 2013, we published a report in which we took stock of the present knowledge on adverse reactions and consumption of NSAIDs as well as reported adverse drug events related to their use. In our report, we focused especially on gastrointestinal (GI) and cardiovascular (CV) adverse reactions since especially these effects have been discussed repeatedly by researchers and authorities alike.

## Brief outline of the report's conclusions

### Number of NSAID users in the period 2003-2012

The NSAID review showed that in the period 2003-2012, 3,012,582 people had redeemed at least one prescription for an NSAID product.

The number of NSAID users fell from 2004 and onwards. The decrease in users was seen within all NSAID groups – with the exception of the group of propionic acid derivatives, which includes ibuprofen – here a sharp increase in users was seen, driven in particular by sales of both prescription-only and over-the-counter ibuprofen. In Denmark, only ibuprofen is available over the counter.

### ADR reports for NSAIDs

Generally, the number of reported adverse reactions followed the consumption of the different NSAIDs. Among the adverse reactions reported the most were symptoms from the gastrointestinal tract, nervous system, heart and general symptoms. 56 reports involved symptoms from the nervous system – e.g. vascular diseases affecting the brain, blood clots in the brain as well as brain haemorrhages. 48 of these reports concerned the medicine Vioxx (rofecoxib), which was deregistered in 2004. The far majority of the adverse reactions were reported in response to a lawsuit in the USA in 2007 against the company holding the marketing authorisation for Vioxx (rofecoxib). The lawsuit included adverse reaction cases from all over the world, including Denmark.

### Adverse drug events reported for NSAID use

Our report also covered the adverse drug events reported for NSAID use. In the period 1 September 2010 to 28 May 2013, the Danish National Agency for Patients' Rights and Complaints had received 1107 drug medication events related to the use of an NSAID product. The majority of the events (nearly 90 %) were classified as no injury or as a minor temporary injury. None of the events had a fatal outcome, and seven of the events were classified as serious.

Already in 2004, a major clinical study raised awareness on the increased risk of acute blood clots in the heart (acute myocardial infarction) in the treatment with Vioxx (rofecoxib). Vioxx was subsequently withdrawn from the market.

# ADR signals 2013

Every week, we monitor our database of all reported adverse reactions to detect any new possible adverse reactions associated with a certain type of medicine (ADR signals). Signals may, however, come from a variety of sources, e.g. monitoring programmes, scientific literature, different types of studies, drug regulatory authorities in other countries, the media or from citizens and healthcare professionals.

A signal occurs when a new possible causal relationship between an adverse reaction and a certain type of medicine is identified. A signal could also reflect a new angle on an already known causality. In addition, we also pay attention to appropriate use of medicines in clinical practice, e.g. checking whether a particular type of medicine is prescribed to the right patients, that established precautions for use of the medicine are observed so that patients avoid discomforts and adverse reactions.

In 2013, we monitored and identified a number of ADR signals from different sources. Assessment and evaluation of signals are a complex and time-consuming process. All signals are therefore prioritised based on a clinical assessment and the likely consequences for patients and public health in general. When a new signal is detected, it first needs to be validated and confirmed before any further measures are taken.

Table 1 briefly describes the signals that we processed in 2013. A signal can be closed any time during the process if for example no causal relationship can be established between the medicine and the adverse reaction. Sometimes this happens early in the process, sometimes not until the evaluation has finished. The signal management process was described in further detail in *The Danish Health and Medicines Authority's annual pharmacovigilance report 2012*.

| Medicine | Signal | Action / communication |
|---|---|---|
| Aluminium adjuvanted vaccines in the childhood immunisation programme | Granuloma development after vaccination possibly due to allergy (type IV) to aluminium. Known but rare adverse reaction. | Article in *Danish Pharmacovigilance Update 31 October* |
| Chlorprothixene (antipsychotic) | Risk of prolonged painful erection in male adults (priapism) | The signal has been forwarded to the EU country which has the main responsibility for monitoring the medicine for further assessment (according to EU procedure). |

| | | |
|---|---|---|
| Vaccine against cervical cancer (HPV vaccine) | Postural Orthostatic Tachycardia Syndrome (POTS) generally giving symptoms such as dizziness, severe fatigue and in some cases fainting. | Article in *Danish Pharmacovigilance Update 26 September* and news update on the DHMA website. Has been discussed by the Pharmacovigilance Risk Assessment Committee (PRAC). The signal has been forwarded to the EU country which has the main responsibility for monitoring the medicine for further assessment (according to EU procedure). |
| Melatonin (for insomnia) | Increased prescription of melatonin to children and adolescents under 25 years of age as well as widespread prescription of melatonin to children and adolescents treated for asthma at the same time. | Continued monitoring of consumption among children and adolescents. Report published on the DHMA website. *Users under 25 years of age of melatonin-containing medicines.* Signal on concurrent prescription of melatonin and asthma medicine is being evaluated. |
| New blood-thinning medicine (new oral anticoagulants – NOAC) | Contraindication in patients with mechanical heart valves due to increased risk of strokes and blood clots around the heart valve. | Article in *Danish Pharmacovigilance Update 19 December 2013* and news update on the DHMA website. Is followed in the programme for monitoring of anticoagulants (NOACs) |
| Docetaxel (cytostatics)* | Risk of nerve damage (irreversible neurotoxicity). | Is processed further in connection with the drug's next periodic safety update report (PSUR), which the companies are responsible for. |
| Glucocorticoids (local use)* | Risk of eye problems – central serous chorioretinopathy (CSCR) – in connection with local use of glucocorticoids. | Signal is being evaluated. |
| Opioid-containing cough suppressants* | Use of opioid-containing cough suppressants in connection with asthma treatment. | Signal is being monitored and will continue to be monitored. |
| Paliperidone (antipsychotic)* | Several reports received over a short period of time on lack of efficacy in paliperidone treatment. | Signal is being evaluated. |

*Table 1. List of ADR signals that the DHMA had focus on in 2013*
*. * Follow-up on signal from 2012*

# Questionnaire among practitioners on the knowledge and use of risk minimising material

With the new European pharmacovigilance legislation, increased focus is put on the evaluation of the risk minimisation measures required for certain types of medicines that pose the risk of serious adverse reactions. The use of educational and information material from the pharmaceutical companies is one of the most commonly used risk minimisation measures in the EU.

In a large-scale project on risk minimisation measures, we conducted a major questionnaire survey among the doctors practising in Denmark in spring 2013. The purpose was to investigate the doctors' knowledge and views on the educational and information material they receive from the pharmaceutical companies when new medicine is introduced and there are risks of serious adverse reactions. The survey also elucidated how and to what extent the doctors use the risk minimisation material.

## Brief outline of survey results

422 doctors completed the electronic questionnaire which was sent to them by email. Based on the replies, we placed them in two groups: doctors with knowledge of the educational and information material and doctors with little or no knowledge of the material. Overall, the questionnaire survey revealed that one in every three respondent doctors had little or no knowledge of the material, and the majority of them read it only rarely or not at all. Two in every three doctors remembered having received this type of material before, but every third doctor only read it rarely or not at all.

### Practising doctors want information on safe and effective use of medicines to be digitised

The doctors generally found it difficult to separate the educational and information material from the other material they receive from the pharmaceutical companies. That the material comes from the pharmaceutical companies directly is a barrier to implementation in itself, and the fact that it is sent by letter and is not digitised is also a significant obstacle. The doctors expressed wishes for future digitisation and integration of the information on safe and effective medicines use into the IT systems and electronic works of references they use in daily practice.

The questionnaire survey gave reason to consider if the drug regulatory authorities and the pharmaceutical companies have chosen the most optimal way of communicating important information on the safe use of new medicine. The survey results have subsequently been used for reflections on the digitisation of Direct Healthcare Professional Communications (DHPCs) submitted to doctors and other healthcare professionals. A DHPC serves the purpose of supporting safe and effective medicine and is sent out when new important safety information on a particular medicine becomes available, and it is prepared by or in collaboration with the DHMA. As with the educational and information material, DHPCs are most often sent out by the pharmaceutical companies to relevant professional groups directly. 48 DHPCs were sent out in 2013.

With help from the Danish Medical Association, practitioners contributed significantly through their participation in the questionnaire survey.

**More about the risk minimisation project**

As part of the risk minimisation project, we conducted two drug consumption analyses in 2011 and 2012 together with Data Delivery and Medicinal Product Statistics at Statens Serum Institut, National Institute for Health Data and Disease Control (SSI). The results were described in the *Danish Health and Medicines Authority's annual pharmacovigilance report 2012*.

See the list of dispatched DHPCs on the website of the DHMA. *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals*.

# Expansion of the Drug Interaction Database

Towards the end of 2013, we initiated collaboration with the departments of clinical pharmacology at Aarhus University Hospital, Odense University Hospital and Bispebjerg Hospital to improve the Drug Interaction Database by expanding the scientific content. The project runs until the summer 2014.

## Grounds for expanding the database

An initiative called "Supplementary electronic decision-making support in the Shared Medication Record" is one of the initiatives featured in the *National action plan for the elderly medical patient (Danish title: National handlingsplan for den ældre medicinske patient)*, published by the Danish Ministry of Health in December 2011. The initiative's aim is to make a number of IT tools and databases available through a joint IT platform for integration in medical systems and the Shared Medication Record. This way doctors can base their decisions on a wider basis, which is to ensure better and correct medication and ultimately enhance patient safety.

The Drug Interaction Database is one of the databases to be integrated in the IT platform.

## Project content

To make sure that important information about the medicine is available in the Drug Interaction Database, it will be expanded with data from the interactions paragraphs of the medicines' summaries of product characteristics. Previously, the database was only updated based on data from published studies, which is problematic especially for new medicines because at the time of authorisation only few publications exist, but often there is much knowledge to find in the medicine's summary of product characteristics. To limit the task, the expansion only covers medicines authorised after 1 January 2008. The expansion also covers the lighter Drug Interaction Database for citizens, *www.medicinkombination.dk*.

In addition, the interactions advised against in the Drug Interaction Database will be cleaned for unimportant information noise to ensure the warnings in the Drug Interaction Database are real and clinically meaningful.

## Collaboration with departments of clinical pharmacology

The routine work with the scientific updating of the Drug Interaction Database is handled by the departments of clinical pharmacology at Aarhus University Hospital, Odense University Hospital and Bispebjerg Hospital. These departments have helped us before in a quality assurance project involving the Drug Interaction Database, and we are very happy to continue working with them in the drug interactions project

# Common labelling of medicines under additional monitoring in the EU

In autumn 2013, a new process in the EU was introduced for the labelling of medicines under additional monitoring. All medicines are monitored closely after marketing in the EU. But medicines under additional monitoring are watched more intensely than other medicines. This could be if there is less knowledge about the medicine in question, if the medicine is new on the market, or if there is only limited information about its long-term use.

Medicines under additional monitoring have a black inverted triangle displayed in their package leaflet and in the summary of product characteristics, together with the following sentence:

**▼ This medicinal product is subject to additional monitoring.**

Medicines that have a ▼alert doctors and patients to pay special attention to discovering and reporting possible adverse reactions to the medicine. Medicines under additional monitoring do not necessarily appear on the list of the medicines subject to stricter reporting requirements.

### EU list of medicines under additional monitoring

A European *list of medicines under additional monitoring* is available. The European Medicines Agency, EMA, first published this list in April 2013, and it is reviewed every month.

Read more about additional monitoring at the DHMA website: *Medicines under additional monitoring*.

# International collaboration in the pharmacovigilance area 2013

The new European pharmacovigilance legislation, enacted in the middle of 2012, brought with it significant changes and improved possibilities for establishing joint monitoring and knowledge of medicines safety and for reacting to signals suggestive of possible safety concerns. International collaboration on medicines safety in 2013 was very much about working in the new processes and measures that are to enhance medicines safety for patients throughout Europe.

The Danish Health and Medicines Authority is an active player in this work, and we are spearheading the safety reviews of a line of medicines in the international collaboration.

The EU's Pharmacovigilance Risk Assessment Committee (PRAC) was formed in 2012 in connection with the implementation of the new legislation. PRAC continually monitors safety aspects of marketed medicines and plans how to best avoid or minimise risks of new medicines. 2013 was a busy year for PRAC. Among other things, it reviewed the benefit-risk balance of a wide range of different medicines, e.g.

- Cholesterol lowering medicines containing nicotinic acid and laropiprant. The assessment was that the risks of combination treatment outweighed the benefits, and the medicine was taken off the European market.

- Contraceptive pills for acne treatment containing cyproterone and ethinylestradiol. The conclusion was that the medicine should be used solely in the treatment of severe acne or unwanted hair growth.

- Use of codeine for pain relief in children. Due to the risk of adverse reactions, because codein is converted into morphine in children to varying degrees, use of the medicine was restricted to children above 12 years of age when pain cannot be relieved with ordinary painkillers.

- Pain-relieving medicines with diclofenac and cardiovascular risks. The review showed that the medicine must not be used in patients with heart problems, and that any initiation of treatment should be monitored closely, as with other corresponding medicines (known as NSAIDs of the type $COX\text{-}_2$ inhibitors).

- Medicine for treatment of acute blood loss (hydroxyethyl-starch solutions (HES)). The final conclusion from this review was that treatment with HES is only considered beneficial for a small group of patients with acute blood loss when other medicine is considered insufficient.

- Contraceptive pills and the risk of blood clots. A review of all available data led to changes in the product information and new measures to make doctors and patients aware of the risk of blood clots and their early warnings signs.

- Acipimox for the treatment of elevated cholesterol levels. In this case, use of the medicine was restricted to adjunct treatment in a small group of patients with high levels of triglycerides, a type of fat, in the blood.

- Coagulation factor VIII, used for the treatment of haemophilia. The review of data did not confirm the suspicion that a particular medicine of this type increased the risk that the patient developed antibodies.

We routinely bring the reviews by PRAC in our monthly newsletter *Danish Pharmacovigilance Update* (issued in Danish and English) and communicate them directly to doctors and relevant organisations.

## SCOPE – Strengthening Collaboration for Operating Pharmacovigilance in EU

In the wake of the new pharmacovigilance legislation in the EU (2012), the EU Commission launched a three-year project, which is to support the member states to use the best standards in the area in fulfilment of the legislation's pharmacovigilance requirements. The project runs until 2016 and is called SCOPE (Strengthening Collaboration for Operating Pharmacovigilance in Europe).

A total of 26 EU member states participate in the SCOPE project – of which 15 contribute actively by working together to develop and disseminate the highest common standards for pharmacovigilance. SCOPE has five subprojects covering different aspects of the new legislation as well as three subprojects intended to ensure coordination, implementation and communication.

### DHMA participates actively

The Danish Health and Medicines Authority participates actively in two subprojects of SCOPE: risk communication and ADR signal management in which the DHMA is project manager in parts of the project.

In the communications project, focus is on developing tools for risk minimisation, a web portal as well as a guide to best practice within risk communication. Likewise, the ADR signal management project is to deliver an adequate common guide for best practices within all areas of signal management, i.e. signal detection, prioritisation and signal evaluation, etc. This work is to be rolled out to all member states through common education plans, which will also involve the development of a training concept.

SCOPE is a project under Joint Action under the EU Commission's Health Programme. Read more about Joint Action and SCOPE on the EU Commission's website *Call 2014: Joint actions*.

# Pharmacovigilance work 2014

In order for us to keep enhancing security and safety of medicine, an important part of our activities is to constantly look for the best methods to register and monitor adverse reactions, and not least to ensure that important safety information is communicated in a targeted manner. To support this, we have teamed up with the Danish Pharmacovigilance Council and other stakeholders to prepare a proposal for a Pharmacovigilance action plan III for implementation in the period from 2014 until end-2016. The focus areas of the action plan include among other things:

- More collaboration, networking and communication,
- Enhanced quality of reports,
- Research, data analyses, data capture and registry studies,
- IT – even better integration between the actors and the analytics tools, Regional action plans and the Danish Healthcare Quality Programme and the Danish pharmacovigilance work in an international perspective, including benchmarking of the Danish pharmacovigilance activities against other agencies.

### Easier ADR reporting

Many of these activities we will launch already in 2014. We still want to make it more simple for doctors and other healthcare professionals to report adverse reactions. A web service has therefore been developed to make ADR reporting easier. It will enable doctors to transfer background data from medical records directly to the web service, i.e. data about the patient and data about the medicine(s) he or she is taking. The new web service will be launched in spring 2014. The web service will ease the burden of ADR reporting significantly and is a breakthrough for pharmacovigilance work.

### Improved quality of ADR reports

We will also be focusing at the quality of reports in 2014. We will therefore set up a quality forum between the pharmaceutical industry and the Danish Medical Association which – together with us – are to help outline the relevant criteria for high-quality ADR reports. An integral part of this work is also reinforced attention to the Danish Healthcare Quality Programme and not least improved collaboration with Danish Regions.

### More ADR reports are still needed

As we make it easier to report adverse reactions and launch initiatives to ensure high-quality ADR reports, it remains important that we receive more reports – especially from doctors and other healthcare professionals – to ensure the best possible basis for monitoring medicines after market entry. As before, we will continue to focus on boosting the number of submitted ADR reports in 2014, and it has been decided, in consultation with the Danish Pharmacovigilance Council, to carry through an initiative to ensure submission of more reports from the mental healthcare area. In the beginning of 2014, we launched a campaign at doctors, medicine users and relatives within mental healthcare to encourage them to report adverse reactions as well from this extremely important area.

In 2014, we will also be organising efforts, partly to increase the number of reports and partly to improve the quality of reports from practitioners.

### International "best practice" in pharmacovigilance work

Our pharmacovigilance activities will in 2014 be subject to international benchmarking. We welcome this review of our quality system and work procedures. It is only healthy and beneficial for an institution like ours to have our international collaboration partners look over our shoulders and offering their advice.

### Implementation of initiatives to support better and safer medicines for induction of labour

In 2013, we prepared an action plan for the monitoring and supervision of the Danish regions' use of labour-inducing medicines. A number of these initiatives are to be implemented in 2014. Among other things, an analysis of all reported adverse reactions from the use of this type of medicines will be carried out. It will be a large, but also very interesting, project, which is to be implemented in collaboration with the Danish Association of Midwives, the Danish Society of Obstetrics and Gynaecology and Danish Regions.

### Expanded collaboration between research institutions and patient and stakeholder organisations

Collaboration and networking with patients and stakeholder organisations are prerequisites for targeting activities and information about adverse reactions. Not only will we be expanding our collaboration with research institutions in 2014, we will also continue to prioritise collaboration – not least with the patient organisations. It is a matter of course that we maintain our professional knowledge, but it is also crucial that we have first-hand knowledge about what the medicine users, know, think and feel – so we should base our work on this knowledge too. Only then can we gain the full potential of the major and important work to which everyone contributes – doctors and other healthcare professionals, patients, relatives and the pharmaceutical companies.