swissmedic

VIGILANCE-NEWS

ANNIVERSARY EDITION NO. 10 – DECEMBER 2012

In this edition:

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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Content

EDITORIAL

10th Edition of Vigilance-News – Past and Future

Dear Reader,

This is our tenth edition of Swissmedic's Vigilance-News. We took this as an opportunity to look through the 9 previous editions in our archives and to mention a few of the new features that have been introduced since then. You also have the chance to test your knowledge on vigilance by taking part in our quiz.

From the very beginning, the first edition of Vigilance-News (called PV-News at that time) in June 2008, we have focused on selected pharmacovigilance signals. These communications, to be found in the "Flash" section, attempt to describe the background of a signal and the related consequences. Today, we fea-

ture not only pharmacovigilance signals from spontaneous reports but also descriptions of risk management and evaluations of the benefit-risk balance. In this edition, we have selected information on the active pharmaceutical ingredients "clozapine" and "metho-trexate".

Since the situation regarding data availability for medicinal products is constantly changing and actualisations for certain products can become necessary, we regularly provide annual updates: e.g. for oral isotretinoin since 2008.

Our annual statistics – another recurring feature – are, published in the summer editions. Evolving from the initial statistics on adverse drug reactions (ADRs) through pharmacovigilance, the Vigilance-News now also includes separate overviews for veterinary medicines, vaccines and haemovigilance.

Contributions on illegal medicinal products, on vigilance related to clinical trials or conference reports bear witness to the constant expansion of the topics covered. The publication in various languages (the Vigilance-News is published in German, French and English) and the new layout are intended to contribute towards reaching as many readers interested in vigilance as possible.

Not only the Vigilance-News is "celebrating" its tenth anniversary, but also Swissmedic itself. We have included a few impressions from the "Swissmedic International Regulatory Symposium" held in Interlaken on 20–21 September 2012, where the new EU pharmacovigilance legislation with its consequences for Switzerland was one of the main topics.

To mention one innovation, Periodic Safety Update Reports (PSURs) have now become Periodic Benefit-Risk Evaluation Reports (PBRERs), with a focus on the evaluation of the safety profile and the benefit-risk balance:
http://www.swissmedic.ch/marktueberwachung/00091/00688/index.html?lang=en&lan=&lan=

The implementation of the system for the electronic exchange of Individual Case Safety Reports (ICSRs) between Swissmedic and the pharmaceutical industry has been accomplished. From 2013 onwards, the co-operation with further marketing authorisation holders will continue. For further information, please see the article "Electronic exchange of individual case safety reports with pharmaceutical companies via the E2B gateway".

On 1 January 2013, Swissmedic's new platform for publishing product information will be made available to the public. An expanded search function and free downloads will be provided, as well as references to Health Professional Communications (HPCs). This publication system, which will be binding for authorisation holders, will provide access both to the latest version of the "Product Information" and the most recently published safety information on a specific product:

http://www.swissmedic.ch/aktuell/00003/01840/index.html?lang=de

Editorial team:

Eva Eyal, Thomas Munz, Helena Bill

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

We would be pleased to receive any comments or requests for further information related to this edition at: vigilance@swissmedic.ch.

To all our readers, we send our best wishes for the future, enjoyable holidays, and a successful start into 2013.

The Editors

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

Clozapine[1]: Focus on agranulocytosis and myocarditis

Introduction

As reported by the World Health Organization, schizophrenia is a severe form of mental illness affecting about 7 per thousand of the adult population, mostly in the age group of 15–35 years. Schizophrenia is a treatable disorder.

Clozapine, a tricyclic dibenzodiazepine derivative, is commonly classified as an atypical antipsychotic. It is one of the antipsychotic treatment options in defined clinical circumstances.

Indications

In Switzerland, clozapine[1] is authorized for the following indications:

- Treatment-resistant schizophrenia
- Reduction (long-term) of the risk of recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder
- Psychosis in the course of Parkinson's disease.

Adverse events

Clozapine may cause several adverse events that, in some cases, may be severe and even life-threatening. Since the introduction of clozapine in Switzerland in the seventies, the initial safety concern has mainly been related to agranulocytosis, but in recent years the focus has shifted to cardiotoxicity, in particular myocarditis.

- **Agranulocytosis**

It must be mentioned that one of the potentially serious side-effects due to the therapy with clozapine is agranulocytosis whose incidence is estimated at 0.7 %, with a potential fatal outcome. However, the incidence and lethality of agranulocytocis have notably decreased since the introduction of the surveillance of the count of leukocytes and granulocytes.

Therefore, it must be re-emphasized that the use of clozapine should be limited to the approved indications and to patients who have initially normal leukocyte findings [white blood cell count (WBC) ≥ 3500/mm^3 (3.5 x 10^9/L), and absolute neutrophil counts (ANC) ≥ 2000/mm^3 (2.0 x 10^9/L)], and in whom regular white blood cell counts and absolute neutrophil counts can be performed as follows: weekly during the first 18 weeks of therapy, and at least every 4 weeks thereafter throughout the treatment. Monitoring must continue throughout the treatment and for 4 weeks after the complete discontinuation of clozapine.

- **Myocarditis**

Clozapine may be associated with the occurrence of myocarditis which has, in some cases, been fatal. The incidence of myocarditis as an adverse event in patients treated with clozapine varies between 0.7 and 1.2 %. The mechanisms are still not well understood. To date, no test is able to predict patients at risk.

Myocarditis should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 months of the treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachycardia) or symptoms that mimic myocardial infarction. Patients starting treatment with clozapine should be actively monitored for myocarditis especially during, but not limited to, the first 4 weeks of therapy. The eosinophil counts are reported to be a poor tool for diagnosis. Rises in CRP[2] level and development of fever may be early indicators of myocarditis and daily ECG and troponine measurements in the presence of fever or following a CRP[2] level of more than 50 mg/L may

be diagnostically useful. The early detection of clozapine-related myocarditis is mandatory as the early recognition may improve clinical outcome. If myocarditis is suspected, clozapine treatment should be promptly stopped and the patient immediately referred to a cardiologist. Patients who develop clozapine-induced myocarditis should not be re-exposed to clozapine.

Pharmacovigilance data from Switzerland concerning agranulocytosis and myocarditis

Since 1990, when the Swiss Regulatory Authority first started its Pharmacovigilance Programme, until October 2012, a total of 520 reports of adverse events has been submitted to Swissmedic. In those reports, clozapine was considered as suspected medicinal product.

In 37 of 520 reports (7.1 %), agranulocytosis was present. Among those 37 cases, there were 3 deaths where a causal relationship was considered based upon chronological and clinical elements. In 28 of 37 cases (75.6 %), there was a resolution of the symptomatology.

As to where myocarditis is concerned, 11 of the 520 reports previously mentioned (2.1 %) could be identified in the Swissmedic database. Among those 11 cases, there was 1 death where a causal relationship was considered based upon the available clinical elements. In 7 of those 11 cases (63.6 %), there was a resolution of the symptomatology.

In general, neither the incidence of adverse events nor a clear causal relationship between the symptomatology and any treatment can be established based on the cumulative data of spontaneous reports.

Conclusion

Clozapine can cause life-threatening agranulocytosis, which mandates weekly hematological monitoring during the first 18 weeks of treatment and monthly monitoring thereafter. Myocarditis presents with heterogeneous and non-specific features, so it is difficult to clinically identify patients with clozapine-related myocarditis.

Therefore, it is, and remains, important for prescribing physicians to closely and carefully monitor patients for any signs of agranulocytosis or myocarditis in order to identify them at an early stage.

Other important and frequent adverse drug reactions include sedation, tachycardia, hypertension, postural hypotension, syncope, elevation of liver enzymes, urinary incontinence, benign hyperthermia, seizures, constipation and weight gain.

For more detailed information on warnings, precautionary measures and adverse reactions, Swissmedic refers readers to the Product Information for Health Professionals on clozapine-containing products[3].

References:

1 *The following clozapine-containing products are currently authorised in Switzerland: Clopin® eco 25/100 and Leponex®*

2 *C-Reactive Protein*

3 *http://www.compendium.ch/home/de*

http://www.compendium.ch/home/fr

Accidental overdose of methotrexate

Julia Abegglen, Olga Frank, Marc-Anton Hochreutener, Rudolf Stoller

As a result of cases of severe intoxication with partially fatal consequences due to daily administration/use of the weekly methotrexate dose, all healthcare professionals should ensure that they provide comprehensive instructions for patients when taking new medication. If there are signs of a possible overdose such as mucositis/stomatitis, anaemia, leukopenia, thrombocytopenia or acute renal failure, the frequency at which patients take the medication has to be verified.

Methotrexate, a cytostatic drug authorised since 1964, belongs to the category of folic acid derivatives that inhibit dihydrofolic acid reductase and thus cell division. In tablet form, it is frequently used to treat rheumatoid arthritis or psoriasis. For this indication, methotrexate is taken only once a week.

In Switzerland and on an international level, reports are received repeatedly on cases of accidental overdose followed by extremely severe intoxication or even death.

In this context, we would like to remind that intoxications can also occur if the dosing is correct, notably with regard to a decline of the renal function, e.g. through dehydration (intercurrent diarrhoea), NSAID use, etc. Those particularly at risk are patients with pre-existing reduced renal function (e.g. elderly patients).

Over the last 10 years, 13 cases of accidental overdose have been reported in Switzerland (including some with parenteral application, total reports for methotrexate: 466), in which methotrexate has wrongly been prescribed, given to patients, or taken by patients, as a once-daily dose instead of a once-weekly one. The cases are evenly distributed over the years, meaning that they are not numerous but nevertheless had severe consequences. Three of those patients died, very probably as a result of the overdose. For that reason, it is all the more important that healthcare professionals are aware of the problem of the accidental overdose, that they give their patients extremely precise instructions, and monitor them. Should there be signs of a possible overdose such as mucositis/stomatitis, anaemia, leukopenia, thrombocytopenia or acute renal failure, it is essential that the frequency at which patients take their medication is verified. The information for healthcare professionals and the patient information for methotrexate products[1] include indeed warnings that the daily instead of the weekly dose can be fatal, but this is not read by every patient.

The Swiss Foundation for Patient Safety has developed and published a "Quick Alert" in collaboration with various experts and specialised organisations: "Methotrexate intoxication → Avoiding oral overdose". The objective of this alert is to enhance awareness among healthcare professionals and to provide relevant, practical instructions to avoid oral intoxications.

The recommendations apply to both single process phases of the medication (e.g. ordering/delivery, prescription) and process phases during the treatment of the patient. For example, methotrexate checklists should be used for prescription, which consider risk factors such as renal insufficiency, affected liver function, lung function disorders, etc. and check interactions with concomitant medications. The patients have to be instructed on the specific characteristic of the weekly dose and receive a written patient information describing the dosage and the risks, including the signs of intoxication and how to react. These recommendations also account for the difficulty of interfaces: for example when a patient is transferred from the hospital to outpatient care. In order to guarantee the continuity of treatment at this interface, the discharge management must be seamless. This includes, for example, a clear, up-to-date medication plan as well as the transmission of the indication requiring a low-dose basic therapy with methotrexate together with the current dosage, the dosing interval and the day of the week on which the medication should be taken. When documenting the fixed day of the week, no abbreviations must be used, since "Mo" could be wrongly interpreted as "Morning".

The detailed recommendations of Quick Alert No. 28 of the Swiss Foundation for Patient Safety can be consulted at or downloaded from its website (www.patientensicherheit.ch) in German or French.

Reporting suspected adverse drug reactions

To report adverse drug reactions, please use the relevant form and send it to your local pharmacovigilance centre. The form is available on the Swissmedic website (www.swissmedic.ch → Go directly to → Reporting undesirable side-effects → Pharmacovigilance) and in the Annex to the Compendium of Medicinal Products. It can also be ordered from Swissmedic (Tel. 00 41 31 322 02 23).

1 Products authorised in Switzerland can be found at http://www.compendium.ch.

Adverse Drug Reactions (ADRs) of oral isotretinoin: Update of the case numbers of the previous year

Swissmedic is issuing an updated overview of oral isotretinoin with regard to the ADR reports recorded in the national database during the period from 1 October 2011 to 30 September 2012, and focusing on severe skin and liver reactions, mental disorders and exposures during pregnancy (see also Vigilance-News of December 2010 and December 2011). Only the key aspects are repeated, since the overall situation remains unchanged.

Oral isotretinoin preparations are authorised in Switzerland for the treatment of severe forms of acne (such as acne nodularis, acne conglobata or acne with the risk of permanent scarring) that have proved resistant to appropriate standard treatment regimes with systemic antibiotics and topical therapies, i.e. only as "last line" treatments.

Owing to the high teratogenic potential of the substance, these preparations may only be prescribed to women of childbearing age when specific precautionary measures are taken as described in the product information.

The good level of efficacy is associated with a serious potential for side-effects, and for that reason, the other precautionary measures mentioned in the product information must also be strictly adhered to.

Pharmacovigilance of isotretinoin focuses on severe ADRs (psychiatric, skin and liver) plus in particular, exposures during pregnancy.

There have been no relevant changes to the overall profile and the distribution to the various organ categories of the ADRs to isotretinoin reported in Switzerland since the last update in the Swissmedic Vigilance-News in December 2011. Between 1 October 2011 and 30 September 2012, 21 initial ADR reports were reported to Swissmedic.

Mental disorders

About 30 % of the accumulated total of all reports received concerns psychiatric symptoms.

In the period from 1 October 2011 to 30 September 2012, a total of three reports on this organ system were received, but none regarding suicide or attempted suicide. Overall, the accumulated total of 11 reports of attempted suicide and 21 of completed suicides is thus unchanged.

One case of depression in an adolescent was reported, which had a close temporal relationship with isotretinoin and the symptoms subsided when it was discontinued. A poorly documented case described panic attacks and an attention deficit hyperactivity disorder (ADHD), but the temporal relationship was not clear and the onset took place a considerable time after the treatment had been discontinued. Finally, a case of psychosis with thought and memory disorders was reported in an adolescent. This occurred during hospitalisation for a severe infection. Isotretinoin and four other medicinal products were suspected as the cause, in addition to causes not related to medicinal pro-ducts.

The numerous spontaneous reports of psychiatric symptoms received over the years continue

to make the recommended precautionary measures necessary, despite the fact that a causal link to the isotretinoin treatment is not proved conclusively. Patients, their relatives and the healthcare professionals who administer isotretinoin are therefore still required to report and react immediately to changes of the mental state (see below).

Rare serious skin conditions

One serious case concerned an adolescent with a haemorrhagic bullous purpura Schönlein-Henoch: the first case of this kind in Switzerland. Here, a plausible temporal relationship was provided without obvious indications of other causes. Vasculitis as a general umbrella term is described in the product information as a very rare ADR.

In addition, there was a new case of erythema nodosum that was unfortunately not well enough documented for a valid assessment. This accumulates the total of such cases to three.

Otherwise, no new cases have been reported for this organ system.

Hepatic Adverse Drug Reactions

No new reports were received during the investigated period.

Exposure during pregnancy

Although isotretinoin should only be dispensed for one month at a time, a negative pregnancy test within the last 7 days is required and a reliable contraceptive must be prescribed, Swissmedic receives reports of exposure during pregnancy every year.

Cumulatively, four reports received to date concern new-born babies whose mothers were under treatment with isotretinoin: these children were born with defects affecting the heart, ear and face.

Five new cases of exposure were reported. In one, the pregnancy was terminated and for the remaining 4, the outcome is unknown. In one case, the pregnancy was not confirmed and confirmation could not be obtained when requesting the information again. In two cases, the exposure took place prior to the pregnancy and in one of them, three months previously. In one case, it was presumed that the precautionary measures were not adhered to due to the infertility of the husband. No new reports on children born with defects were received.

Comment regarding another oral retinoid with a different indication

The active pharmaceutical ingredient alitretinoin, with the trade name Toctino®, is used for the "Treatment of **adults** with refractory, severe chronic eczema of the hands and who have received extensive local treatment for at least 4 weeks and have not responded to it. The prior treatment includes avoiding contact with triggers, skin protection and potent topical corticosteroids."

It is therefore the last option for an indication that is considerably less frequent than severe acne.

The contraindications, precautionary measures and warnings that are essential to respect concern the same main aspects, and particularly the danger of birth defects when taken during pregnancy. The entire safety sections in the product information are to a large extent identical with those for isotretinoin.

Of the cumulatively 14 case reports received to date, and with the exception of one case of depression, none concerned the particularly mentioned important areas.

Reminder of the key messages due to their importance:

Oral isotretinoin preparations may only be prescribed by doctors who are familiar with the use of systemic retinoids in the treatment of severe acne and who have full knowledge of the risks of isotretinoin treatment and the necessary precautionary measures/controls.

Patients and their families must be made aware of the risk of mood swings or even depression and the fact that this must be reported without

delay to their healthcare professional. The prescribing doctor also has to pay careful attention to any signs of depression and/or any similar symptoms to ensure an early diagnosis, particularly in patients who have already suffered from psychiatric disorders in the past. Discontinuing isotretinoin alone might not be sufficient to alleviate the symptoms and psychiatric or psychological measures might be required without delay.

In the light of the high teratogenic potential of isotretinoin, it is essential to adhere to the precautionary measures in women of child-bearing age.

Detailed information about the warnings, precautionary measures (teratogenicity) and adverse reactions can be found in the product information for isotretinoin preparations (www.compendium.ch). The following oral isotretinoin products are currently authorised in Switzerland: Roaccutan®, Curakne®, Tretinac®, Isotretinoin-Teva® and Isotretinoin Mepha®.

Assessment and reporting of drug-induced liver injury

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Introduction

Drug-induced liver injury (DILI) is not only one of the most pathophysiologically and clinically complex and interesting adverse drug reactions (ADRs) [1], but from a regulatory viewpoint also involves special challenges and is therefore of particular significance for drug safety. Thus, DILI is the most frequent cause of acute liver failure in Western countries and one of the most frequent reasons for withdrawal from the market or changes in the product information of already marketed medicinal products [2, 3]. Since idiosyncratic liver toxicity typically occurs with a frequency of less than 1:10'000 exposed patients and epidemiological studies are only rarely sufficiently large and of appropriate design to allow for a reliable risk quantification [4], cases collected by pharmacovigilance systems often play a central role in prompt regulatory decisions concerning DILI [5]. This short article is therefore intended to support the assessment and reporting of DILI in routine pharmacovigilance. In this sense, we also present in **Figure 1** a practical work-up algorithm for suspected DILI.

Work-up

Likewise with other ADRs, the initial suspicion of a possible drug-induced cause is the first important step towards the correct and timely diagnosis. This is crucial to enable the causal medicinal product to be discontinued immediately if necessary and thus to prevent further progression leading, in the worst case, to acute liver failure. An extensive, active and, if necessary, repeated drug history, in particular giving details of the duration of intake and including phytotherapeutics, dietary supplements and environmental toxins (which are possibly the cause of a significant number of so-called idiopathic liver failures), is therefore essential [6]. The typical latency periods amount to between a few days and approximately 6 weeks and are usually shorter when the course is cytolytic rather than cholestatic.

A basic rule states that drug-induced liver injury can mimic any other liver disease both clinically and histologically. There are nevertheless often typical signature patterns for individual drugs. Possible clinical symptoms of drug-induced liver injury are abdominal pain, fatigue, nausea and vomiting, icterus and dark-coloured urine. With immune-mediated hepatotoxicity, fever and skin reactions can also occur. The most important laboratory parameters for the diagnosis and the process assessment are alanine aminotransferase (ALT) and alkaline phosphatase (AP). They are also used for the classification of cytolytic vs. cholestatic DILI **(Box 1)**. It has to be noted that the initial determination of the liver values is decisive after the suspected diagnosis, particularly since the pattern can change over time. Bilirubin values are likewise important, particularly as a prognostic marker. A liver bi-

opsy is usually not indicated when DILI is suspected, but may sometimes be necessary for differential diagnosis. A lymphocyte transformation test is complex and requires specialised centres (e.g. Bern), but it can represent an important contribution in rare individual cases [7]. The identification and validation of new laboratory markers for hepatotoxicity is being vigorously pursued and there is hope for a diagnostic investigation of DILI with improved sensitivity and specificity in the future.

The differential diagnosis for the exclusion of other causes of increased liver values **(Box 2)** includes in the first step particularly the search for viral hepatitis and obstructive bile duct diseases, as well as ischaemia and sepsis. In the further course diagnostic work-up is then ideally supported by hepatologists.

In addition, so-called extrinsic evidence must be considered. Apart from the mandatory current literature search, the 2nd edition of the textbook edited by Kaplowitz and DeLeve is a comprehensive, well-structured source of information [8] highly recommended for routine use.

Causality assessment

In routine pharmacovigilance causality assessment of DILI follows the standard CIOMS criteria and is thus based in particular on the temporal relationship of the intake of suspected drugs and the exclusion of other possible causes. In addition, guidelines and assessment scales [9, 10] have also been developed specifically for DILI. Particular emphasis should be given to the RUCAM-CIOMS scale [11], which is particularly favoured in the regulatory environment. Even if its use is not mandatory for reports within the Swiss pharmacovigilance system, it is nevertheless very helpful in order to ensure that all important assessment criteria are always systematically determined and documented. A version for use in the daily routine can be requested from the authors, and we also implemented it into the iOS App "iLiver" (available free of charge).

Management

In particular with cytolytic hepatotoxicity with rapid and strong rise (>10x) of the ALT, as well as in so-called "Hy's cases" (ALT ≥3x upper limit of normal (ULN) and total bilirubin >2x ULN and initial AP <2x ULN), the suspect drugs must be discontinued immediately, since these cases are associated with an increased risk of acute liver failure. On the other hand, in patients with a slow and small rise in liver values, it can be justifiable to discontinue the drugs one after the other, in a sequence that considers a causality ranking for all suspected drugs in an individual patient, since this has the advantage that the causality can then better be assigned if a "positive dechallenge" occurs. In cases with a lack of therapeutic alternatives and/or a particularly important indication (e.g. antibiotic therapy with tuberculosis), continuation of the therapy can also be justified under close monitoring of the liver values if the values remain stable (usually ALT <5x ULN) and no clinical symptoms of hepatopathy occur.

Pharmacogenetics of hepatotoxicity

The pharmacogenetics of the DILI which can almost always be regarded as multifactorial, are therefore extremely complex and prevent, at least in the near future, a reliable prognosis for individual patients, based on genetic analyses only [1]. The identification of genetically controlled mechanisms and risk factors is nevertheless of great importance, both preclinically and clinically, for the understanding and prevention of drug-induced liver injury. A large prospective international study on genetic risk factors is currently being coordinated in Zurich and suitable cases can be reported and included there (further information available from the authors).

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Boxes and figures

Box 1: Enzymatic classification of drug-induced liver injury

$$R = \frac{\text{ALT value / ALT ULN}}{\text{AP value / AP ULN}}$$

ALT = alanine aminotransferase
AP = alkaline phosphatase
ULN = upper limit of normal

Interpretation:

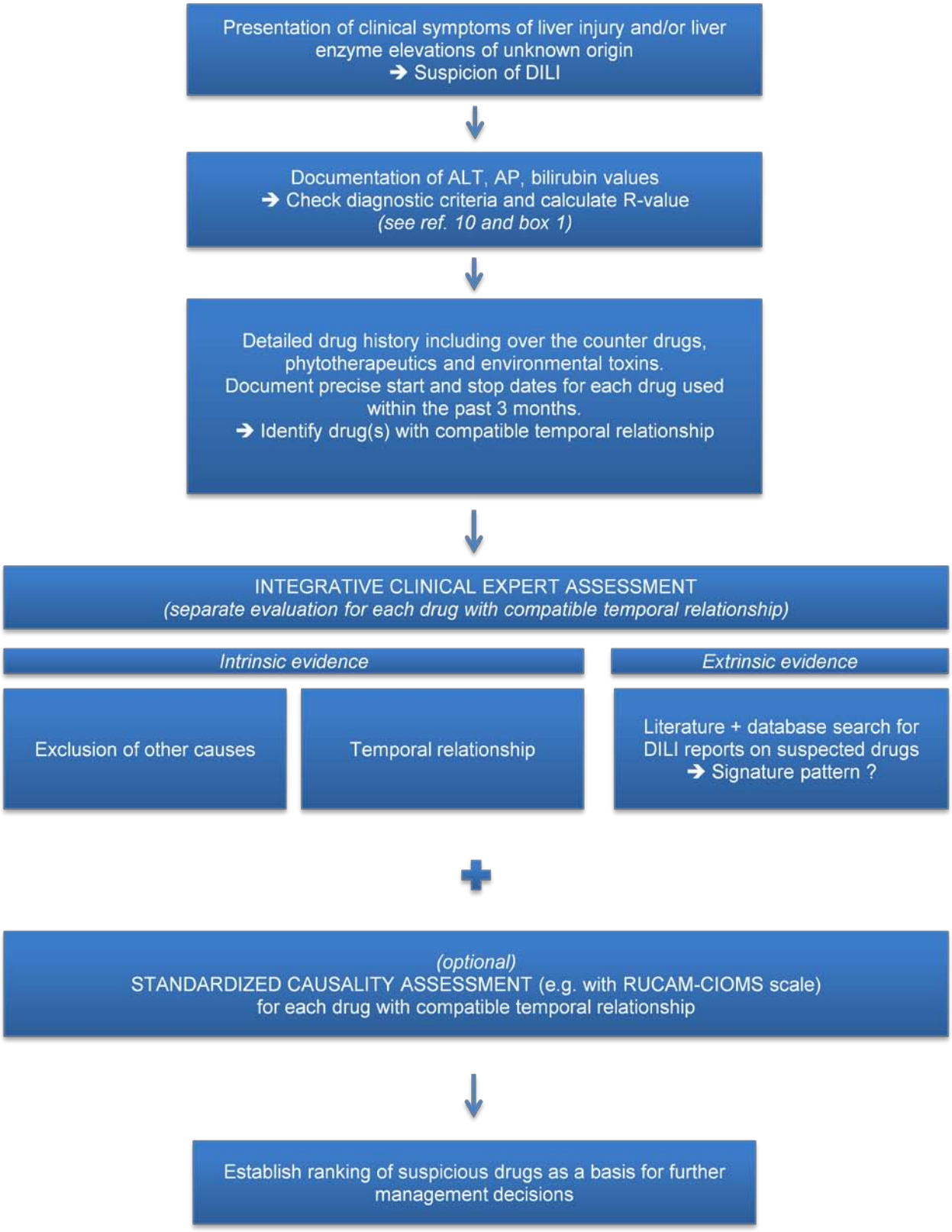
R ≥5 = Hepatocellular pattern of DILI;
R >2 and <5 = Mixed pattern of DILI;
R ≤2 = Cholestatic pattern of DILI.

Box 2: Differential diagnosis in cases of suspected drug-induced liver injury

- Viral hepatitis (HAV, HBV, HCV, HEV, EBV, CMV, HSV)
- Benign obstructive hepatobiliary disease
- Autoimmune hepatitis
- Wilson's disease, hemochromatosis, alpha 1-antitrypsin deficiency
- Alcoholic liver disease
- Bacterial or fungal sepsis
- Congestive heart failure, ischemic liver disease
- Primary or metastatic malignancy of the liver or biliary tract
- Primary biliary cirrhosis, primary sclerosing cholangitis
- Non-alcoholic fatty liver disease and non alcoholic steatohepatitis

Figure 1: Clarification algorithm for suspected drug-induced liver injury

WORK-UP ALGORITHM FOR DRUG-INDUCED LIVER INJURY



NEW AT SWISSMEDIC AS OF DECEMBER 2012

ELECTRONIC EXCHANGE OF INDIVIDUAL CASE SAFETY REPORTS WITH PHARMACEUTICAL COMPANIES VIA E2B-GATEWAY

After an intensive pilot phase Swissmedic will, as of December 2012, be exchanging individual case reports of adverse drug reactions with five companies from the pharmaceutical industry. The exchanges of case reports will operate in both directions and within the production environment. This form of transmission has considerable advantages for both Swissmedic and pharmaceutical companies:

- Real-time transmission of data/reports
- Increased consistency, since there is no repetitive data entry
- Increased efficiency in the use of resources
- Automatic linking of follow-up reports
- Automatic identification of duplicate reports by control of various pre-allocated reference numbers
- Alignment with international safety reporting standards

Considering these advantages, Swissmedic will favour this form of transmission in the future and extend it to become the preferred method of communication for ICSRs. As of the second quarter 2013 and once the corresponding technical infrastructure and support mechanism have been established, Swissmedic will implement data transmission via gateway with further interested companies. In order to provide pharmaceutical companies that are interested an overview on the needed technical, organisational and procedural pre-requirements, Swissmedic will hold an introductory workshop to provide information on it prior to the next phase, on 5 December 2012. Representatives of companies already participating in the pilot phase, from the gateway operator and from Swissmedic will be present in this workshop aiming to provide a comprehensive picture on the current situation:

http://www.swissmedic.ch/aktuell/00051/02058/index.html?lang=en

Swissmedic considers the launching of this electronic data exchange system on adverse drug reactions as a significant step forward to efficient data management and to guarantee patient safety.

FOCUS

PHARMACOVIGILANCE AND SPONTANEOUS REPORTS OF ADVERSE DRUG REACTIONS 10 YEARS AFTER THE IMPLEMENTATION OF THE THERAPEUTIC PRODUCTS ACT

The objective of pharmacovigilance [1] is to improve knowledge of known adverse reactions (ADRs) and – more rarely – to identify new ones and to share this information with the medical community and the patients. A good example of a known risk is the difficulty of diagnosing pulmonary embolisms in young women taking combined hormonal contraceptives. An example of a new risk is the occurrence of nephrogenic systemic fibrosis (NSF) in patients with renal insufficiency after the administration of gadolinium-based contrast agents. This implies that reports sent to Swissmedic, whether submitted by a healthcare professional or not, focus on the unexpected aspects and the remarkable characteristics of ADRs. The "Good Pharmacovigilance Practice" moreover defines quality criteria for ADR reports. The aim of this article is to provide an overview of spontaneous reporting in 2012, to remind that reporting ADRs is mandatory and to describe the prerogatives that would allow Swissmedic to improve the safety of medicines.

I. Historical background

1. General aspects

Although the notion of adverse effects (AEs) resulting from medicinal products can be traced back to ancient times, it was only in the middle of the 19th century that serious complications arising after the administration of certain medicines attracted the attention of the medical community: chloroform and ventricular fibrillation leading to the death of the patient under general anaesthesia (the product was abandoned for that reason at the beginning of the 20th century), arsenic and hepatic cytolysis (1922), thalidomide prescribed during pregnancy (1957–1961) and foetal malformations (foetal phocomelia / micromelia).

Given the universal nature of the distribution of medicinal products, WHO and the national professional associations rapidly pooled their efforts in order to create various working platforms and databases, e.g.:

- The "WHO Pilot Research Project for International Drug Monitoring" launched in 1968;
- The "Uppsala Monitoring Center (UMC)", the WHO Collaborating Centre which has been managing the programme since 1978 with over 130 member countries and which runs the WHO global database with over 7.5 million reports;
- The "International Society of Pharmacoepidemiology" founded in 1989;
- The "International Conference on Harmonisation" created in 1990;
- The "European (International) Society of Pharmacovigilance" founded in 1992.

These collaborations have allowed to collect and evaluate numerous risks, that have led to precautionary measures being taken and more rarely to the withdrawal from the market of medicinal products with an unfavourable risk benefit profile.

Although pharmacovigilance is a dynamic speciality, it is nevertheless still considered marginal for the medical profession, as demonstrated by the limited number of publications on the subject whether in Switzerland (6 publications per year on average in ten years in the Swiss Medical Journal and 19 in total since 2001 in the Swiss Medical Forum) or abroad (93 documents in the PubMed database under the heading "Signal detection pharmacovigilance").

We therefore consider it useful, on the occasion of this jubilee, to reiterate good pharmacovigilance practices.

2. Pharmacovigilance in Switzerland

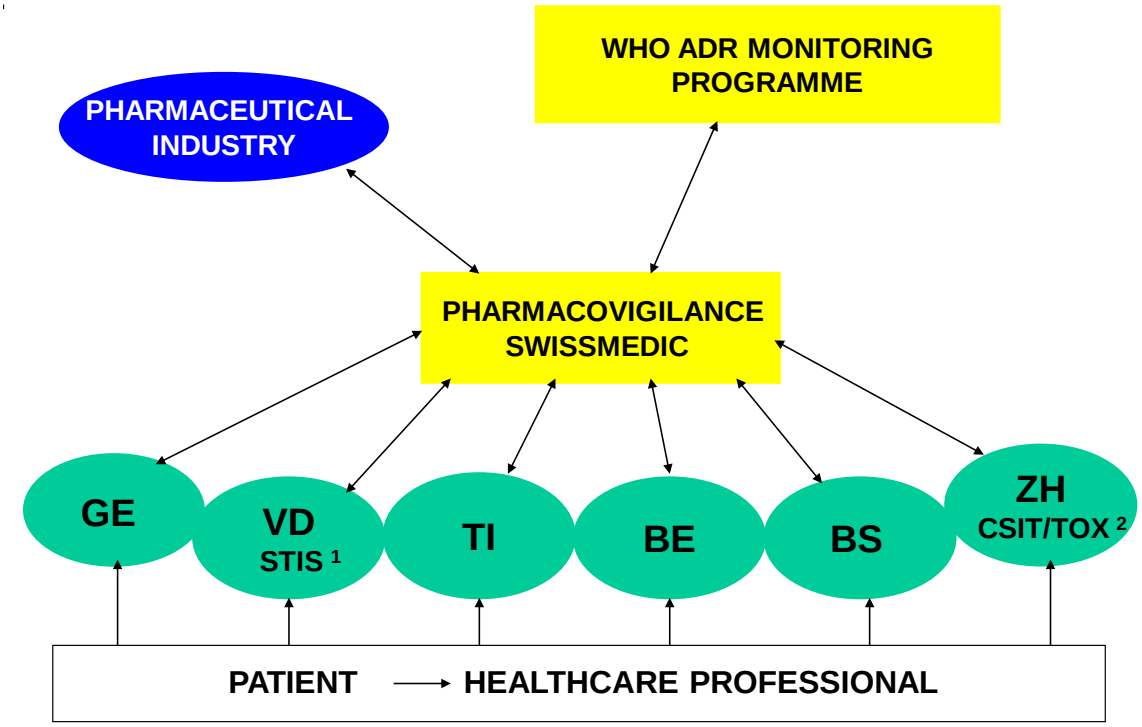
The efficacy and safety of use of a new molecule is initially studied, within the framework of phase 2 or 3 trials, in groups limited to a few thousand patients selected according to precisely defined criteria. Only the most frequent ADRs (frequency > 1 to 2 %) are identified at this point. It is only after marketing authorisation, when the medicinal product has been administered to a much wider population, that rarer ADRs can be identified. This leads to updates of the safety profile and possibly a re-evaluation of the risk-benefit balance.

The most widespread method for detecting ADRs is spontaneous notification: a small series of correctly documented cases can in fact be sufficient to launch an alert and justify rapid decisions regarding the protection of patients.

Swissmedic (the Swiss Agency for Therapeutic Products) was founded in 2002 from a merger of the Intercantonal Office for the Control of Medicines and the Therapeutic Products Section of the Swiss Federal Office of Public Health. By virtue of the Therapeutic Products Act (TPA, Articles 58 and 59), which came into force the same year, Swissmedic is responsible for "supervising the safety of therapeutic products", for collecting and evaluating reports and "taking the necessary administrative measures". These measures range from updating the product information leaflet (Article 67, para. 1) to suspending a market authorisation (Article 66, para. 2, letter b).

Any person professionally administering or dispensing therapeutic products (Article 59, para. 3) or manufacturing or distributing them must notify the Agency of occurring ADRs. Consumers or patients (Article 59, para. 4) may also do so.

The reports must be sent to the Regional Pharmacovigilance Centres (as shown in the illustration below).



1 STIS = Swiss Teratogen Information Service
Risks concerning medications during pregnancy

2 CSIT = Centre suisse d'information toxicologique /TOX -Zentrum

II. Therapeutic Products Act: The legal obligation for healthcare professionals to report suspected adverse drug reactions

1. Definition of an adverse drug reaction (ADR)

An ADR is, in the strict sense of the WHO definition, any undesirable experience that has happened to the patient while taking a drug, that is suspected to be caused by the drug. Cases of abuse (unjustified prolonged use, excessive doses or those taken in the absence of a medical indication), dependency and drug addiction, in accordance with the definition of the tolerance conditions of the medicinal product, must be declared. This also applies to complications observed when taking unauthorised or illegal medicinal products.

2. The report

What should be reported, by whom, and where the report should be sent, is described in detail on the Swissmedic website, at:
http://www.swissmedic.ch/marktueberwachung/00091/00136/00137/index.html?lang=en

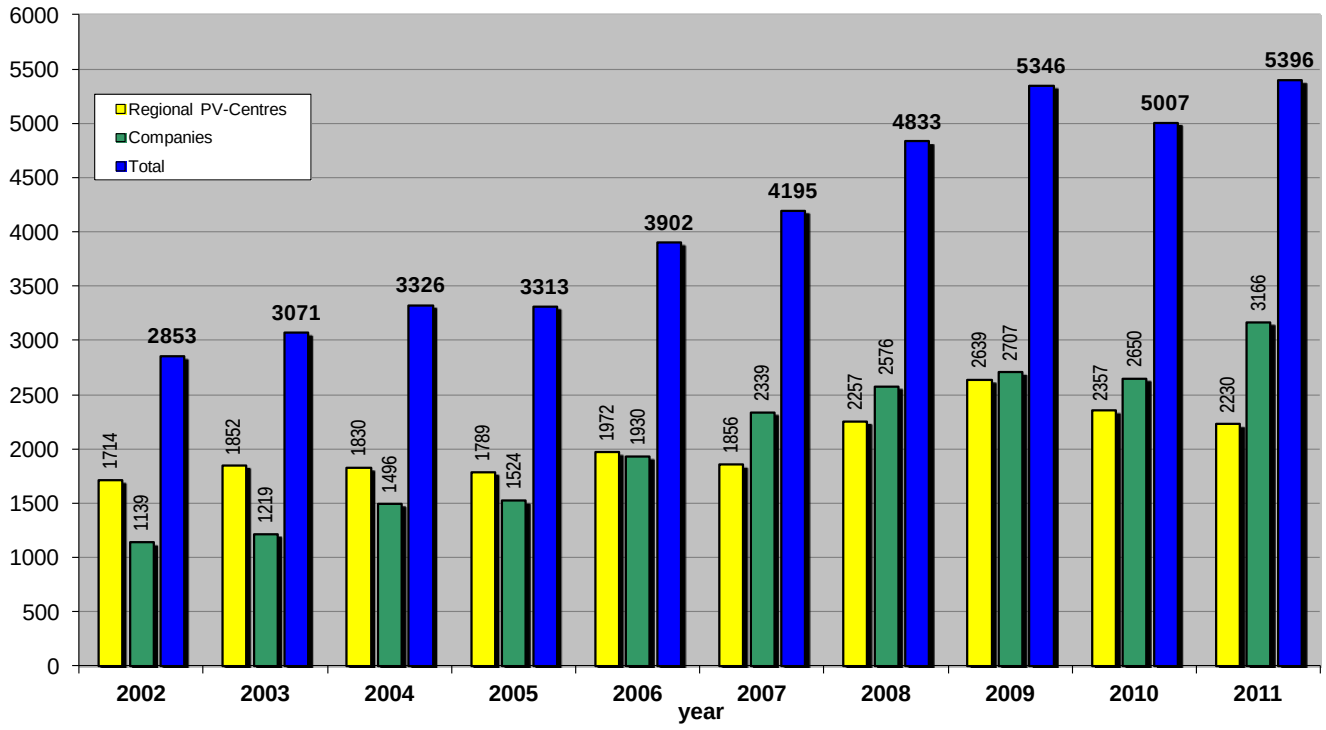
3. What happens to the report after that?

Once the Regional Pharmacovigilance Centre receives a report, it sends an acknowledgement of receipt to the sender, which includes the reference number of the case and related comments. The centre will analyse the information received and forward it (after it has been fully anonymised) to the National Pharmacovigilance Centre (Swissmedic) in Bern. Swissmedic maintains the national database and forwards serious cases or cases of new adverse reactions to the manufacturers or distributors concerned. The manufacturers may also – on their request – obtain access to all information concerning one

of their products. Finally, Swissmedic forwards the reports to the international WHO database in Uppsala / Sweden. This database currently contains nearly 8 million reports, which are also available to the National Centre for specific searches.

The number of reports entered into the Swissmedic database over the last 10 years is shown below. There is a progressive increase until 2008, followed by a stabilisation superimposed on the continuous increase in number of reports made by industry. However, quantity does not necessarily also mean quality.

Swissmedic Pharmacovigilance-Centre: Reporting Frequency



III. The report's quality is a fundamental condition

The daily work of pharmacovigilance mainly consists of improving knowledge related to already known ADRs. One good example is that of pulmonary embolisms that occur in young women taking combined hormonal contraceptives. The reports relating to this risk, which has been well known for decades, clearly illustrate the difficulties in diagnosing the condition in such a population, to recognize it as an ADR, to assess the significance of risk factors, and to make the appropriate recommendations to the users. Similarly, the latest reports on agranulocytosis under metamizole reveal that awareness about this risk is decreasing.

Detecting of new risks (nephrogenic systemic fibrosis following gadolinium injection in patients with renal insufficiency, maxillary osteonecrosis and atypical femur fractures under bisphosphonates) is also important, but this is not the sole *"raison d'être"* of pharmacovigilance.

To achieve these mentioned objectives, i. e. to be able to validate and ultimately make use of the information in a safety report, this must fulfil minimal quality requirements: it must comply with Good Pharmacovigilance Practice and must contain certain important / critical information.

- Good Pharmacovigilance Practice relates to the methods for collecting, managing, researching and evaluating the ADRs sent by healthcare professionals and patients, with the objective of preventing any harm to patients.
- Critical information includes:
  - The specific reason that led to a report - what concerned me, the reporter, which information I want to submit primarily and share with the persons concerned;
  - The source of the report, meaning there will be differences depending on whether it is submitted by a healthcare professional or a patient;
  - The patient's age and sex as potential risk factors (and to avoid report duplication);
  - The description (main symptoms) and chronology of the ADR (date of onset, progression, improvement after discontinuing treatment);
  - Medication(s) administered (incl. start and stop dates, dose, route, therapeutic indication);
  - Predisposing risk factors / concomitant disease (allergy, renal / hepatic / pulmonary damage, alcohol consumption, etc.);
  - The differential diagnosis: alternative explanations not related to medication (e.g. for liver damage, a personal history of alcohol consumption, biliary obstruction, viral serology).

IV. Possibilities and limitations of the system

A database in which spontaneous reports are collated allows to identify safety signals. Over recent years, however, observational studies and analysis of clinical trials (meta-analysis) have been helpful in identifying medicines as triggers of several diseases or ADRs and to evaluate their impact [2, 3].

For example, it has been possible to identify the relation between:

- Hormonal replacement treatment and breast cancer;
- NSAIDs and cardiovascular diseases;
- Serotonin reuptake inhibitors (SSRIs) and risk of suicide in children;
- Neuroleptics in elderly subjects or patients with dementia and stroke;
- Inhaled anticholinergics and infarction;
- Antidiabetics (glitazones) and infarction or fracture;
- Bisphosphonates and auricular fibrillation or low-energy fractures;
- Omeprazole and other proton pump inhibitors and fractures.

Every year worldwide, tens of thousands of potentially fatal cases of gastrointestinal haemorrhage are caused by NSAIDs, anticoagulants or platelet inhibitors.

However, these pathologies are so frequent, that – paradoxically – they are not often the subject of spontaneous reports. Rare and new adverse events are those attracting the attention of physicians more frequently, and are the pre-

ferred subject of a report, as this is the case for ADRs that arouse the interest of the media. Consequently, most market withdrawals over recent years have taken place because an ADR corresponding to rare diseases has been discovered.

One of the limitations of the system is underreporting, since reporting is based on the motivation of the observer of the ADR (physician, other healthcare professional, patient). Furthermore, the system does not allow a definite statement about the frequency of an ADR – since neither the total number of the ADRs nor the number of treated patients are collected systematically.

As a result, the knowledge and prevention of ADRs calls for reinforcing the existing organisational structure but also for developing more proactive pharmacovigilance.

V. Advantages for the patients and healthcare professionals

ADRs are the cause of 3 to 7% of hospitalisations [4] and the 4th largest cause of death in industrialised countries [WHO – Fact Sheets].

Pharmacovigilance can, and therefore must, play a major role in terms of public health, because it allows:

- Healthcare professionals to use medicinal products rationally, depending on their pharmacological properties and on the risks of ADRs;
- Patients to know how to identify the cause of more or less disturbing symptoms (taste disorders, loss of hair, drowsiness, etc.), as well as the risks of severe diseases (cardiovascular events, diabetes, cancer, etc.).

VI. Conclusion

In 10 years, much has been accomplished but much remains to be done, including:

- Continue and reinforce the ongoing training and the understanding of pharmacovigilance among healthcare professionals and among those in charge of pharmacovigilance in pharmaceutical companies. This is a central issue and will allow to improve the quality of the reports and thus the effectiveness of the system.
- Reinforce collaboration with university hospitals.

For several years, Swissmedic has been publishing pharmacovigilance data on its website, and, in collaboration with the Regional Pharmacovigilance-Centers, also in scientific journals. The availability of this information about risks of medicinal products and about the decision-taking process is an ethical obligation towards patients and essential for maintaining the public's trust.

References

1 *Pharmacovigilance: ensuring the safe use of medicines – in WHO Policy Perspectives on Medicines – WHO/EDM/2004.9*
2 *Laporte JR. Connaissance des effets indésirables des médicaments: pour une pharmacovigilance plus ambitieuse in Prescrire 2010*
3 *An agenda for UK clinical pharmacology. Pharmacovigilance by Edwards J.E in Br. J. Clin. Pharmacol. 73; 979-982; 2012*
4 *Egger SS., Raymond G., Schlienger G., Krähenbühl S. Vorgehen bei unerwünschten Arzneimittelwirkungen. Schweiz. Med Forum 5;292-296; 2005*

CONFERENCE

THE SWISSMEDIC INTERNATIONAL REGULATORY SYMPOSIUM – A HUGE SUCCESS!

To celebrate its ten years of existence, Swissmedic invited high-profile experts from Switzerland and abroad to a scientific conference in Interlaken from 20 to 21 September 2012. The discussions addressed current topics and new developments with regard to the control of therapeutic products.

Federal Councillor Alain Berset, President of the Agency Council Christine Beerli and Swissmedic's Director Jürg H. Schnetzer opened the symposium. The over 300 participants – including experts from the health sector, members of industry associations, representatives of patient and consumer organisations, politics and the authorities, and Swissmedic staff members – followed the interesting presentations and podium discussions.

Swissmedic also received a great deal of praise from Federal Councillor Alain Berset. His highly pertinent comment was that Swissmedic had, in recent years, developed from being something like a "problem child" to one at the "top of the class", which at present can expand and continue its work on healthy basis.

The activities of a regulatory authority for therapeutic products in the health policy environment constituted the topic for the first day. Swissmedic took the opportunity to present the first results of a study commissioned by the Agency Council and carried out by the Centre for Innovation in Regulatory Science (CIRS) in London, which confirmed its competitiveness. The presentations and the podium discussion moderated by Franz Fischlin of the Swiss national television news, revealed consistent challenges: increasing complexity and requirements with regard to product authorisations, empty product pipelines, a difficult economic situation, or the so-called "efficacy-effectiveness gap".

The second day focused on the safety of therapeutic products: "No therapeutic product without risk: what does this mean for individuals?" Professor Franco Cavalli from the Oncology Institute of Switzerland's Italian-speaking region spoke on risk acceptance by patients and risk management. He explained the difficulty of assessing risks, since any evaluation had to take into account and weigh up the interests of the (over-)optimistic researcher, the expectations of the patients, and the legal framework conditions. Information provided to patients is decisive, especially during clinical trials, and the patient's autonomy within the disease process needs to be actively encouraged.

Dr. Tatsuya Kondo, Director of the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), presented the topic "The benefit/risk balance during the life cycle of a drug", and explained his agency's activities aiming the introduction of a new risk management concept. The objective thereof was to minimise risks both within the framework of the authorisation process and after authorisation, by means of market monitoring.

In his address "Risk awareness – how to best communicate risks to the general public", Dr. Frederic Bouder from the University of Maastricht stressed the importance of active planning for the authorities and for industry. "Scandals" led to loss of confidence and rendered risk communication more complicate. Frederic Bouder recommended involving the public and stakeholders much more actively, expanding scientifically based risk communication and providing regular training on it, and involving independent advisory bodies in risk communication. He also considered other key elements such as prevention and transparency of regulatory authorities, and especially in setting out their strategies and ensuring the traceability of decisions taken.

Professor Pierre Dayer of Geneva University Hospital, a member of the Swissmedic Medicines Expert Committee (SMEC), presented the

Pharmacovigilance system in Switzerland as compared to that of the EU.

Finally, Dr Axel Thiele of the German Agency for Medicinal Products and Medical Devices (BfArM) presented the new EU legislation aiming to enhance pharmacovigilance. The new provisions are intended to avoid duplication among the authorities, to reduce the burden on industry, to create a harmonised level of safety, and to involve patients more closely.

The key changes were:

- A new definition of the term "side effect" (a response to a medicinal product which is noxious and unintended), without the former passage “in normal therapeutic use”.
- Simplified electronic reporting of adverse drug reactions (ADRs) via the Eudravigilance information network and management system
- Involvement of patients: greater emphasis will be placed on the fact that patients are also a group that can report suspected side effects. In future, the patient information leaflet will include the relevant link. In Switzerland, adverse reactions reported by patients are captured since the implementation of the TPA (Therapeutic Products Act) in 2002.
- Expansion of the provisions relating to PSURs (Periodic Safety Update Report, regularly updated reports on the safety of a medicinal product considering its benefit)
- Creation of a new committee for risk assessment in the area of pharmacovigilance on a European level (Pharmacovigilance Risk Assessment Committee, PRAC).

To conclude the symposium, Swissmedic's Press Relations Officer Daniel Lüthi moderated a second podium discussion on the topic "How many risks are acceptable?" The discussions highlighted the key importance of the quality of authorisation evaluations and of market monitoring, the responsibility of healthcare professionals, and the individual responsibility of patients.

Link:
"10 years of Swissmedic" – Welcome address by Federal Councillor Alain Berset (only available in German and French):
(http://www.news.admin.ch/message/index.html?lang=de&msg-id=46031)

ANNIVERSARY QUIZ

Most of the questions and answers are related to earlier editions of the PV-News or Vigilance-News.
You can find the answers easily in the editions indicated!
There is only one correct answer.

1. **Of the ADR reports recorded by Swissmedic, around 60 % are "serious" and 40 % "non-serious".**
   What was the ratio of "labelled"/"unlabelled" for the "serious" reports?
   (June 2008)

   ❑ **(S)** 2 : 1
   ❑ **(M)** 1 : 1
   ❑ **(V)** 3 : 1
   ❑ **(L)** 1 : 2

2. **(Oral) Isotretinoin products for the treatment of acne are being monitored by Swissmedic.**
   What unexpected drug reactions led to this?
   (November 2008)

   ❑ **(O)** Fatal methaemoglobinaemia
   ❑ **(Y)** DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)
   ❑ **(W)** Psychiatric symptoms
   ❑ **(M)** QTc changes
   ❑ **(G)** Pisa syndrome

3. **A DHPC (Direct Healthcare Professional Communication) was issued in May 2010 regarding Sirolimus (Rapamune®).** *(June 2010)*
   Sirolimus is also called Rapamycin. Which island is it associated with?

   ❑ **(O)** Madagaskar
   ❑ **(E)** Easter Island
   ❑ **(I)** New Caledonia
   ❑ **(N)** Tasmania
   ❑ **(M)** La Réunion

4. **Nephrogenic systemic fibrosis (NSF) and contrast agents:**
   Which group of contrast agents is associated with it? *(December 2010)*

   ❑ **(E)** Contrast agents containing barium
   ❑ **(A)** Radiolabelled contrast agents
   ❑ **(N)** Contrast agents containing gadolinium
   ❑ **(H)** Iodine-based contrast agents
   ❑ **(D)** Ultrasound contrast agents

5. How is methylphenidate prescribed according to the indication in Switzerland? Which statement is false? *(December 2010)*

- ❑ **(S)** Indication only by recognised, validated diagnosis criteria, with diagnosis by physicians familiar with the particular disease.
- ❑ **(O)** Part of a concomitant, comprehensive therapy plan, which typically also includes psychological, educational and social measures.
- ❑ **(P)** Not used for all children with ADHD (Attention Deficit Hyperactivity Disorder), and particularly not in the case of symptoms caused by the secondary environment or other underlying psychiatric disorders.
- ❑ **(E)** To treat normal fatigue.

6. Haemovigilance: magnitude of some transfusion risks in Switzerland
Which of the risks is incorrect? *(June 2011)*

- ❑ **(C)** Haemolytic transfusion risks: 1 : 20'000 Transfusionen
- ❑ **(H)** Sepsis from bacterial contamination: 1 : 11'000 units of platelet concentrate
- ❑ **(A)** Hepatitis B Virus: 1 : 170'000 donations
- ❑ **(R)** Hepatitis C Virus: 1 : 3,2 million donations
- ❑ **(S)** HIV: 1 : 3,4 million donations

7. Vaccinovigilance: How many ADRs were reported following vaccinations in Switzerland? *(June 2011)*

- ❑ **(M)** 156'565 reports from 2001 – 2010
- ❑ **(F)** 1565 reports per million vaccinations
- ❑ **(G)** 200 deaths from 2001 – 2010
- ❑ **(I)** 63'000 AEFIs (adverse events following immunisation) in the pandemic year 2009
- ❑ **(N)** None of the answers is correct.

8. What regulatory measures were taken regarding adverse drug reactions with Rosiglitazone *(June 2011)*

- ❑ **(V)** Warnings and precautionary measures regarding venous thromboembolism were included in the product information for healthcare professionals.
- ❑ **(N)** The initial dose was adjusted and contraindication for severe heart failure was included.
- ❑ **(A)** Healthcare Professional Communication and market withdrawal.
- ❑ **(M)** All of the answers are correct.

9. "Near miss events" in haemovigilance are *(June 2011)***:**

- ❑ **(U)** Situations in which the amounts of blood needed for the transfusion are provided only just in time due to lack of available blood reserves.
- ❑ **(A)** Transfusions in the immediate vicinity / among the entourage of a Miss Switzerland, meaning considerable media potential.
- ❑ **(L)** Errors that are discovered and corrected before the transfusion takes place.
- ❑ **(E)** None of the answers is correct.

10. Antiarrhythmics: Which is the right answer? *(December 2011)*

- ❑ **(I)** Dronedarone can no longer be considered as an alternative to amiodarone if lung damage was present prior to the treatment.
- ❑ **(E)** Amiodarone can be used as an alternative to dronedarone in the case of thyroid gland disease.
- ❑ **(V)** Ibutilide can be used if the medical history includes Torsade de pointes (TdP).
- ❑ **(K)** Propafenone or flecainide must not be stopped before treatment with dronedarone or amiodarone since they are Class I c and respectively Class III a antiarrhythmics.

11. Which work or compendium that is published annually has existed the longest?

- ❑ **(G)** Le Dictionnaire VIDAL® (France)
- ❑ **(H)** Die ROTE LISTE® (Germany)
- ❑ **(I)** PDR® Physicians' Desk Reference (USA)
- ❑ **(R)** The Swiss Compendium of Medicines®

12. Which statement regarding PML (progressive multifocal leukoencephalopathy) is incorrect? *(December 2011)*

- ❑ **(Y)** It is an opportunistic infection of the nervous system.
- ❑ **(S)** PML is often fatal or causes permanent damage.
- ❑ **(R)** Today, PML is an adverse reaction to new, potent immunosuppressives.
- ❑ **(I)** One major cause is Gilenya® (fingolimod), which is authorised in Switzerland for the treatment of multiple sclerosis (MS).

13. Which of the ADRs below are considered serious in accordance with international ICH criteria *(December 2011)*

- ❑ **(D)** Near-death experiences
- ❑ **(M)** Lifelong threats to health
- ❑ **(V)** Persistent disabilities or incapacities
- ❑ **(P)** None of the answers is correct.

In reverse order, the letters checked spell out the solution word:

1	2	3	4	5	6	7	8	9	10	11	12	13

Please return to: vigilance@swissmedic.ch by 31 January 2013.

Prize: The winner will receive a certificate (the reception date by Swissmedic becomes decisive. In case of several correct answers received simultaneously, there will be a draw).

Conditions of participation: Swissmedic employees may not take part. No correspondence will be entered into. There is no right of appeal. The winner will be notified personally.

INFORMATION ON THE SAFETY OF MEDICINES – PUBLISHED ON THE SWISSMEDIC WEBSITE

Wichtige Mitteilung zu Inflexal V
29.11.2012 *

HPC - Infusionslösungen mit Hydroxyethylstärke (HES)
28.11.2012 *

DHPC Macugen® (Pegaptanib): Risiko starker Erhöhung des Augeninnendrucks bei intravitrealer Injektion ohne das vorgeschriebene vorherige Verwerfen überschüssigen Volumens
26.11.2012 *

Update zu Calcitonin und Krebsrisiko bei Langzeitbehandlung
12.11.2012 *

Publikation der Arzneimittelinformation durch Swissmedic, Stand der Arbeiten
09.11.2012 *

DHCP - Xarelto® (Rivaroxaban)
03.11.2012 *

DHPC – Prolia (Denosumab): Risiko atypischer Femurfrakturen – Neue Vorsichtsmassnahmen
31.10.2012 *

DHPC – Cosmegen (Daktinomycin): Widerruf der Zulassung aus wirtschaftlichen Gründen zum 30. November 2012
30.10.2012 *

DHPC - Gilenya (Fingolimod): Neue Kontraindikationen und Überwachungs-Empfehlungen bei Therapiebeginn wegen kardialer Risiken
09.10.2012 *

Risk Management (PSURs, PV Planning) / Information from Swissmedic regarding the conversion of Periodic Safety Update Reports (PSURs) in the EU
08.10.2012

Swiss authorities seize medicines
04.10.2012

10 years of Swissmedic: The Swissmedic International Regulatory Symposium – a great success!
02.10.2012

DHPC – Meprodil (Meprobamat): Neubeurteilung des Nutzen-Risiko-Verhältnisses und Marktrückzug am 31. Oktober 2012
28.09.2012 *

DHPC – Tysabri (Natalizumab) – STRATIFY JCV Testfrequenz alle 6 statt 12 Monate
25.09.2012 *

Antibiotics in veterinary medicine: fewer sales – resistance situation remains critical
10.09.2012

Botulinumtoxin vom Typ A: Zugelassene Arzneimittel und Indikationen, korrekte Anwendung und unerwünschte Wirkungen
07.09.2012 *

MEDIENMITTEILUNG Eisenbehandlungen bei Schwangeren
17.08.2012 *

Please find the complete list at the following web address:
http://www.swissmedic.ch/aktuell/00003/index.html?lang=en

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