swissmedic

VIGILANCE – NEWS

EDITION NO. 9 - JUNE 2012

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Report of a suspected adverse drug reaction (ADR):

The ADR reporting form can be filled in electronically:

MU101_20_001d_FO Meldung einer vermuteten unerwünschten Arzneimittelwirkung (UAW) (German)

MU101_20_001f_FO Annonce d'effets indésirables suspectés d'un médicament (EI) (French)

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EDITORIAL

Pharmacovigilance – fast information and evaluated data

Dear Reader,

Swissmedic regularly receives enquiries regarding the safety profile of medicinal products. In order to provide responses to the extremely heterogeneous questions raised by the different interested parties, Swissmedic needs to have various forms of data analysis available for reference.

While patients and their relatives usually require rapid information about a possible adverse drug reaction (ADR) when taking a specific medicinal product, providing a response to questions submitted by healthcare professionals and representatives of the media usually calls for comprehensive research and analysis of data which may cover several years and various active sub-

stances. An overview of the reports received by Swissmedic last year with regard to human and veterinary medicines and on events related to blood transfusions can be found in the first part of this issue of Vigilance-News.

The extent to which the new social media can be of use within the surveillance of medicines is a question that is frequently discussed. On the one hand, it is a positive move for adverse drug reactions to be addressed in blogs and Internet forums, but on the other hand, indiscriminate "information" can also lead to patients becoming considerably insecure. It is therefore important, in this respect, to bring in expert knowledge. Since physicians and pharmacists are the patients' direct dialogue partners, these professionals should constantly remain abreast of any risk minimization measures – and be brought up to date rapidly, with the relevant information.

An extremely useful tool in this respect is the "Direct Healthcare Professional Communication (DHPC)", which informs of a safety signal and its consequences. It is usually also published on the Swissmedic website and appears as an announcement in the Swiss Medical Journal and in the pharmaJounal. In this regard, an information sheet was recently published for the marketing authorization holders on the Swissmedic website in order to facilitate the handling of DHPCs. The DHPC was also a workshop topic at this year's Swissmedic information event on the safety of medicines, held on 23 April 2012 (see report on the conference). May we remind you that it is also possible to subscribe to individual sections of the Swissmedic website, such as that concerning HPC, at: (www.swissmedic.ch).

Once again, this issue is aimed at contributing towards providing an insight into new, important findings with regard to the safety of medicines, such as those regarding Fingolimod or Carbamazepine.

We would be pleased to receive input from our readers, and look forward to your comments at vigilance@swissmedic.ch.

The editors

Editorial team:

Eva Eyal, Thomas Munz, Helena Bill

We want to thank all colleagues for their contribution to the realization of this issue of Vigilance-News.

FLASH : SIGNALS RELATING TO THE SAFETY OF MEDICINES FROM THE SWISS DATABASE OF THE VIGILANCE UNIT

Drug hypersensitivity and the HLA[1] complex

Drug-induced hypersensitivity reactions represent a heterogeneous group of adverse drug reactions which are usually and generally considered to be dose independent and unpredictable. These reactions manifest with a wide range of symptoms, i.e. from mild skin rashes (e.g., maculopapular exanthems) to severe, even life threatening and potentially fatal hypersensitivity reactions with systemic symptoms and multiple organ involvement (e.g. Stevens-Johnson-syndrome (SJS) / toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis, AGEP). They can be initiated by various chemical compounds. It is thought that the pathophysiological mechanisms underlying hypersensitivity reactions are immune mediated. This has resulted in the investigation of the genes deemed responsible for these reactions and in the pharmacogenetic testing to predict the risk of drug-induced hypersensitivity reactions.

Recent studies have reported strong genetic associations between different HLA alleles and susceptibility to drug hypersensitivity. The genetic associations can be drug specific as well as phenotype and ethnicity specific.

The most commonly discussed example is carbamazepine-induced SJS/TEN, carbamazepine being used primarily in the treatment of epilepsy and bipolar disorder, as well as trigeminal or glossopharyngeal neuralgia and alcohol withdrawal syndrome. While a strong association has been demonstrated between HLA-B*1502 and SJS/TEN in Han Chinese and Thai populations, there appears to be no clinically significant association in Caucasians or Japanese individuals, presumably because of the relative rarity of the HLA-B*1502 allele in these population groups, as reflected in the corresponding product information.

In contrast to carbamazepine, abacavir hypersensitivity is associated with HLA-B*5701 in patients of all ethnic backgrounds, including Caucasians and Black Africans, abacavir being a nucleoside reverse transcriptase inhibitor used as an anti-HIV agent. It is interesting to note that the HLA-B*5701 allele occurs at approximately 5% frequency in European populations, 1% in Asian populations and less than 1% in African populations.

Two retrospective genetic studies in North European and Japanese populations found a higher risk of occurrence of skin/hypersensitivity reactions in HLA-A*3101-positive patients on carbamazepine. In Europe, McCormack and colleagues[2] examined the association of the HLA-A*3101 allele with carbamazepine-induced hypersensitivity reactions in people with northern European ancestry: In a comparison of 145 participants of North European descent with carbamazepine-induced hypersensitivity reactions (including SJS-TEN, drug hypersensitivity syndrome, and maculopapular exanthems) and 257 controls who took carbamazepine without hypersensitivity reactions, the risk for both severe and milder skin/hypersensitivity reactions was significantly higher in presence of HLA-A*3101. The presence of the allele increased the risk from 5.0% to 26%. In Japan, Ozeki and colleagues.[3] studied 61 patients with reactions and 376 controls who tolerated carbamazepine. They, too, found a strong association of HLA-A*3101 with SJS-TEN and drug-induced hypersensitivity syndrome in the investigated Japa-

[1] *Human Leukocyte Antigen*

[2] *McCormack M. et al. (2011) HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med; 364(12): 1134-43*

[3] *Ozeki T. et al. (2011) Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. Hum Mol Genet; 20(5): 1034-41*

nese population. These relevant findings have led to an update of the Swiss product information for carbamazepine as explained in the Health Professional Communication published beginning of March 2012 on the Swissmedic website (see link below):
http://www.swissmedic.ch/marktueberwachung/00091/00092/01919/index.html?lang=en

Although pharmacogenetic testing may be clinically useful, it is important to keep in mind that genotyping should not substitute for clinical vigilance. In fact, clinical observation and close monitoring of patients should still be conducted even if they are negative for the HLA alleles implicated in hypersensitivity. The presence of HLA alleles may predict that risk but hypersensitivity reactions may nonetheless occur in the absence of HLA alleles.

Fingolimod (Gilenya®) and bradycardia after first administration

The active pharmaceutical ingredient Fingolimod was authorized in Switzerland on 3 January 2011 for the treatment of relapsing – remitting multiple sclerosis (MS), and two months later also in the EU. Fingolimod is phosphorylated to its active metabolite in vivo, and is the first sphingosine 1-phosphate (S1P) receptor modulator with a dose-dependent capacity to reduce peripheral lymphocytes. The receptor is widely distributed in various body tissues, meaning that Fingolimod presents additional, dosage-dependent biological effects. The most important of these are a temporary reduction of the heart rate and a delayed atrio-ventricular conduction at the beginning of treatment, a slight increase in airway resistance, a slight increase in blood pressure, possible macular oedema, and an asymptomatic increase of liver enzymes. In addition to the new mechanism of action, a partial, targeted weakening of the immune system, the galenic form as oral tablet also constitutes a major innovation in medical practice. To date, for this area of indication, only medicinal products with parenteral forms of administration have been authorized.

The negative chronotropic effects discovered at the relatively early stages of development of the substance are most marked during the first six hours following the first administration, with normalization occurring within one month if the treatment is continued. This side effect led to contraindications, warnings, and strict mandatory precautionary measures, also regarding pre-existing cardiac disease and concomitant medication. The product information in particular states the necessity of clinical monitoring for six hours after the first administration, with an ECG being recorded at the start and after six hours. In addition, criteria were defined regarding when monitoring is to be extended or when treatment should be halted.

In December 2011, in the USA a death was spontaneously reported. A 59-year-old woman died in her bed during the night following the first administration of Fingolimod. Her heart rate and blood pressure had been monitored for six hours

following administration with no noticeable anomalies, but no ECG had been recorded. The cause of death could not be identified conclusively, nonetheless an autopsy had been performed. Therefore, the causality between Fingolimod treatment and the death was considered possible based on close time correlation between the patient's death and the first administration. This report led the European Medicines Authority (EMA) to issue a Direct Healthcare Professional Communication (DHPC) in January 2012 ordering stricter monitoring measures and to open a formal investigation procedure. The investigation procedure focused on the re-analysis of all deaths reported pre- and post-marketing and of all cases involving cardiac arrhythmia. These data were also submitted to Swissmedic by the marketing authorization holders. Analysis of the data indicated no necessity for immediate measures to be taken on the Swiss market particularly given the fact that the labelling in Switzerland was a priori stricter. Unlike in the EU and the USA, the product information in Switzerland already included mandatory ECG recordings at the time of authorization. There had been no reports of deaths or of severe arrhythmia in Switzerland at the time (and none have been received to date).

On 20 April 2012, the EMA issued a press release regarding the completion of its investigation procedure. The EMA's main conclusion was that the risk – benefit balance remained positive if the new safety measures decided were respected. The main new precautionary measures in the EU are ongoing ECG monitoring during the first 6 hours, with 12-channel ECG recordings at hours 0 and 6 (an immediate measure already implemented in January), and a relative contraindication for patients with pre-existing cardiac or cerebrovascular disease or those taking heart rate lowering medication. Should treatment with Fingolimod be started in such cases, based on a case-by case assessment, a cardiologist must be consulted and at least an overnight ECG monitoring must be carried out. Although at the time of authorization the provisions of the EU (and also of the USA) were originally less strict than in Switzerland, their wording is now stricter than that in the Swiss product information to date. An application for amendment of the Swiss product information is currently being processed by Swissmedic. The new, moderately stricter wording to be implemented in Switzerland will be the same as in the EU, provided that the in-depth evaluation confirms them to be useful and sufficient. It is also then planned to issue a DHPC in Switzerland.

Two further remarks in conclusion: This article addresses only the cardiac problems. For an overview of all important risks and precautionary measures, it is imperative to consult the product information. Based on currently available data, Fingolimod is an important treatment option for MS, a severe neurological disease, but given the broad distribution in various organs of the S1P receptor, particularly careful monitoring is essential. As exposure to the product increases – to date a total of 30,000 patients have been treated worldwide – new, unexpected safety signals may emerge at any time. If these should occur, it will be necessary to analyze them carefully and rapidly and to take risk minimization measures: primarily in the interests of patient safety, but secondly also in the interests of the product and thus the treatment options for MS.

Press reports following the completion of the EMA investigation procedure were unfortunately lacking in precision. The Swiss agency sda and – for example – the electronic specialist news agency DIA Daily hastily presented the above-mentioned relative contraindications as absolute contraindications.

Counterfeit cancer medicine discovered in the USA

In February of this year, the US Food and Drug Administration (FDA) published a warning and a recall of a counterfeit version of the cancer medicine Avastin. Probably for cost reasons, some 19 clinics and oncology practices had obtained Avastin from an English pharmaceutical trader rather than the Avastin authorized by the FDA. The counterfeit product contained no active pharmaceutical ingredient and was distributed via several intermediaries, including a firm in Switzerland. The origin of the product, presented in an English-language packaging, has not yet been clarified since the traces have at present disappeared somewhere in the Middle East.

The counterfeit product was in fact discovered thanks to the alertness of an end user: the batch number on the bottle did not correspond to the batch number on the box.

Swissmedic calls upon clinics and physicians to examine any medicinal products obtained directly from abroad more closely, and also to take reports by patients of unusual unexpected reactions into account as being a possible indication that the products could be falsified ones. Suspected cases of counterfeit medicinal products can be reported to Swissmedic via:
market.surveillance@swissmedic.ch or
tel. 031 323 16 63.

STATISTICAL REVIEW 2011

VIGILANCE OF HUMAN MEDICINES: DESCRIPTIVE STATISTICS OF ADVERSE DRUG REACTIONS FROM SPONTANEOUS REPORTS RECEIVED IN SWITZERLAND

1. Reports of serious adverse drug reactions* (ADRs) by organ class (System Organ Class, SOC)

During the period 1 January to 31 December 2011, Swissmedic recorded 3,903 case reports in its national ADR database, VigiFlow, of which 3,349 (86%) contained at least one serious ADR. A total of 554 case reports (14%) contained exclusively non-serious ADRs.

The 3,903 case reports contained a total of 14,826 single adverse reactions, i.e. on average 3.8 events per case report.

Diagram 1: Reports of serious ADRs by organ class

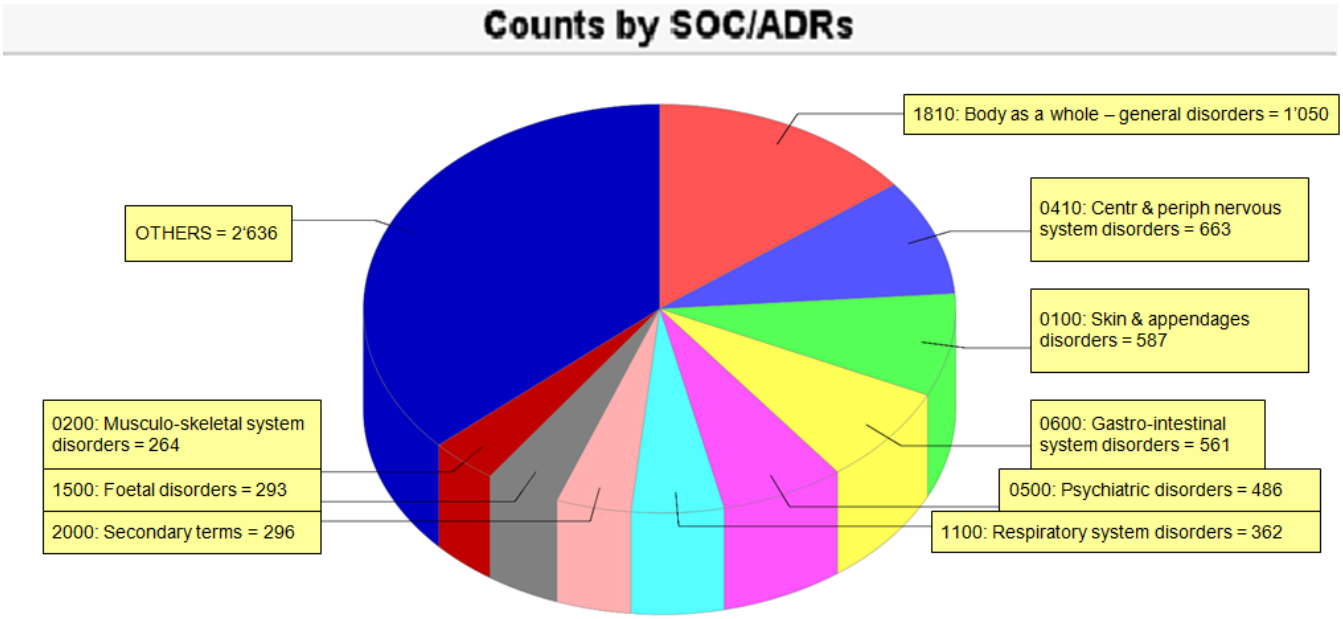


Diagram 1 shows that the most frequently occurring ADRs among the 3,349 reports received containing serious ADRs concerned the following organ classes (SOC/WHO Adverse Reaction Terminology):

- Body as a whole – general disorders
- Central and peripheral nervous system disorders
- Skin and appendages disorders
- Gastro-intestinal system disorders
- Psychiatric disorders
- Respiratory system disorders
- Secondary Terms
- Foetal disorders
- Musculoskeletal system disorders

All other serious ADRs were placed in the group "others" and not broken down further. The distribution remains virtually unchanged compared with the previous year.

Of the 3,903 reports received by Swissmedic in 2011, 55% came from the regional pharmacovigilance centres, and 45% from pharmaceutical companies.

The case reports are classified according to their seriousness: "serious", as internationally defined by ICH**, is an ADR which is fatal, life-threatening, leads to a hospitalization/prolonged hospitalization or a permanent damage or disability, results in a congenital anomaly or is otherwise medically important. When interpreting the frequency of occurrence, the fact that only serious or unknown ADRs need to be reported in Switzerland should be taken into consideration. Given the resources available at Swissmedic, no complete data input of non-serious case reports was carried out in 2011. This explains the low proportion of non-serious case reports in the total number.

The fact that these are suspected cases should also be taken into consideration: a causal link between exposure to a medicinal product and the adverse event is not per se given in each case.

- Death 5.3 %
- Life-threatening 3.4%
- Hospitalization 33%
- Permanent damage or disability 2.3%
- Congenital anomaly 0.3%
- Medically important ADRs 49%

➢ Intermediate total: overall proportion of serious ADRs 86% (3,349) plus non-serious ADRs 14% (554)

➢ Overall total: serious and non-serious ADRs 100% (3,903)

2. Reports of serious ADRs: Mention in the product information*** and cases of interactions

In 36% of all ADR reports, at least one serious ADR was mentioned that is not adequately addressed in the current version of the product information.

Serious ADRs that are not, or insufficiently, addressed in the product information can be critical and may indicate a new risk related to the medicinal product that might require risk minimizing action, such as the publication of Healthcare Professional Communications, a revision of the information for healthcare professionals and the patient information in Switzerland, or even a re-evaluation procedure of the risk – benefit balance of a medicinal product. Even non-serious ADRs that are not addressed in the product information can lead to measures being taken and in particular to updating the information for healthcare professionals and the patient information.

3. Reports of ADRs by sex and age group

- Of the 3,903 reports received in 2011, 2,072 concerned female patients (53%) and 1,463 concerned male patients (37%). The patient's sex was not stated in 10% of the cases.

- The age distribution of the reports was as follows:
  - Adults 47%
  - Seniors 18%
  - Infants and children 4.2%
  - Adolescents 1.7%
  - Not stated 28%

4. Reports of ADRs by active pharmaceutical ingredient

The most frequently reported active pharmaceutical ingredients in cases of suspected ADRs were analgesics and antipyretics, psychotropic medicines and anti-epileptics, anticoagulants and hormonal contraceptives. The other reports were divided between numerous medicinal products.

* *Source "Swissmedic pharmacovigilance database"*

** *International Conference of Harmonisation ICH*

*** *Note: "ADRs not addressed in the product information" also applied to ADRs that are not addressed to a sufficient extent.*

HAEMOVIGILANCE: AN OVERVIEW

Approximately 400,000 transfusions are administered annually in Switzerland. 77% of them are red cell concentrate transfusions, 15% are plasma transfusions, and 8% concern platelet concentrates. Since 2002, reporting of all suspected adverse reactions in association with transfusions is mandatory in Switzerland. Swissmedic analyses these reports with the aim of deriving possible measures to further increase transfusion safety in Switzerland. The key data and recommendations arising from the reports are published in annual haemovigilance reports. Current developments that have an impact on transfusion safety are also included in the annual report.

There are three basic categories of reports: transfusion reactions, transfusion errors or mistransfusions and Near Miss events. In recent years, around three quarters of all reports concerned transfusion reactions. Transfusion errors accounted for 1.5 – 3% and the rest concerned Near Miss events (NM). Especially the number of NM reports shows a steadily rising trend.

A suspected transfusion reaction is reported if a patient shows clinical signs and/or laboratory test results in temporal relation to a transfusion indicating a possible adverse effect of the transfusion. In addition to a description of the event, the report contains an assessment of the degree of severity and the imputability, i.e. whether the causal link between the symptoms and the transfusion is considered certain, probable, possible, unlikely, or is excluded.

Any observation of a deviation from standing procedures for the preparation and administration of a transfusion which is discovered before the begin of a transfusion, is reported as Near Miss event.

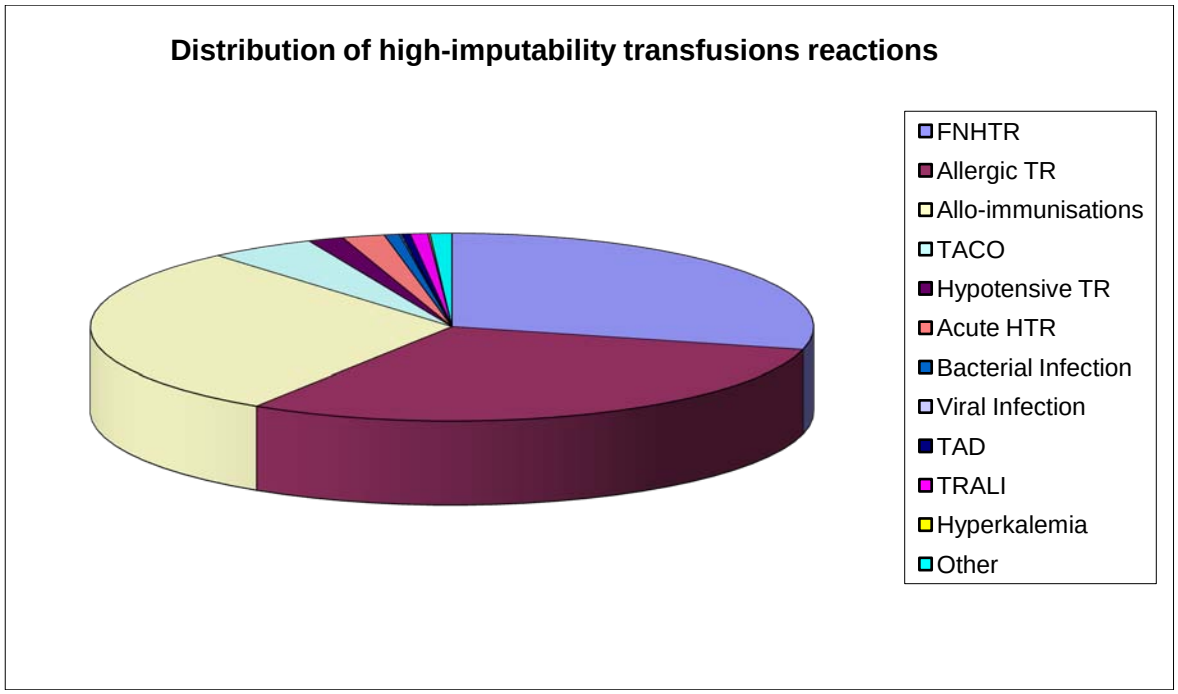
If such a deviation is detected after the transfusion has begun – irrespective of the administered quantity of blood and whether the patient

presents symptoms or not – it is reported as transfusion error. The customary international term for these incidents is "incorrect blood component transfused" (IBCT).

The reporting and analysis of near misses and IBCTs serve as means to identify weak points in the transfusion process and/or possible measures to increase transfusion safety.

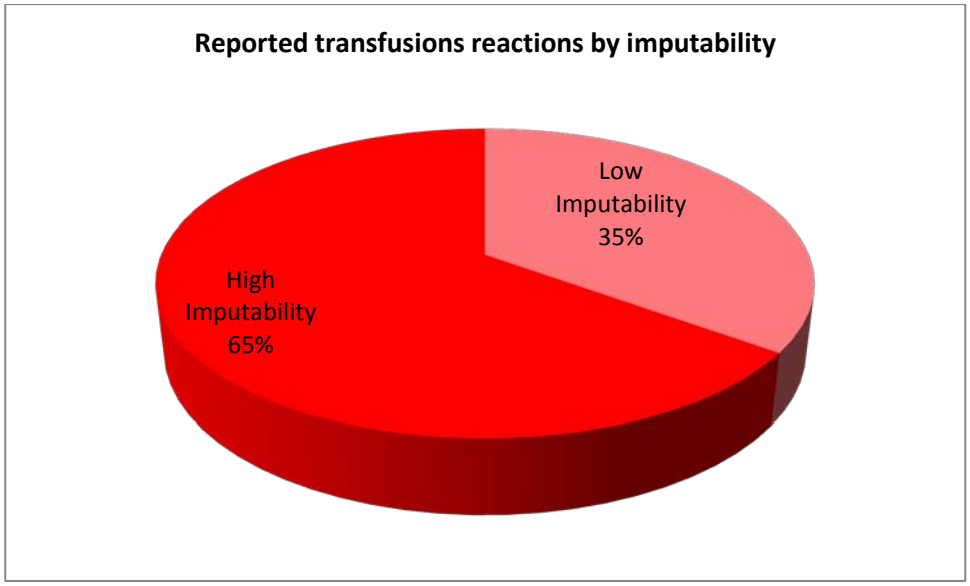
The relative proportions of the various categories of all reported transfusion reactions have remained stable over the past few years. The distribution for 2010 was already presented in the May 2011 issue of Vigilance-News. The distribution over the last 5 years is shown in figure 1.

Figure 1



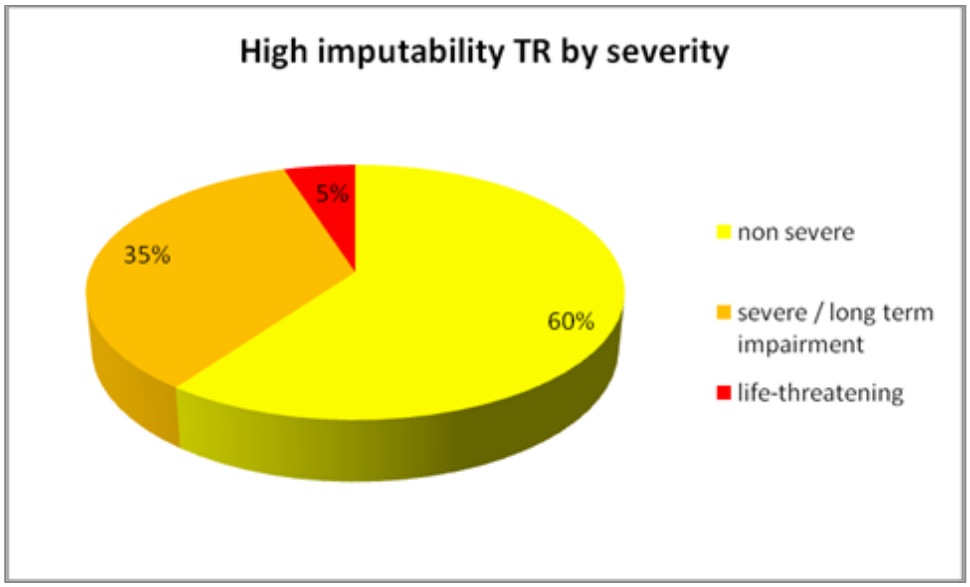
The reported transfusion reactions are classified as high-imputability events if the transfusion is certainly or probably the cause for the observed signs and symptoms. All the others are considered low-imputability reports. Up to two thirds of the roughly 1000 annually reported transfusion reactions are high-imputability events. This indicates not only a high level of willingness to report (approx. 1 reported transfusion reaction per 400 transfusions), but also a keen sense for discerning relevant events. In order to assess the risks of transfusion, the number of transfusions administered is put in correlation to the number of high-imputability events. Only high-imputability events enter into the further evaluation.

Figure 2



Statistically, 1 transfusion reaction occurs for every 675 transfusions in Switzerland. The rate for the most frequently reported category can be quantified as 1 : 2,000 and for the least frequent as 1 : 400,000.

Figure 3

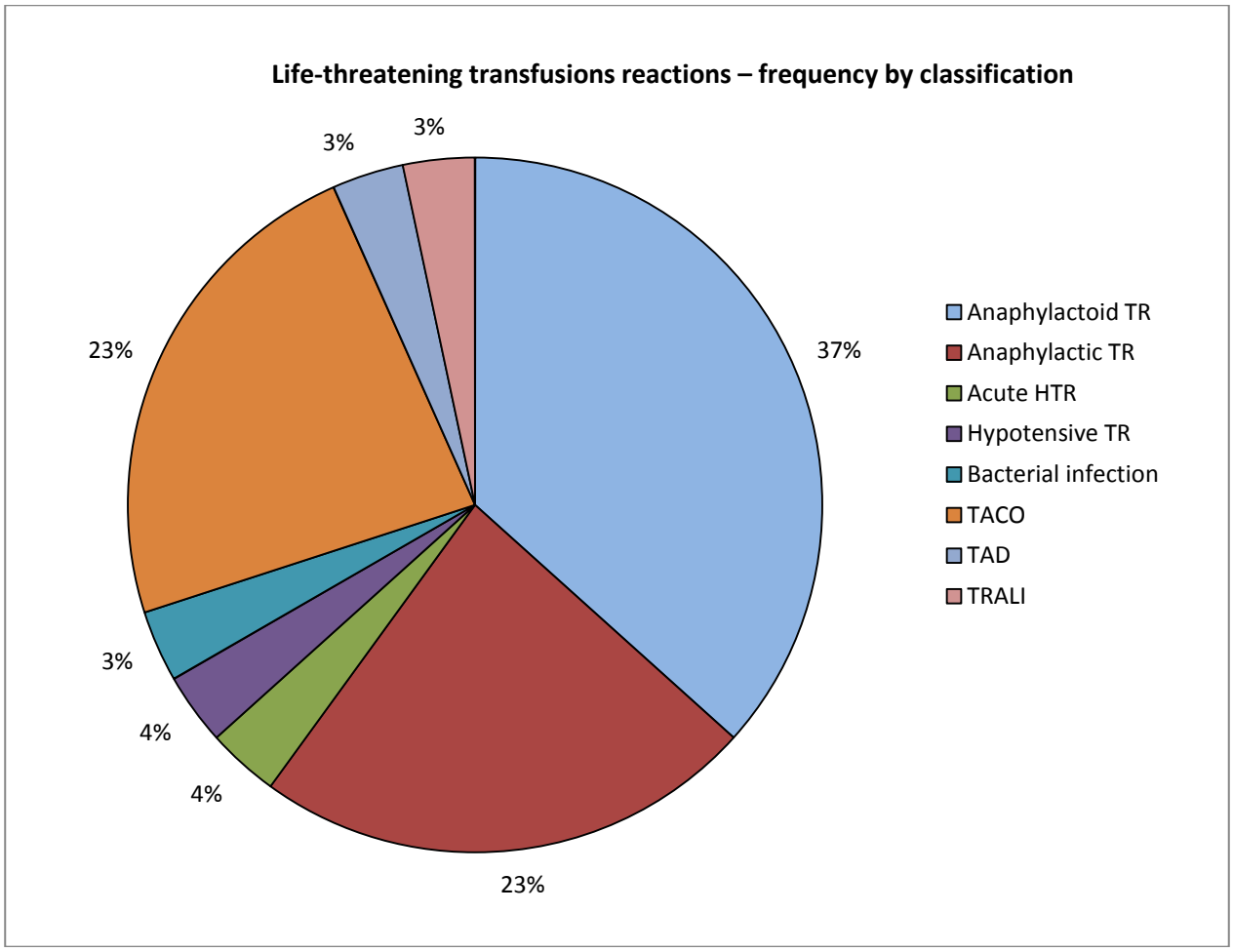


Severity of the reported transfusion reactions

Nearly two-thirds of all transfusion reactions reported are non severe and only 5% represent a life-threatening situation for the patient involved. Overall, severe transfusion reactions occur at a rate of 1 : 15,000 transfusions, and the range for the various categories of events is between 1 : 20,000 and 1 : 400,000.

The risks of transmitting viral infections by way of transfusion were quantified by the National Reference Center for Blood-transmissible Infections and were also presented in May 2011. The risks are 1 : 3.4 million for HIV, 1 : 3.2 million for HCV and 1 : 170‘000 for HBV.

Figure 4



As figure 4 shows, approximately 60% of the life-threatening transfusion reactions are allergic reactions, and about another quarter of the reactions are caused by circulatory overload (TACO).

The annual haemovigilance report for 2011 contains detailed analysis of the presented data and will be available at the following link in summer 2012:
http://www.swissmedic.ch/marktueberwachung/00159/00160/00437/index.html?lang=en

VACCINOVIGILANCE : SUMMARY OF ADVERSE EVENTS FOLLOWING IMMUNIZATION REPORTED IN SWITZERLAND

Executive summary

In 2011, 143 reports of AEFIs were received by Swissmedic, representing a slightly decreased number compared with previous years and also a very low rate of spontaneous reports considering the high number (millions) of immunizations performed. Importantly, no death cases following vaccination were recorded during this year. As previously, Swissmedic continues to actively encourage good quality spontaneous reporting of AEFIs. Since 2010, important topics with regard to AEFIs are discussed in Swissmedic on regular basis during the meetings of the Human Medicines Expert Committee.

Figure 1: Number of AEFI reports per month and gender

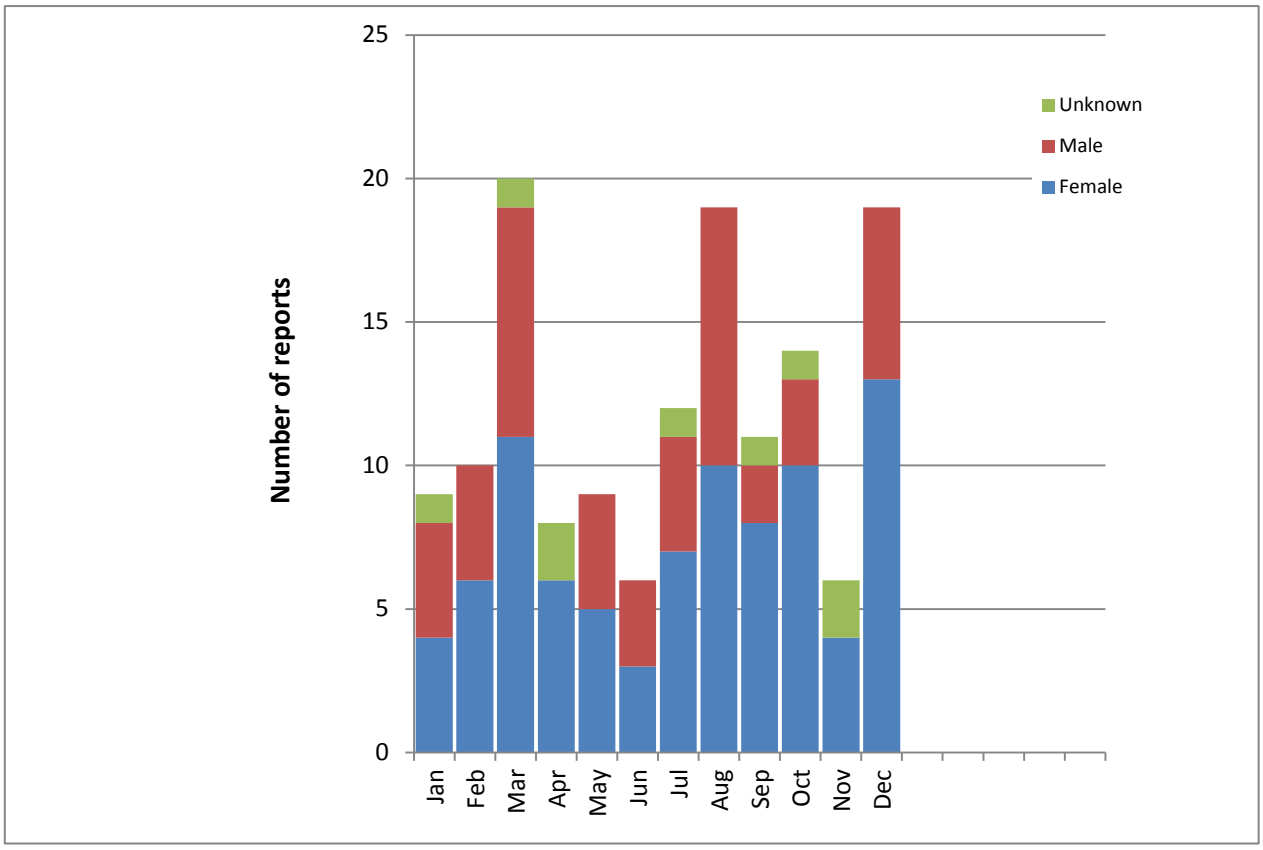


Figure 1 shows the number of AEFI reports received in 2011, as grouped by calendar months and compared by gender. The 3 months with the highest reporting of AEFI were March (20 reports received), August (19 reports) and December (19 reports). Throughout the year, the number of reports concerning females (87 reports) was almost twice as high as the number of reports regarding males (47 reports) and this difference was highest in the last quarter of the year (27 reports of women vs. 9 reports of men). In 9 AEFI reports, the gender of the persons remained unknown.

Figure 2: Number of AEFI reports per age group and gender

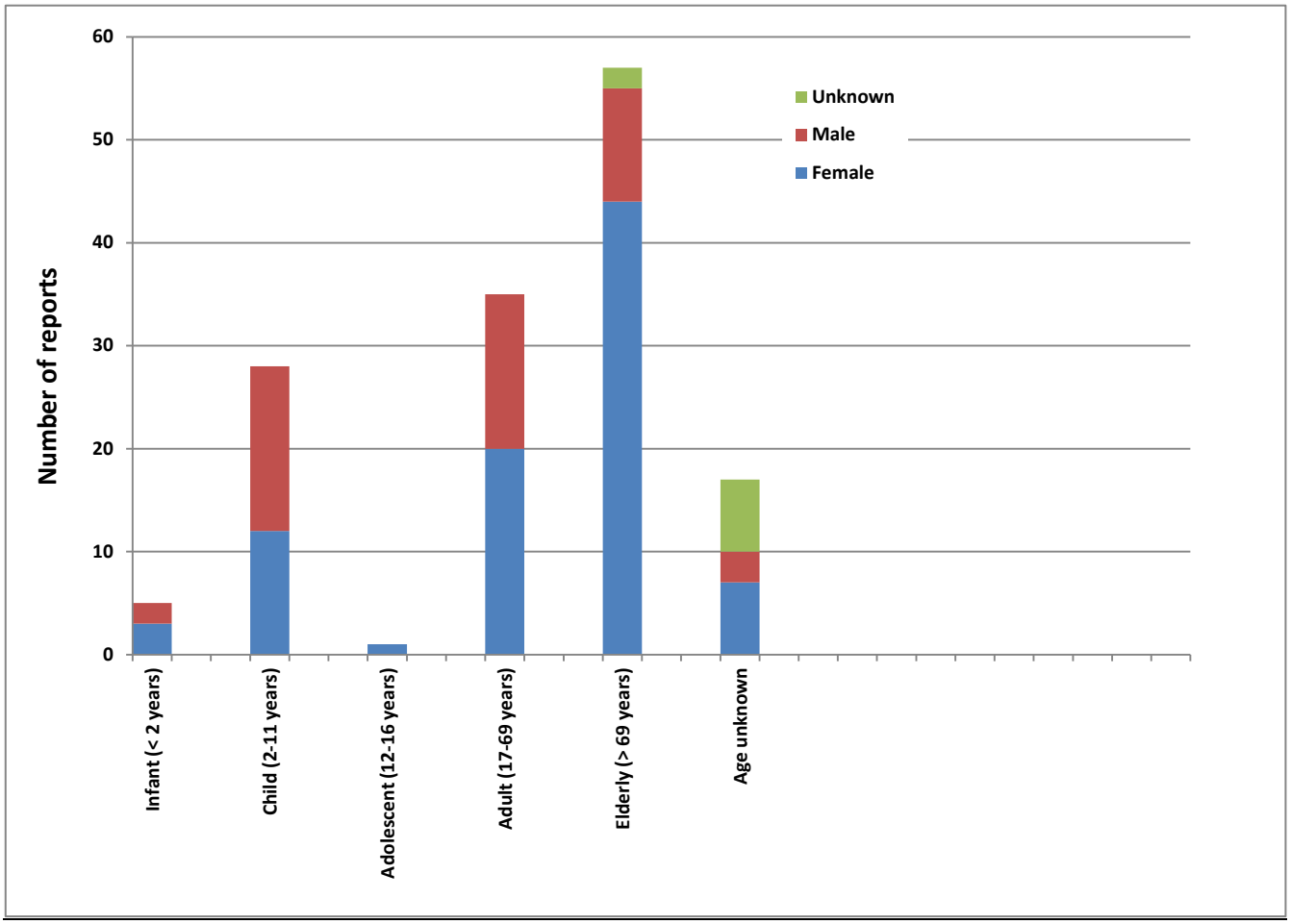


Figure 2 compares the number of reports between age groups and gender. The largest number of AEFI reports involved elderly persons (57 reports), followed by adults (35 reports) and children (28 reports). The difference in gender is apparent in this view as well, the largest discrepancy being recorded in the elderly group (44 reports of females vs. 11 males). In 9 cases (reports), the age of the patients was not recorded.

Figure 3: Number of reports per vaccine group (ATC code) and seriousness

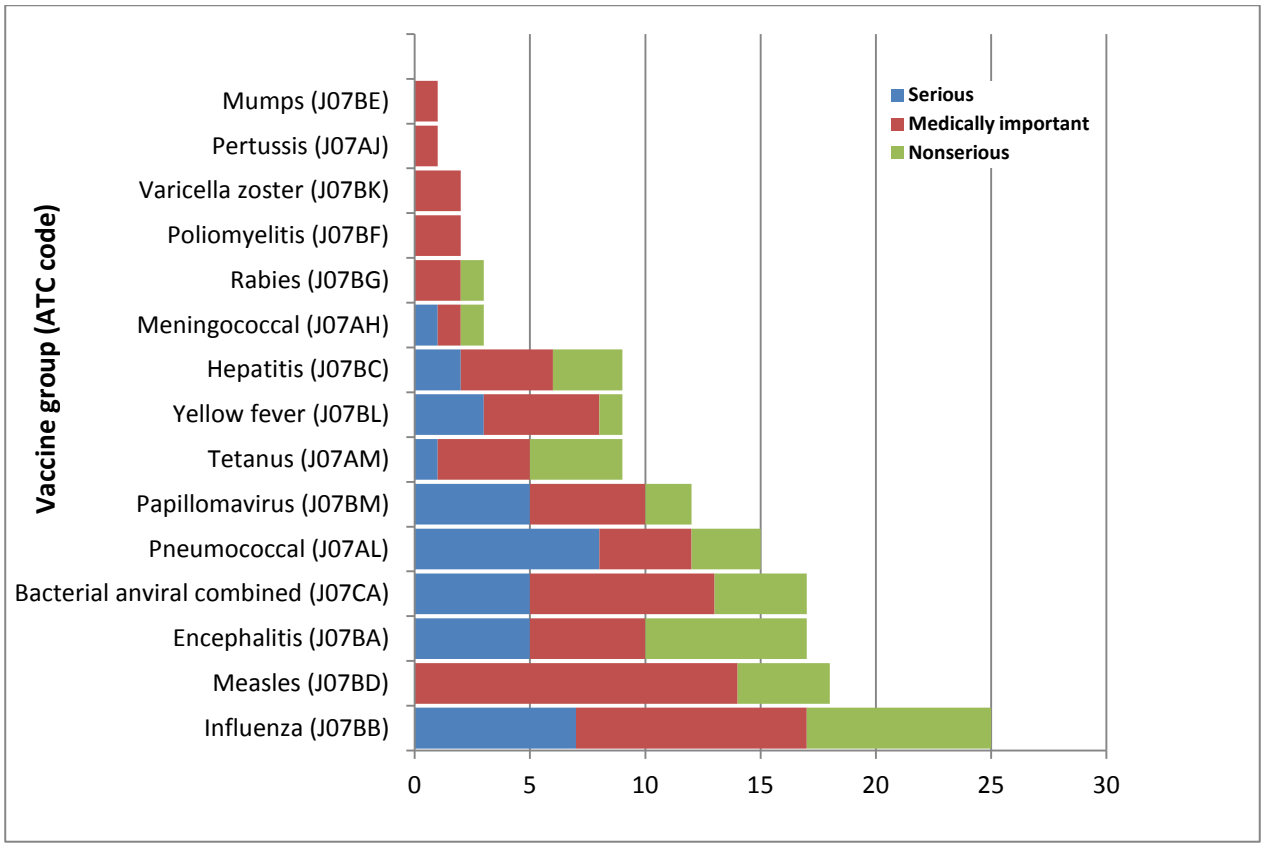


Figure 3 shows the number of spontaneous AEFI reports grouped per vaccine group (ATC code) and seriousness. There are no data available regarding the number of doses administered in each vaccine group and therefore this figure does not show which vaccine group displayed a higher AEFI rate (as number per 100'000 doses). Generally, a safety report is assessed as "serious" if it involves an adverse event leading to death, to hospitalization or to prolongation of an existing hospitalization, if it was life threatening or resulted in a significant or persistent disability or a congenital anomaly. A report is assessed as "medically important" if it does not fulfill the criteria for "seriousness" but it involves a medically significant event. All other reports are assessed as "not serious" (e.g. expected or self-limiting adverse events with good recovering). Of the 143 spontaneous reports, 26.6% were not-serious, 47.6% were medically important events and 25.9% of the AEFIs included events with serious consequences.

Figure 4: Number of AEFI reports in Switzerland by System Organ Classes

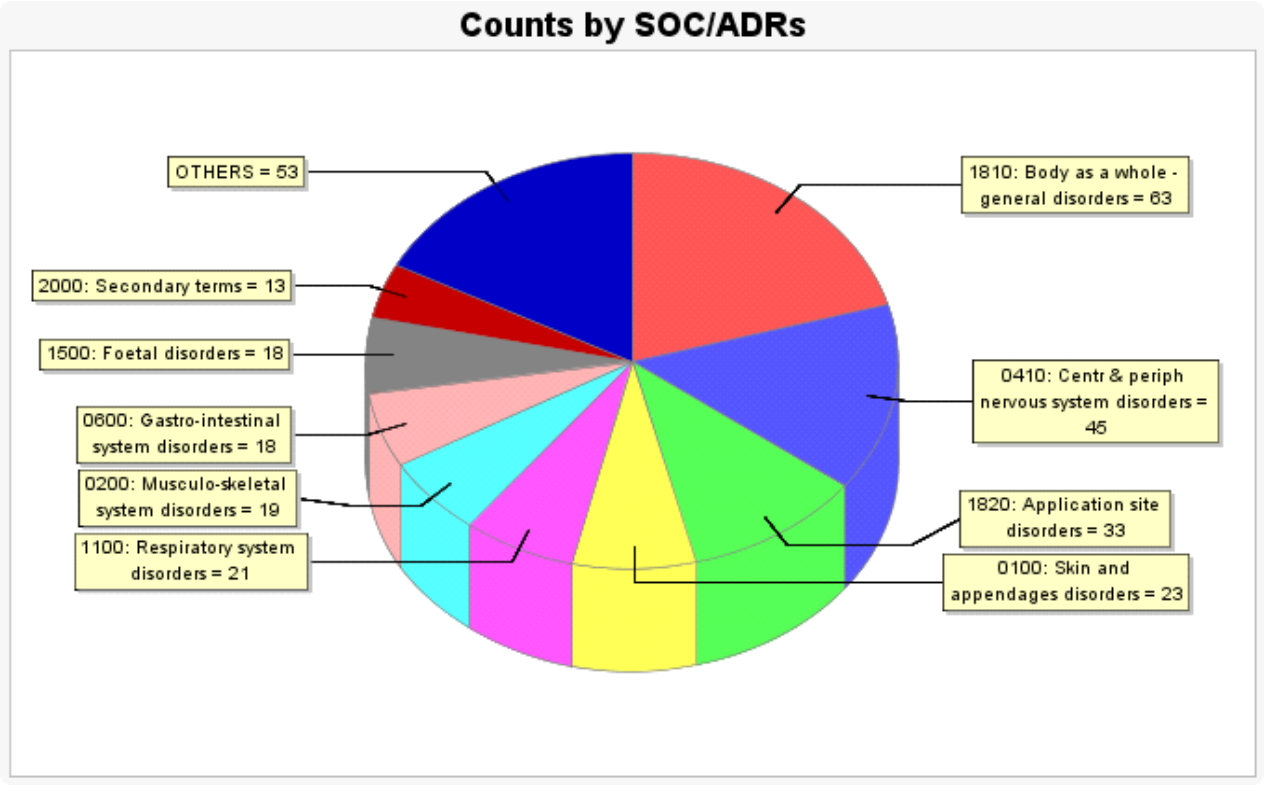


Figure 4 provides an overview on the AEFI reports received during 2011, grouped per System Organ Classes (SOCs) concerned. Following five organ classes were most frequently involved in reports after immunization: Body as a whole – general disorders, Nervous system, Application site disorders, Skin and appendages, and Respiratory system. The group 'Others' is a heterogeneous group of SOCs and is not further described.

Figure 5: AEFI reports by vaccine group (ATC code) and top 3 involved System Organ Classes

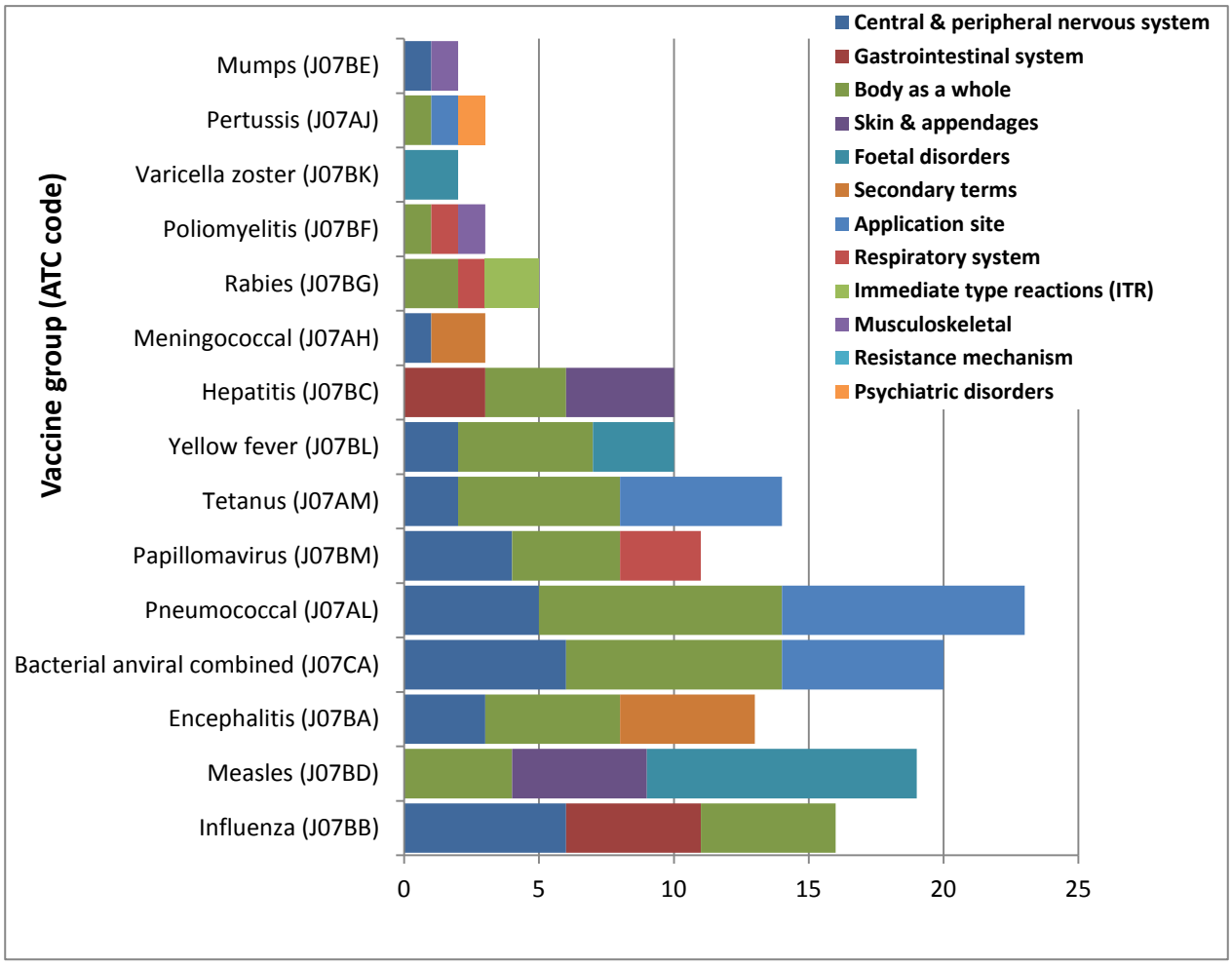


Figure 5 shows the AEFI reports by vaccine group (ATC code) and top 3 system organ classes. Notably, drug exposures during pregnancy or before pregnancy are coded and counted under Foetal disorders. Thus, in figure 5 they are 13 exposures in pregnancy (8 with measles vaccine, 3 with yellow fever vaccine, 2 with varicella zoster vaccine) and 2 cases of exposure before pregnancy (1 with measles vaccine, 1 with MMR vaccine). No congenital anomalies were reported/recorded following immunization in 2011.

Figure 6: Number of reports per vaccine group (ATC code) and labelling

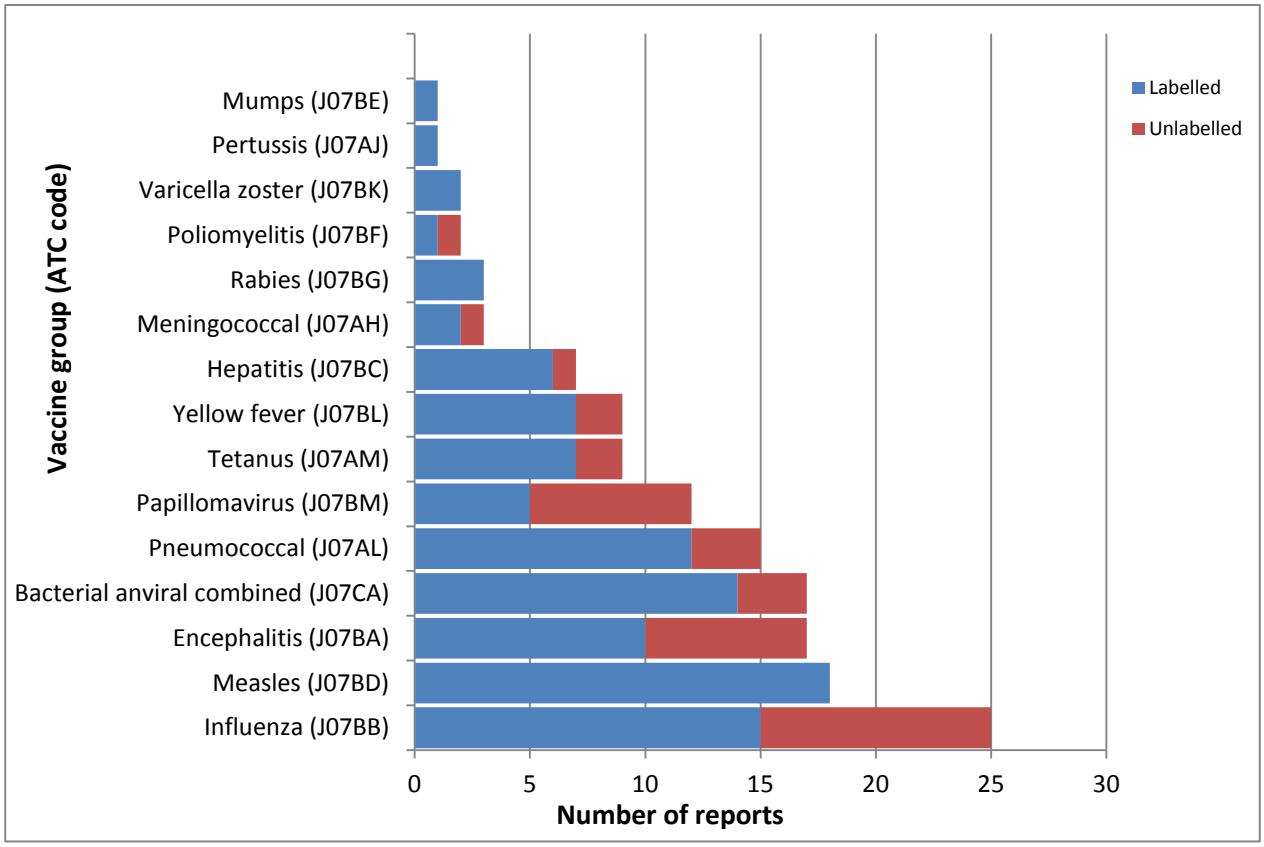


Figure 6 shows the number of AEFI reports per vaccine group (ATC code) and labelling status. Vaccine groups with higher numbers of reports containing unlabelled AEFIs were Influenza (10 of 25 reports), Encephalitis (7 of 17 reports) and Papillomavirus (7 of 12 reports).

Table 1: Overview on the 10 most frequent AEFIs of all reports

Adverse event	System Organ Class	Number of reports
Injection site reaction	Application site disorders	53
Fever	Body as a whole – general disorders	27
Drug exposure in pregnancy	Foetal disorders	16
Headache	Central and peripheral nervous system disorders	10
Exanthema (Rash)	Skin and appendages disorders	10
Nausea	Gastro-intestinal system disorders	7
Myalgia	Musculo-skeletal system disorders	7
Vaccine failure	Resistance mechanism disorders	6
Diarrhoea	Gastro-intestinal system disorders	5
Dyspnoea	Respiratory system disorders	5

Table 1 displays the 10 most frequently adverse events following immunization as reported during 2011: injection site reactions, fever, drug exposure in pregnancy, headache, exanthema (rash), nausea, myalgia, vaccine failure, diarrhoea and dyspnoea.

Table 2: The most 10 frequent AEFIs classified as "Serious" or "Medically Important"

Adverse event	System Organ Class	Number of reports
Injection site reaction	Application site disorders	36
Fever	Body as a whole – general disorders	21
Drug exposure in pregnancy	Foetal disorders	15
Exanthema (Rash)	Skin and appendages disorders	8
Headache	Central and peripheral nervous system disorders	7
Nausea	Gastro-intestinal system disorders	6
Vaccine failure	Resistance mechanism disorders	6
Diarrhoea	Gastro-intestinal system disorders	5
Dyspnoea	Respiratory system disorders	5
Dizziness	Central and peripheral nervous system disorders	4

Table 2 summarizes the 10 most frequent AEFIs assessed as "serious" or "medically important". The two tables are displaying very similar distributions of AEFIs, however more cases of dizziness and less cases of myalgia have been assessed as "serious" or "medically important".

Among other serious or medically important AEFIs during 2011, 2 cases of convulsions were reported (both recovered) and 3 cases of fever convulsions after immunization of children (all recovered).

One case of paralysis was reported after tetanus vaccine (outcome "recovered"), 1 case of facial paralysis after Human papilloma vaccine (outcome "unknown"), 1 case of paresis after vaccination against tick-borne encephalitis (outcome "unknown") and 1 case of paraplegia in a 30-year-old woman immunized with a combination of vaccines – Yellow fever, Hepatitis A, Tetanus, Polio, Diphtheria, Typhoid vaccine (outcome "not recovered"). Two cases of Guillain-Barré syndrome were reported in relation with Influenza vaccines in 2011, a 13-year-old female (outcome "recovered") and an 84-year-old woman ("not recovered").

No fatal cases concerning AEFIs were reported during 2011.

VIGILANCE OF VETERINARY MEDICINES

OVERVIEW

In comparison to 2010, the number of adverse reactions reported in 2011 increased slightly to 167 reports (2010: 160). Similarly to previous years, most of the reports (48.5%, 81) were submitted by distributors or manufacturers, followed by those from practicing veterinarians (22.2%, 37 reports). It should be noted that many practitioners inform the distributor, who then forwards the report to Swissmedic due to legal obligation. A total of 38 reports (22.75%) were submitted from the Swiss Toxicological Information Centre (STIZ) in Zurich, and 4 others from animal owners who may participate voluntarily in the reporting system.

Breakdown by animal species and categories of medicines

Table 1 shows the reports submitted sorted according to animal species. The largest number of reports concerned reactions following the administration of veterinary medicines to dogs (85, 51%) and cats (27, 16%). For livestock, reports on bulls, cows and calves constitute the largest group (37). Fewer than 5 reports each were received for the entire year for all other animal species, with the exception of horses (7 reports).

The breakdown by categories of medicines, sorted by ATCvet Code, is shown in table 2. This also shows that over the years, the distribution is stable with the largest number of reports concerning antiparasitics (65, 38.9%), followed by anti-infectives (33, 19.8%) and non-steroidal anti-inflammatory drugs (ATC vet Code QM, 19, 11.4%). These three classes belong to the most widely used veterinary medicines, for both domestic animals and livestock.

Ivermectin poisoning in a pony: new treatment possibility

In 2011, two reported cases concerned an overdose of Ivermectin-based deworming paste administered to ponies. One case presented no complications, unlike the other in which a miniature Shetland pony of just 26 kg received the dose appropriate for a 600 kg horse, a 27-fold overdose of 5.4 mg/kg Ivermectin instead of the recommended 0.2 mg/kg[4]. The animal was taken to the Tierspital in Zurich presenting generalized epileptic seizures followed by loss of consciousness on admission. No palpebral, pupillary or menace reflex could be triggered. At first, the pony was treated with infusions and Sarmezanil, a benzodiazepine antagonist. This was unsuccessful, and 71 hours after the accidental overdose, the animal showed no improvement of the neurological symptoms. For that reason, a 20% lipid emulsion (soya bean oil in water) was administered experimentally. Such emulsions are originally intended for parenteral nutrition of humans, but have already successfully been used in experimental settings to treat poisoning with lipophilic active substances such as bupivacaine, clomipramine, verapamil, or propranolol[5] in human medicine. Since this treatment had never been described for horses, a protocol written for small animals[6] was used: the pony was first given a total of 234 ml of the lipid emulsion as a bolus of 1.5 ml/kg, followed by 0.25 ml/kg/min over 30 minutes. A slight improvement was observed after this time: pupillary reflexes reappeared, and the animal reacted to light impulses. After a second treatment following the same protocol, the animal was able to stand, and had regained a nearly normal neurological status. It still remained blind for a further 5 days,

[4] *Bruenisholz H, Kupper J, Muentener C et al. Treatment of ivermectin overdose in a miniature Shetland pony using intravenous administration of a lipid emulsion, J Vet Intern Med; 26 : 407-411, 2012*

[5] *Fernandez AL, Lee JA, Rahilly L, et al. The use of intravenous lipid emulsion as an antidote in veterinary toxicology. J Vet Emerg Crit Care; 21 : 309–320, 2011*

[6] *Pritchard J. Treating ivermectin toxicity in cats. Vet Rec 2010; 166 : 766*
Crandell DE, Weinberg GL. Moxidectin toxicosis in a puppy successfully treated with intravenous lipids. J Vet Emerg Crit Care 19 ;181-186, 2009

but could be discharged, in good health, 8 days after the second treatment.
Ivermectin belongs to the avermectin class of antiparasitics and presents an extremely broad spectrum comprising a large number of nematodes and arthropods. In humans, it is also used to treat onchocerciasis, intestinal strongyloidiasis or various types of filariasis. Ivermectin acts by permanently opening the GABA-regulated chloride channels, which leads to flaccid paralysis of the parasites. As an extremely lipophilic molecule, ivermectin crosses the blood-brain barrier of mammals. Its safe use on mammals is based on the P-glycoprotein which pumps the ivermectin out of the central nervous system again so that no accumulation can take place. Neurological symptoms can therefore only occur if the excretory function fails, such as in the case of a defective MDR-1 encoding gene (for example in dogs such as collies, bobtails, etc.,[7]), if the blood-brain barrier is not sufficiently developed (such as in new-born animals and those less than 4 months old[8]) or, as in the present case, following a massive overdose leading to saturation of the excretion. In the present case, ivermectin reached a peak concentration of 1930 ng/ml in the plasma, compared with 21-82 ng/ml in a normal situation[9]. There are various theories regarding the positive effect of an intravenous lipid solution, of which the "lipid sink" theory represents the most probable: it postulates that a lipophilic molecule is transferred from the central nervous system to the lipid fraction of the blood, which is greatly enlarged by the infusion, via an equilibrium shift[10].

Ivermectin is finally eliminated from the organism by means of hepatic metabolism and direct excretion. The blood values measured during the present case appear to confirm this theory. The extent to which such a treatment would be successful for dogs with a defective P-glycoprotein remains open.

Causality assessment

In 15% of the reports, it was possible to confirm a causal link between the application and the reaction ("probable"), and for 39%, at least one alternative cause existed ("possible"). For the other reports, either too little information was available (39%) or a link could be excluded with certainty (7%).

Adverse reactions to veterinary vaccines

In addition to the reports regarding veterinary medicines authorised by Swissmedic, the Swiss Institute for Virology and Immunoprophylaxis (IVI) in Mittelhäusern – as the competent authorization and supervisory authority for veterinary vaccines – received 60 reports regarding adverse reactions to these products. Some 35 of them concerned dogs, and 11 concerned cats. Most of them were allergic reactions or generally decreased state of health. Further analysis of these reports is not yet available.

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[7] *Geyer J, Döring B, Godoy JR et al. Frequency of the nt230 (del4) MDR1 mutation in Collies and related dog breeds in Germany. J Vet Pharmacol Ther; 28: 545-551, 2005*

[8] *Watchko JF, Daood MJ, Mahmood B et al. P-glycoprotein and bilirubin disposition. J Perinatol; 21(Suppl 1): S43-S47, 2001*

[9] *Perez R, Cabezas I, Godoy C et al. Pharmacokinetics of doramectin and ivermectin after oral administration in horses. Vet J; 163: 161-167, 2002*

[10] *Fernandez AL, Lee JA, Rahilly J et al. The use of intravenous lipid emulsion as an antidote in veterinary toxicology. Vet Emerg Crit Care; 21: 309-320, 2011*

Table 1: Reports received in 2011, by animal species

Animal species	Number	% Total
Dog	85	51 %
Cat	27	16 %
Horse / donkey	7	4 %
Cow / calf	37	22 %
Pig	3	2 %
Pets / zoo animals	3	2 %
Human	3	2 %
No species[11]	2	1 %
Total	**167**	**100 %**

Table 2: Reports received in 2011, sorted by ATCvet Code

The QZ code is fictitious but allows the specific grouping of reports to reconverted products (i.e. not used for the authorized animal species and/or indication)

Category of medicines according to ATCvet code	Number of reports (% of total)	
QA: Alimentary tract	4	(2.4 %)
QB: Blood and blood forming organs	1	(0.6 %)
QC: Cardiovascular system	2	(1.2 %)
QG: Genito-urinary system and sex hormones	9	(5.4 %)
QH: Hormonal preparations (except hormones and insulin derivatives)	9	(5.4 %)
QJ: Anti-infectives	33	(19.8 %)
QM: Musculo-skeletal system	19	(11.4 %)
QN: Nervous system	4	(2.4 %)
QP: Antiparasitics	65	(38.9 %)
QR: Respiratory system	2	(1.2 %)
QS: Sensory organs	1	(0.6 %)
QZ: Re-designated products	15	(9 %)
ALP registered products, animal care products, etc.	3	(1.8 %)
Total	**167**	**(100 %)**

[11] *Two reports concerned the misuse of a product, without symptoms, and could not be attributed to any species*

CONFERENCES

GOOD PHARMACOVIGILANCE PRACTICE AND "THE BIG CASE"

SWISSMEDIC CONFERENCE ON THE SAFETY OF MEDICINES 23RD APRIL 2012 IN BERN

Key messages on the outcome are:

- There is a need for communication between Swissmedic and the experts.
- Firms should inform Swissmedic at an early stage in the case of an important safety signal.
- Swissmedic should be informed of ongoing discussions or negotiations with foreign authorities and of risk minimization measures.
- "Be Prepared": an internal procedure for risk communication and radical measures should be established (documents, definition of responsibilities).
- Pharmacovigilance reports must target on the compilation of signals.

This conference, organised by the Safety of Medicines division, was intended for employees of the pharmaceutical industry responsible for vigilance and safety of medicines. It was aimed at staff with various backgrounds, who were expected to have a certain degree of professional experience in the safety of medicines sector.

A report on the last Swissmedic conference, focusing on "Exchange between firms and Swissmedic" and "Risk communication" was published in the Vigilance-News, issued in December 2010. The priorities of this year's event were different, i. e. the focus was on workshops.

The participants were split up into small groups and tasked with proposing a practical action plan for the firm in accordance with Swissmedic for a given realistic scenario.

The scene was set for the participants by means of presentations held by stakeholders: the local physician, a representative of the clinical sector, the academic sector, and also the industry itself, here in the person of the medical director of an international company.

On registering for the workshops, participants could choose between the subjects "Risk Management" and "Pharmacovigilance".

The "Risk Management" group addressed the issue of the Direct Healthcare Professional Communication (DHPC) and market withdrawal of a product. The points to be dealt with were:

- What should be communicated to Swissmedic, and how?
- Which documents are required by the authorities?
- How can the message of a publication or a trial result be transcribed constructively into the DHPC?
- What do the recipients need in terms of additional information?
- Who are the recipients (etc.)?

Given that around 50 DHPCs have been issued within two years, the participants were treating an issue that can arise at any time. On the other hand, Swissmedic has plenty of experience with certain modes of response on the part of the industry. However, it was clear to everybody that the facts are the decisive factor, and that good co-operation with the authorities can not only limit the damage, but also offers a number of advantages.

Involving the various stakeholders, even if there was a certain amount of criticism, was appreciated as realistic and considered an added value. Because of the large number of participants, the

workshops were run twice, which encourages us to continue them.

Since the conference, an information sheet on implementation has been published on the Swissmedic website: "DHPC: Content, recipients, publication, template": http://www.swissmedic.ch/marktueberwachung/00091/00092/index.html?lang=en

The "List of Health Professional Communication 'Dear Doctor' Letters" is updated regularly and also published on the Swissmedic website (in German).

For the "Pharmacovigilance" group, the topics "Index case" and "Signal management process" were selected.

In the "Signal management process" workshop, a signal assessment investigation for 3 different active pharmaceutical ingredients was played through (via line listings). Points of discussion included the quality of the information, the populations concerned, data from the scientific literature, and risk minimization measures. All were in agreement that the patient and the doctor or pharmacist should be alert to any unusual symptom as soon as a medicinal product has been prescribed, in order to recognise possible signals rapidly and treat them accordingly. Here, too, transparent and prompt communication between the authorisation holder and the authorities is of great importance.

INFORMATION ON THE SAFETY OF MEDICINES PUBLISHED ON THE SWISSMEDIC WEBSITE

Swissmedic schliesst Überprüfungsverfahren der Präparate mit Methylphenidat ab – „Class Labelling“
25.06.2012 *

Press Release Anapen
08.06.2012 *

Workshop: GCP Inspections
06.06.2012

DHPC – Cerubidin (Daunorubicin) – Widerruf der Zulassung
25.05.2012 *

Vorgehen bei Widerruf, Sistierung eines Certificate of Suitability
08.05.2012 *

DHPC - Orale Antidiabetika mit Pioglitazon (Actos®, Competact® und Generika*): Einschränkung der Behandlungsdauer auf maximal zwei Jahre, ausser bei überwiegendem Nutzen im Verhältnis zum Blasenkrebsrisiko
30.04.2012 *

Guidance document DHPC
23.04.2012

China: Fraudulent procedure with regard to the manufacture of gelatine
23.04.2012

New information on medical devices: Macrolane und ähnliche Produkte auf Hyaluronsäure-Basis: Anwendungseinschränkung für Brustvergrösserung
19.04.2012 *

Publikation der Arzneimittelinformation durch Swissmedic, Stand der Arbeiten
05.04.2012 *

Leitlinien - Botox: Information versus Werbung
04.04.2012 *

Nachtrag 7.4 der Europäischen Pharmakopöe in Kraft
01.04.2012 *

Defective "PIP" silicone-filled breast implants: Current status
07.02.2012

Beschaffung von Arzneimitteln, die in der Schweiz nicht verfügbar sind
13.01.2012 *

Please find the complete list at the following web address:
http://www.swissmedic.ch/aktuell/00002/index.html?lang=en

****in German and/or French only***