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Vigilance News

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Special issue

The history and development of pharmacovigilance in Switzerland over the last three decades

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Impressum

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We would like to thank all colleagues for their contribution to producing this edition of Swissmedic Vigilance News.

Contact
Please send any suggestions or feedback on this issue of Vigilance News to news.vigilance@swissmedic.ch.

Report of an adverse drug reaction (ADR)

Swissmedic recommends using the reporting portal (direct-entry or XML file upload)

Online reporting portal ElViS:
www.swissmedic.ch/elvis

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Editorial

Dear Reader

Today you are receiving a special issue of Swissmedic's Vigilance News.

We normally report on current safety signals, individual case reports of adverse drug reactions (ADR) or recent Direct Healthcare Professional Communications (DHPC).

This special issue focuses instead on the history and development of pharmacovigilance in Switzerland over the last three decades. A contemporary witness – Rudolf Stoller, Senior Expert and former Head of the Safety of Medicines division for many years – tells us of his own experiences. Although they occurred in the past, the examples he has chosen describe situations which still occur today and which illustrate the importance of drug safety in the patient – physician – medicinal product setting.

Despite all the advances in good pharmacovigilance practices (GVP), we must never lose sight of one element: the patient around whom everything revolves. We are not simply dealing with numbers, but with human beings.

We would like to thank the author, who will soon be embarking on his well-deserved retirement, for sharing his experiences with us and our readers, and offer him our best wishes for the future.

The Editors

Three decades of pharmacovigilance

"It's anecdotes"

Created almost 30 years ago, the structures in the Swiss pharmacovigilance network have survived to this day. Since then, pharmacovigilance – both in Switzerland and internationally – has developed to an extent that those who were involved in its launch could hardly have imagined. But apart from a brief outline of the beginnings, we do not intend to trace this development here. Taking a few examples from everyday life – in the form of snapshots – I will merely illustrate certain aspects that I consider to be important or that were simply formative experiences, in a loose, random sequence in the spirit of the phrase that we often hear in pharmacovigilance: "It's anecdotes". However, these are, in fact, usually important stories told by patients and their relatives. Spontaneous reporting is a matter of learning from such stories for the next patient – this "medicine-based evidence" and "evidence-based medicine" complement each other. They should not be played off against each other.

The beginnings

In 1990, the "IOCM Pharmacovigilance Centre" officially started work as an organisational unit of the Intercantonal Office for the Control of Medicines, IOCM, after a short pilot phase. As the regulatory body responsible for medicines in our country, the IOCM was the precursor of Swissmedic, which started in 2002. There were three important elements:

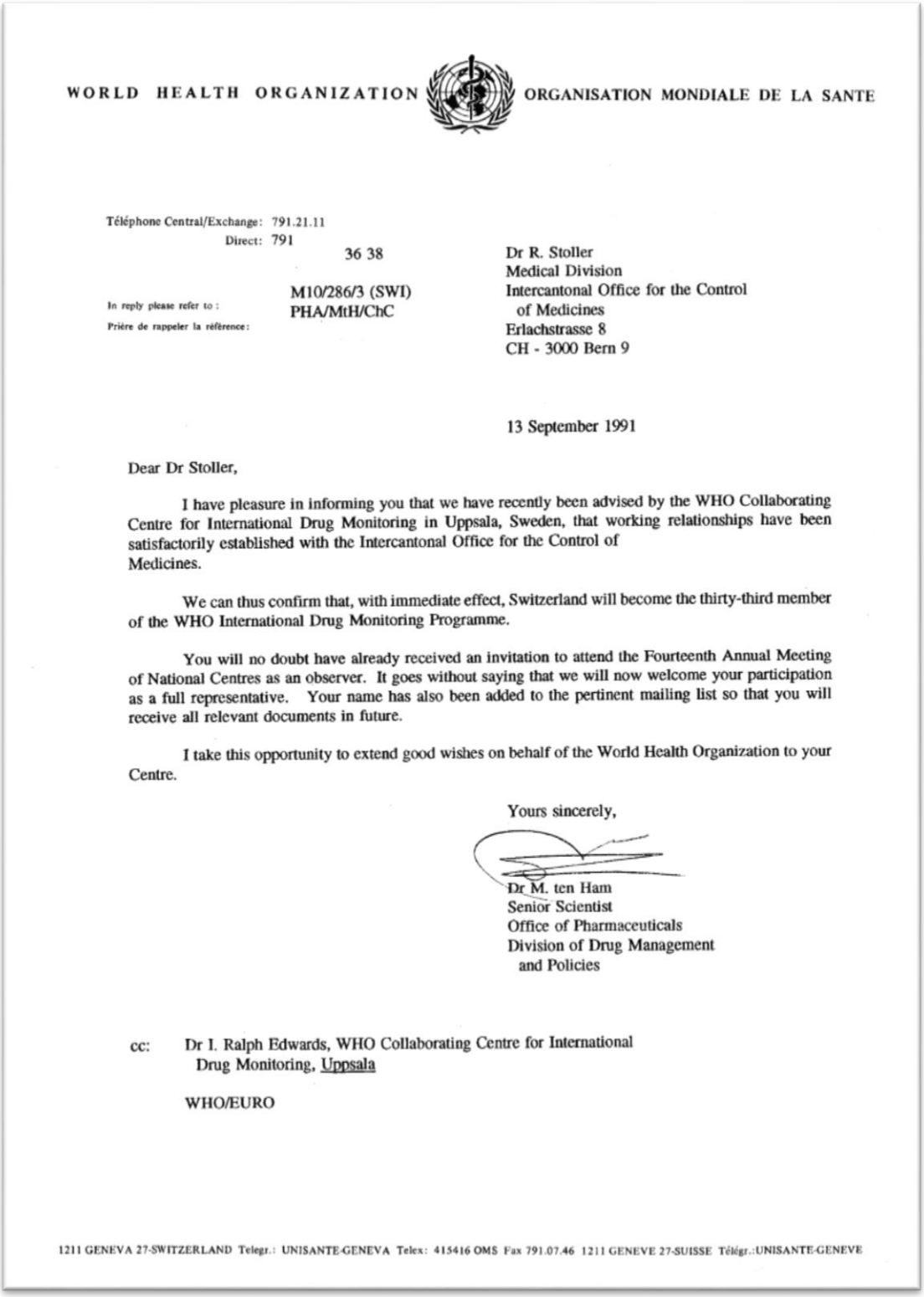
- cooperation with the existing agencies and centres in Switzerland,
- cooperation with the "WHO Collaborating Centre for International Drug Monitoring" in Uppsala (now the Uppsala Monitoring Centre, UMC),
- the assessment of reports independently of companies.

The IOCM Pharmacovigilance Centre collaborated with its official counterpart SANZ, the Swiss Drug Monitoring Centre in Chur, which had been established as a private foundation 11 years previously, in 1979. In 1991 – at the same time as Nicaragua – the IOCM became the thirty third member of the "WHO Programme for International Drug Monitoring". The UMC and the network of sister authorities provided, and continue to provide, the crucial momentum.

The IOCM Pharmacovigilance Centre relied primarily on reports of adverse drug reactions (ADR) submitted by the departments and units of clinical pharmacology in Swiss university hospitals. So, the reporting process occurred close to the patient and close to the treating physician, who would forward reports not to the authority, but to his colleagues in a university hospital of his choice, often his first or advanced training institution.

The clinical pharmacologists, initially those in Geneva and Lausanne in particular, made a key contribution to the development of the network. To this day, the regional centres, in the French and German speaking part of Switzerland, later joined by the centre at Ospedale Civico in Lugano, still form the "Pharmacovigilance Network", which is firmly established in all linguistic regions of

Switzerland. Another key factor was the inclusion of STIS (Swiss Teratogen Information Service) in Lausanne, which deals with Swiss reports of risks during pregnancy, and Tox Info Suisse in Zurich (cases of poisoning due to medicines).



WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

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In reply please refer to :
Prière de rappeler la référence:
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PHA/MtH/ChC

Dr R. Stoller
Medical Division
Intercantonal Office for the Control of Medicines
Erlachstrasse 8
CH - 3000 Bern 9

13 September 1991

Dear Dr Stoller,

I have pleasure in informing you that we have recently been advised by the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, that working relationships have been satisfactorily established with the Intercantonal Office for the Control of Medicines.

We can thus confirm that, with immediate effect, Switzerland will become the thirty-third member of the WHO International Drug Monitoring Programme.

You will no doubt have already received an invitation to attend the Fourteenth Annual Meeting of National Centres as an observer. It goes without saying that we will now welcome your participation as a full representative. Your name has also been added to the pertinent mailing list so that you will receive all relevant documents in future.

I take this opportunity to extend good wishes on behalf of the World Health Organization to your Centre.

Yours sincerely,

Dr M. ten Ham
Senior Scientist
Office of Pharmaceuticals
Division of Drug Management and Policies

cc: Dr I. Ralph Edwards, WHO Collaborating Centre for International Drug Monitoring, Uppsala

WHO/EURO

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On 13 September 1991, the WHO confirmed Switzerland's membership of the WHO International Drug Monitoring Programme to the IOCM.

Metamizole versus aspirin – or comparing apples and oranges

Metamizole – then

At the start of the 1990s, the painkiller metamizole (Novaminsulfon) became a prescription-only medicine in Switzerland, Germany and certain other countries. A key reason for this was the risk of agranulocytosis, a complication classically referred to as a "type B" (bizarre) adverse drug reaction – unpredictable, occurring surprisingly, out of the blue and independently of dose. In addition – and considered even more dangerous – its mortality rate was put at around 10%. The large-scale epidemiological investigation (Boston study) produced inconsistent results with differing odds ratios in various countries and regions. The same applies to the calculated incidences – one frequently cited definitive figure was 1:20,000.

Aspirin, on the other hand, continues to be available over-the-counter – subject to the specified dosage strengths, dosages and pack sizes – even though gastrointestinal micro bleeding occurs in the majority of patients, and gastrointestinal ulcers, or even perforations, readily occur at higher cumulative doses in one in 1,000 treated individuals, in some cases with a fatal outcome.

- So, despite its low incidence, the surprising and dose-independent occurrence of agranulocytosis proved to be the key factor in the decision to classify metamizole as a prescription-only medicine. It should be noted that aspirin was not included in this re-examination procedure. And it should be added that the comparison of the benefit-risk profile of the two active substances was, and continues to be problematic – as in many other situations where radical risk-minimising measures are involved.

Metamizole – now

Metamizole has since enjoyed growing popularity as a prescription-only medicine and is increasingly used, e.g. for postoperative pain. It is also often used in combination with paracetamol, although scant evidence is available to indicate a synergistic effect. As expected, increasing reports of agranulocytosis have also been recorded by Swissmedic in recent years. A crucial factor in this context is that the diagnosis was only suspected at a late stage in some patients – fever, angina, ulcers in the mouth and genital and perineal area are warning signs that patients and healthcare professionals need to watch out for.

- Pharmacovigilance is much more about dealing with risks inadequately taken into account in everyday clinical practice rather than dealing with new ADR. Warnings in the product information should be supplemented by regular reminders in order to raise awareness among a new generation of physicians and pharmacists. In its Vigilance News, Swissmedic has repeatedly reminded professionals about the necessary precautions when prescribing metamizole and the need to instruct patients accordingly. In 2012, a publication in the "Swiss Medical Forum" addressed this subject (1); later articles on metamizole in this supplement to "Schweizerische Ärztezeitung" (Swiss medical journal) reiterated these important instructions.

Hormonal contraceptives

The scenario where the awareness of known risks declines and the risks in question need to be rediscovered is being repeated. Cases of venous thromboembolism associated with combined hormonal contraceptives are another example. This risk was the subject of public discussion even in the years following the introduction of the pill (when it still contained a high oestrogen dose), and became a hot media topic again in 1995. At that time, contrary to expectations, epidemiological studies showed a doubling of the risk for the modern third-generation preparations compared to that for the second-generation contraceptives. Some countries even experienced a veritable "pill scare". A similar situation occurred when, after 2009, combined pills containing drospirenone – a progestogen with anti-androgenic properties – were associated with an increased risk of thromboembolism. This year, in addition to the known psychiatric side effects (including depression), a possible effect on the suicide risk is being evaluated. It almost seems as if every generation has to rediscover certain ADR.

Drug-induced liver injury

Beclobrate – or the lucky blood donor

In 1990, 5 years after beclobrate was authorised, we received two reports of irreversible liver failure with a fatal outcome in patients taking this new fibrate-based lipid-lowering drug. The substance was authorised only in Switzerland and had a limited market volume at that time. A DHPC (Direct Healthcare Professional Communication) drew the attention of healthcare professionals to this new risk, which had not been identified from the clinical trial data, and specified corresponding precautionary measures. Shortly thereafter, we received a report about a young male patient who showed greatly elevated transaminase levels shortly after starting treatment with beclobrate. He had not shown any symptoms of illness, and the abnormal liver enzyme levels had been discovered during screening for a blood donation – he was a regular blood donor. They returned to normal after the drug was discontinued, and the drug remained the only plausible cause.

- We can assume that he had been spared a serious, possibly life-threatening, episode of drug-induced hepatitis thanks to this chance finding. Not just him, but other patients as well – the three post-marketing reports of severe liver injuries in a still limited patient population had been sufficient to cause beclobrate to be withdrawn from the market, since it was not a life-saving drug and since therapeutic alternatives were available.

Conflicting messages – or what does negative re-exposure mean?

There have also been reports, this time at the international level in Switzerland and the USA, of several patients with serious, and in some cases fatal, drug-induced liver injury, who had received a new antiparkinsonian drug shortly after its market launch. Adverse effects on the liver had already been known at the time of authorisation. A rise in transaminase levels to more than three times the upper limit of normal had been observed in 1% of patients in clinical trials. The product information therefore called for regular monitoring of liver enzymes. However, this warning was followed by a sentence stating that, in clinical trials, the transaminase levels returned to normal in those patients who continued the treatment despite elevated levels.

- The post-marketing reports then showed that the monitoring had not been carried out consistently in some patients – not surprising in view of the difficulties associated with a visit to the physician for some Parkinson patients. However, the

conflicting message in the product information has probably also been a contributory factor. While the reference to the "negative rechallenge" was supported by data for some patients, it wrongly called into question the need for discontinuation. On the other hand, this section should not give the impression that monitoring of the liver enzymes – for example on a monthly basis – will detect liver injury at a sufficiently early stage. It cannot always prevent life-threatening, subfulminant and fulminant courses.

Risks in pregnancy

A conference in Berlin at the end of the 1990s reflected whether a thalidomide catastrophe would still be possible today. In view of the developments in drug safety since the 1960s, prompted specifically by the thalidomide disaster, the answers were largely reassuring. It did emerge, however, that teratogenic risks are no longer accorded such a high priority in pharmacovigilance decades after the scandal. This was partly due to the creation, in the interim, of corresponding specialist centres, databases, registers and epidemiological methods.

The fact that the connection between developmental disorders in children and maternal exposure to valproate in pregnancy was only detected at a late stage, roughly a decade after the malformation risk was identified, and that the severity and frequency of developmental disorders were only noticed even later – as a result of the NEAD study published in 2013 (2) – has now led to serious questions that need to be addressed by all concerned.

To date, there have been 24 reports in Switzerland of serious developmental disorders in children and adolescents, specifically concerning mental and psychological development, including autism and related disorders. While most of these were reported after the information campaign in 2015, some involve disorders that manifested themselves years beforehand. Which factors have delayed the detection of this signal and the risk-minimising measures – both internationally and in Switzerland – and what can we learn from this?

What were the contributory factors?

- The risk was difficult to detect – long latency period and low "drug-attributable fraction of risk":
  - Developmental disorders in children only manifest themselves years after the maternal exposure; this connection is not directly apparent. This contrasts with teratogenic risks in the stricter sense, which are detected as malformations during pregnancy or shortly after birth.
  - Disorders of psychomotor development are multifactorial, and genetic and psychosocial causes are usually the first factors to be considered. Drugs tend to remain in the background as possible causes.

  The spontaneous reporting system usually reacts sensitively and quickly to new risks, even rare ones. However, it has its limitations when it comes to ADR that manifest themselves at a late stage – often termed "type D" (delayed) reactions, e.g. carcinogenicity. The same applies to illnesses that are not usually caused by drugs and therefore show a low drug attributable fraction of risk. A classic example would be cardiovascular risks and the corresponding market withdrawal of Vioxx® (rofecoxib) in 2005.

- Advances in the ultrasound monitoring of pregnancy may have raised expectations that malformations can be reliably detected and that this known risk of the substance is therefore "under control". This probably lowered the inhibition threshold for using valproate in pregnancy.
- Prescribing practice has been slow to respond to the development of new antiepileptic agents. Whereas the available alternatives such as phenytoin and carbamazepine were also associated with teratogenic risks back in the early 1990s (albeit to a lesser extent than valproate), these were followed by the arrival on the market of new drugs that were considered to be less harmful and, still later, also much safer in respect of neurological developmental disorders.
- Antiepileptic drugs very often constitute a long-term treatment. Possible problems in the event of a future pregnancy should be considered and addressed even when they are prescribed to adolescents. Wherever possible, exposure in pregnancy should be avoided and the treatment switched beforehand.

Lessons for the future

- The more surprising and serious an ADR is, the more attention it merits, particularly if the causality is initially called into question, which is often the case with unusual risks.
- In retrospect, as regards developmental disorders and valproate, more attention should have been paid to one aspect that should always be noted in spontaneous reporting: developmental disorders associated with valproate often involve characteristic signs of dysmorphia, particularly of the face. Such a specific pattern is a strong indication of a causative role of the drug long before this is confirmed by epidemiological results.
- Prescribing practice in this context is crucial. This should be taken into account and followed up as part of the risk management plan.
- Established prescribing habits are difficult to change. Agencies such as professional associations, universities, patient organisations and cantonal authorities are important players in achieving a successful outcome. According to a study in the EU, the repeated tightening of restrictions in the case of valproate – warnings in the product information, DHPC, instruction materials, acknowledgement form for patients, subsequently supplemented by a patient card and pictogram on the pack – failed to work as hoped. We have isolated examples of this in Switzerland as well. To prevent unplanned pregnancies occurring under treatment with valproate effectively and across the board, requires a comprehensive programme that is comparable with the one implemented for oral retinoids for the treatment of acne and that involves physicians, pharmacists and patients.

Three decades of pharmacovigilance – a few conclusions

- **Pharmacovigilance is designed to help patients**. These are not "cases", not even "interesting cases" or "clinical pearls", to quote one description still used in medical training events. Patients come to us with questions about their – often serious – conditions, and with the aim of sparing other patients a similar scenario. One patient who had contacted an authorisation holder about a disabling ADR and raised the question of compensation, reported that the company had sent over a lawyer. He summed up his disappointment with this encounter with the following words: "if there had just been one word of compassion…"
- **"Subjective ADR" should not be viewed less seriously than "objective" ones**. The assessment should never question the existence of the symptom – e.g. loss of hypoglycaemia warning symptoms with human insulins, or depression progressing to suicidal thoughts with oral retinoids – but should rather focus on the connection with the drug. If the symptoms recur when the drug is re-administered to some patients, then this counts as weighty "medicine-based evidence". However, the psychiatric problems that are connected with oral retinoids also illustrate how difficult it is to distinguish between the role of risk factors – particularly the problems of adolescence – and the drug itself. The medicine then becomes just one of the factors to be taken into account. Therefore, it is not sufficient to discontinue the retinoid; rather, the psychiatric symptoms often require specific investigation and treatment.
- Most ADR are dose-dependent. **The inadequate adaptation of the dose to kidney function is still one of the principal causes of ADR**.
- The product information is designed to guide the prescriber before a drug is administered and, if necessary, during the treatment. **In addition to important ADR, therefore, important warning symptoms should also be listed**. For erythema exsudativum multiforme/toxic epidermal necrolysis (TEN), a reference should be made, for example, to previous fever and to painful, spreading skin lesions followed by blister formation. The symptoms of agranulocytosis have already been mentioned. And however banal it might seem: whenever drugs that frequently lead to anaphylaxis or other serious hypersensitivity reactions are administered, the patient should always be asked how well the last administration was tolerated. Seen from this standpoint, it is not correct to state that type B reactions are "not predictable" or that "no risk factors" are involved.

Pericolo in pillole / Rivoglio la mia casa | Puntata intera del 3.02.2017

Drug safety also involves informing the public objectively about the risks associated with therapeutic products – author Rudolf Stoller taking part in "Patti Chiari", the consumer affairs programme broadcast by RSI, Switzerland's Italian-language TV channel. A report entitled "Pericolo in pillole" discussed the risks to unborn children of exposure to the highly teratogenic active substance isotretinoin.

Let us leave the last word to two great women, both unfortunately deceased:

Kathrin Mühlemann, the former director of the Institute for Infectious Diseases and a professor at the University of Bern, liked to describe herself as the "professor of handwashing", since this simple measure achieves so much in her field. **It is also true in pharmacovigilance that the important things are simple.**

Winifred Castle, MD and FFPM (Fellow of Faculty of Pharmaceutical Medicine), played a key role in the development of pharmacovigilance before and after the turn of the century in various companies, for example as "Vice-President International Drug Surveillance" in the then Glaxo Inc. She was also involved in CIOMS Working Groups. Long before we would talk about integrating the safety of drugs and their safe use, she put the purpose of pharmacovigilance in a nutshell:

"Be helpful!"

Literature

(1) Theiler R, Wyrisch B. Rationale Schmerztherapie – oder doch nicht? Schweiz Med Forum. 2012;12:645–51
(2) Meador KJ et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 March;12(3):244–252. doi:10.1016/S1474-4422(12)70323-X.

Information on the Swissmedic website[1]

Healthcare Professional Communication

09.05.2018
DHPC – Klacid® / Klaciped® (Clarithromycin)
Interaktionen von Clarithromycin mit Domperidon

13.04.2018
DHPC – Encepur N, Encepur N Kinder, Td-pur
Naturkautschuklatex in der Nadelschutzkappe der Fertigspritze mit fixer Injektionsnadel

13.04.2018
DHPC – Information on leaking syringes of various GSK vaccines
GlaxoSmithKline AG has provided information on syringe leaks that may occur with various vaccines during reconstitution or administration.

09.04.2018
DHPC – Vancomycin
Vancomycin: Einschränkungen der Indikationen für die orale Anwendung sowie neues angepasstes Dosierungsschema nach Alter und Gewicht für die intravenöse Anwendung

04.04.2018
DHPC – Buccolam (Midazolam)
Wichtige sicherheitsrelevante Information – möglicher Produktemangel

29.03.2018
DHPC – Hinweise zur korrekten Anwendung von Parsabiv® (Etelcalcetide)
Bei dialysepflichtigen Patienten mit chronischer Nierenerkrankung

28.03.2018
DHPC – Insuman® Infusat (Humaninsulin)
Einstellung der Vermarktung am 4. Mai 2018

21.03.2018
DHPC – Actemra® (Tocilizumab)
Berichte über interstitielle Lungenerkrankungen

15.03.2018
DHPC – Esmya® (Ulipristal)
Anwendungseinschränkungen, neue Warnhinweise bezüglich schwerer Leberschäden und Empfehlungen zur Überwachung

13.03.2018
DHPC – Zinbryta® Fertigspritze, Fertigpen (DACLIZUMAB beta)
Widerruf der Zulassung in der Schweiz

02.03.2018
HPC – MS-Medikament Zinbryta® wird international vom Markt genommen
Swissmedic wurde über neue schwerwiegenden Nebenwirkungen in Verbindung mit dem Präparat Zinbryta (Wirkstoff Daclizumab) informiert.

31.01.2018
DHPC – Zinbryta (DACLIZUMAB beta) Fertigspritze / Fertigpen
Einschränkung der Anwendung aufgrund des Risikos von fulminantem Leberversagen und Anpassung der Arzneimittelinformation

29.01.2018
HPC – Systemisch angewendete Fluorochinolone
Wichtige Anwendungseinschränkungen aufgrund des Sicherheitsprofiles

20.01.2018
DHPC – Ofev® (Nintedanib)
Schwere Leberschäden und die Notwendigkeit einer regelmässigen Überwachung der Leberfunktion

18.01.2018
HPC – Iberogast® Tinktur
Risiko von Leberschädigungen: Anpassung der Arzneimittelinformation

04.01.2018
DHPC – VELCADE® 3.5mg, Lyophilisat
Wichtige sicherheitsrelevante Information

[1] Most of the links are available in German/French only

22.12.2017
DHPC – Eligard® (Leuprorelinacetat)
Medikationsfehler in Zusammenhang mit Flüssigkeitsaustritt aufgrund Überdrehens der Sicherheitsnadel

21.12.2017
DHPC – Fiasp® ultra-fast-acting (Insulin Aspart) und Tresiba® 100E/ml (Insulin Deglutec)
Verwechslungsgefahr des schnell wirkenden Mahlzeiten-Insulins mit dem langwirkenden Basalinsulin

14.12.2017
DHPC – Xofigo® (Radium-223-Dichlorid)
Erhöhtes Todesfall- und Frakturrisiko in einer randomisierten klinischen Studie zu Xofigo in Kombination mit Abirateronacetat und Prednison/Prednisolon

17.11.2017
DHPC – Dantrolen i.v., Injektionslösung
Die Firma Norgine AG informiert über wichtige, die Anwendung von Dantrolen i.v., Injektionslösung betreffende Änderungen.

16.11.2017
DHPC – Buccolam (Midazolam Hydrochlorid)
Wichtige sicherheitsrelevante Information – möglicher Produktemangel

Announcements

23.05.2018
Reclassification of medicinal products: status update
Project to reclassify medicinal products in other dispensing categories in connection with the revision of the Therapeutic Products Act.

20.04.2018
Warning about the dietary supplement Liquid XXX
Dietary supplement with vitamins as liquid concentrate

04.04.2018
New Information sheet on Drug Safety Signals
MU101_20_005e_MB Drug Safety Signals

03.04.2018
Swissmedic has a new Executive Director – new leadership team complete
Raimund Bruhin takes up his post.

20.03.2018
Swissmedic opens the consultation procedure on the amendment of ordinances of the Swiss Agency for Therapeutic Products in connection with the implementation of the Medicrime Convention
Draft consolidation legislation: Agency Council MPLO/Medicrime Ordinance

01.03.2018
19 new psychoactive substances added to Narcotics List
Press release

08.02.2018
Statistics illegally imported medicinal products 2017
In 2017, 1,060 shipments of illegally imported therapeutic products were seized, including medically important medicinal products that are subject to strict prescribing limits.

08.01.2018
Launch of eGov CPP service on 8 January 2018
With immediate effect, e-mail orders will no longer be accepted.

18.12.2017
ICH Meeting in Geneva, Switzerland, 11–16 November 2017
ICH decision on multi-regional clinical trials aims to benefit public health

08.12.2017
Federal Council appoints new member of the Agency Council
The Federal Council has appointed Marie-Denise Schaller to the Agency Council.

07.12.2017
Good Manufacturing Practice (GMP)
Procedure for discrepancies between EU and PIC/S GMP

15.11.2017
The Swiss Federal Council appoints Raimund Bruhin as new Executive Director of Swissmedic
Media release

15.11.2017
New indications - faster access for patients to medicines
Report of the Swiss Federal Council on the postulate 16.4096

13.11.2017
Umteilung von Arzneimitteln in andere Abgabekategorien
Stand der Arbeiten

08.11.2017
New forms for prescription of narcotics by medical professionals
The forms for prescription of narcotics by medical professionals have been amended.

06.11.2017
As of 8 January 2018: product certificates (CPP) to be ordered exclusively via eGov CPP service
The definitive changeover to the eGov CPP

The complete list is available at the following web address www.swissmedic.ch/updates-en