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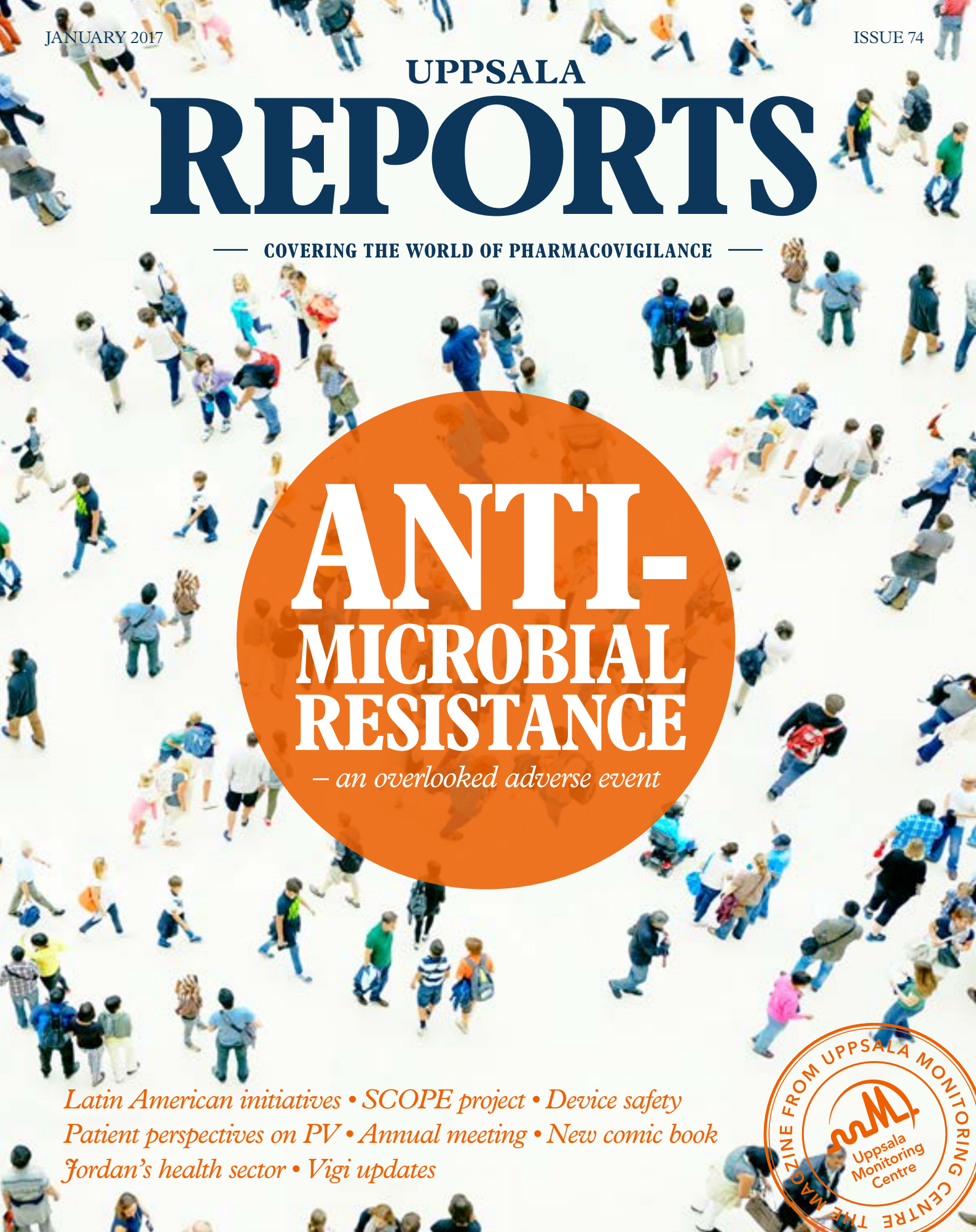
UPPSALA
# REPORTS
COVERING THE WORLD OF PHARMACOVIGILANCE



# ANTI-MICROBIAL RESISTANCE
*– an overlooked adverse event*

*Latin American initiatives • SCOPE project • Device safety*
*Patient perspectives on PV • Annual meeting • New comic book*
*Jordan's health sector • Vigi updates*

THE MAGAZINE FROM UPPSALA MONITORING CENTRE
Uppsala Monitoring Centre

# Director´s message

**WHY AM I DOING WHAT I'M DOING?** This is a question I often ask myself; sometimes more as a rhetorical sigh when I feel frustrated or generally a bit frazzled after a particularly challenging time; other times in a more probing way, seeking to understand what inspires and motivates me, and how I can use that knowledge to find contentment and a sense of achievement in my work.

So what are my main driving forces? Apart from the obvious – doing something useful, helping people, contributing to better knowledge and better practices in my field of work – much of the answer lies in the good meeting. Not meeting as in 'meeting in a conference room with an agenda and with a record produced afterwards to remind us what we talked about and decided' – but the meeting between people, individuals seeking and finding a common ground where they explore thoughts and ideas, listen to each other, try to understand, get new insights, sometimes reach conclusions, and leave with a feeling of fulfilment and connection. Good meetings are based on conversation that is interesting, engaging, challenging, constructive; one that leads forward, solves problems, where knowledge is exchanged, advice given and received, ideas are sounded out, and differences are resolved.

Some people are natural 'minglers' and cherish quick exchanges of pleasantries over a drink, whilst putting meatballs on cocktail sticks into their mouths; I prefer the deeper engagement that – usually – requires more time and less messy environments than those offered at cocktail parties or welcome receptions. But on rare occasions, if the conversation immediately hits the right note, even an introvert can make an instant bond at these kind of events, a connection that is almost tangible. Those moments can be pure magic!

In the good meeting, the conversation is not shallow; it examines and explores, turns arguments inside out and upside down, but it stops short at penetrating psychological depths so profoundly that it causes intolerable distress – however I do think temporary discomfort must be tolerated if a resolution can be achieved, or at least seen as possible – but only if that sentiment is shared!

**"When we stop trying to understand other points of views than our own, winning an argument becomes more important than resolving a problem."**

I like doing practical things and producing tangible results, and I enjoy working on my own – but when I look back at what I consider the happy moments of my life, they almost invariably are the good times I have shared with other people – the good meetings with good conversations. The food we ate, the clothes worn, the ambiance of the room; all that is important – but what I remember afterwards is what we talked about, how I got to know other people a bit better and how the interaction between us influenced and touched me. And how good I felt!

So why am I going on about this? What's so important about people, conversations, the good meeting? Well, I have a feeling that many of the problems in the world today, small and big, have their origin in an inability to connect with other people, understand them and find a way forward, together. When we stop trying to understand other points of views than our own, winning an argument becomes more important than resolving a problem, and dialogue is replaced by dictates. This leads to something far worse than simple misunderstandings: a rejection of the other. That's how conflicts start.

Resolving conflicts, to me, is never a pleasure in itself, but it is a necessity; and when a resolution has been reached I do feel some sense of achievement. But to be really content I'd much rather spend my time involved in good conversations and productive dialogues that solve problems and prevent conflicts from occurring in the first place.

As it takes two to tango – it takes two to talk. Let's engage in open, honest and constructive dialogue wherever and whenever possible. Start the good conversation before it's too late!

Marie Lindquist, Director


Uppsala Monitoring Centre

**UPPSALA REPORTS** *Covering the world of pharmacovigilance*

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SEOUL

# APEC knuckles down on Asia Pacific medicines safety

*To achieve regulatory harmonisation in pharmacovigilance in its member economies, the Asia-Pacific Economic Cooperation (APEC) organised a medicines safety workshop in South Korea in September 2016.*

**THE APEC HARMONIZATION CENTER** (AHC) Pharmacovigilance Workshop and Training Centers of Excellence (CoE) Pilot took place in Seoul, South Korea, in early September 2016. These events were arranged as part of the on-going activities of the APEC Regulatory Harmonization Steering Committee Roadmap to promote regulatory convergence in pharmacovigilance in the APEC economies by 2020.

APEC consists of 21 economies located around the Pacific Rim, of which 18 – all but Papua New Guinea, Hong Kong, and Taiwan – are full members of the WHO Programme for International Drug Monitoring.

At the Seoul gathering, the APEC Harmonization Center held a workshop, while the Korea Institute of Drug Safety and Risk Management (KIDS) hosted the three-day CoE Pilot programme. This workshop was organised as a part of the AHC's 'Roadmap to Promote Regulatory Convergence on Pharmacovigilance and Medical Device Vigilance'. Similar workshops have been organised in 2012, 2013, and 2015.

This year, the workshop included 12 speakers and panellists from a variety of countries and organisations, including the US Food and Drug Administration, the Ministry of Food and Drug Safety (MFDS) in Korea, national pharmacovigilance centres (NCs) in the APEC region, as well as WHO, UMC, and the Dutch pharmacovigilance centre Lareb. It was attended by approximately 200 people, largely representing Korean professionals working within the industry, MFDS, and KIDS. Over the course of three sessions, there were presentations on pharmacovigilance activities within and beyond the APEC region, the collection and reporting of adverse events, and approaches to benefit–risk assessment.

The CoE Pilot training was attended by approximately 60 persons, both regulators and pharmacovigilance experts from countries within the APEC region: Taiwan, Japan, Malaysia, the United States, Singapore, Indonesia, Chile, Thailand, Peru, Philippines, and the Republic of Korea (MFDS, KIDS, AHC). Each day of the training course was composed of morning lectures followed by afternoon small-group sessions, which allowed for cooperative work on the lecture material, as well as providing opportunities for sharing information on how different NCs function and how they deal with safety concerns.

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Looking out over downtown Seoul and the Han River.

Photo: Shutterstock





# Reporting adverse events in published and unpublished studies

**The recent article "Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review" aims to quantify the under-reporting of adverse events (AEs) in published medical literature, compared with unpublished sources.**

The article, published in PLOS Medicine and written by Su Golder, Yoon K. Loke, Kath Wright, and Gill Norman, reviewed 28 studies that provided a comparison of information on AEs according to whether the study was published or unpublished.

The researchers found that fewer published studies reported information on AEs compared with unpublished studies; that both a lower number of AEs and a narrower range of named AEs are reported in published studies compared to unpublished studies; and that the inclusion of unpublished data in meta-analyses leads to more precise conclusions on harms.

The authors' assessment was that there is a substantial amount of unpublished data on AEs which may be "hidden" from health-care providers and patients in the form of unpublished data. They suggest that it is not possible to have a complete understanding of the safety profile of an intervention at the time therapeutic decisions are made by physicians and patients.

An important limitation of the signal detection work that we do at UMC is the lack of "denominator data" when identifying potential safety concerns from spontaneous data. In other words, we are unable to estimate how frequently a specific adverse event occurs when it arises in the post-marketing period as we do not know how many people have taken the drug in question. It would be very interesting to investigate if those signals identified in early post-marketing use have been previously observed in clinical trials but not reported.

There is a growing movement calling for full disclosure and unrestricted access to clinical trial data, as exemplified in campaigns such as AllTrials. Given the potential for unpublished data to be an important source of information on harm from medicines, UMC fully supports the authors' call for a new policy and action to make adverse event data readily accessible to the public.

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READ MORE:

Golder, S., et al, Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review, PLOS Medicine, 2016.

# New educational offering on the epidemiology of vaccine safety at ICPE

**Vaccines are key tools for global public health. Increasingly, pharmacoepidemiological studies are providing the critical evidence needed for risk-benefit assessment to inform immunisation policy.**

This is true both for mature immunisation programmes with successful control and elimination of the targeted vaccine-preventable diseases (VPD), as well as for low- and middle-income countries (LMIC) where innovative vaccines against challenging diseases such as HIV/AIDS, Dengue, Ebola, malaria, etc. are under development.

The annual International Conference of Pharmacoepidemiology (ICPE) has had a vaccine-specific session for more than 10 years, and a Vaccine Special Interest Group (VAXSIG) was formed in 2014. One of the goals of the VAXSIG is to offer educational activities together with the ISPE Education Committee on vaccine-related epidemiology. The VAXSIG pre-conference course on vaccine safety was offered for the second time at the 31st ICPE in Dublin in August 2016.

This beginner-to-intermediate level half-day course aims to establish an understanding of some of the ways in which vaccine safety is monitored post-licensing, including passive surveillance methods, common observational vaccine-safety study designs and methods, active vaccine-safety surveillance using sequential analysis, and how to investigate signals that arise from active surveillance.

The faculty of this year's course was a mixture of experts from the United States, representing government, academia, and industry. The five topics covered were introduction to vaccine safety and policy overview by Dr Robert Chen of the US Centers for Disease Control and Prevention (CDC); passive vaccine-safety surveillance in practice by Dr Steven Bailey from Pfizer; common observational vaccine study designs and methods by Dr Patricia Saddier from Merck; near real-time surveillance methodology by Dr Martin Kuldorff from Harvard University; and active vaccine-safety surveillance in practice by Dr Katherine Yi, also from Harvard. The course was directed by Dr Syed Rizwanuddin Ahmad, currently a pharmacovigilance consultant and a former safety reviewer at the U.S. Food and Drug Administration (US-FDA).

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VIGIBASE

## VigiBase: Embracing the new & strengthening the established

**In less than a year, the number of individual case safety reports (ICSRs) in VigiBase, the WHO global ICSRs database, has increased from 12 million to over 14 million reports.**

Within the scope of drug safety surveillance, collecting ICSRs is a fundamental precursor to detecting signals of adverse drug reactions (ADRs). Countries who are members of the WHO Programme for International Drug Monitoring (WHO PIDM) are always strongly encouraged to share their reports with VigiBase.

There are many aspects that play a role in the quantity and frequency of reports submitted by each member country. One aspect could be the global change in the culture of ADR reporting, as pharmacovigilance gains popularity and recognition among healthcare professionals and patients. Another aspect could be the resolving of a technical obstacle in the ICSRs submission process, which can result in a surge of reports received by VigiBase. The increase could even be due to the growing number of countries participating in the WHO PIDM, this following the addition of three new countries in 2016, bringing the total to 125 full members.

Nevertheless, as we welcome and introduce the newest member countries to UMC and VigiBase, it is important that the pre-existing relationships with other member countries are strengthened and maintained. One of the key elements contributing to the strengthening of these relationships is the diverse language skills available at UMC; the recent addition of Arabic, French and Portuguese speakers on the UMC staff has enabled easier communication with the national centres using these official languages. Subsequently, UMC has noticed a re-energizing at these national centres resulting in an increase in ICSRs sent to VigiBase.

It is thanks to the combined efforts all member countries that this positive trend has come about. UMC strongly advocates for the importance of ICSR sharing because that is what makes all the difference in global drug safety.

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Photo: Shutterstock

VIGIFLOW

## Enhanced VigiFlow to be rolled out in 2017

**VigiFlow will be enhanced with direct reporting interfaces for healthcare professionals, public health programmes, patients, and the pharmaceutical industry. The improvements to the VigiFlow system are to support user needs, update standards, and reflect new legislation.**

The improved VigiFlow will:

- Be compliant with upgraded international standards
- Better support data entry of adverse drug reaction and AEFI reports to VigiFlow
- Support the recording of the results of additional causality assessment methods
- Support direct reporting from healthcare professionals, public health programmes, patients, and pharmaceutical industry

To be compliant with international standards and to utilise the enhanced functionalities in VigiFlow, MedDRA is required as the medical terminology. Conversion of WHO-ART and ICD to MedDRA is necessary, and to facilitate this process Uppsala Monitoring Centre will provide mapping suggestions from WHO-ART and ICD terms to MedDRA terms; a manual review will then be required by each national pharmacovigilance centre (NC). Some of the entries from ICD might not have a corresponding term in MedDRA, which may result in manual re-assessment of the coding.

The enhanced VigiFlow will be released during 2017. UMC will contact each NC to decide a roll-out schedule for their country. The goal is to have all NCs using the enhanced VigiFlow by the end of 2018.

UMC has engaged a reference group consisting of current VigiFlow users who will be asked to provide input, for example on how to optimise the user interface.

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# SCOPE shares insights into European Union pharmacovigilance practices

*Representatives from 20 EU countries assembled in the United Kingdom in October to attend training sessions on adverse drug reaction reports and different methods for collecting them.*

**THE STRENGTHENING** Collaborations to Operate Pharmacovigilance in Europe (SCOPE) Joint Action project has now been running for three years, and the core activities are nearing completion. SCOPE recently held a number of training sessions to share the findings of the past years' work with the pharmacovigilance network, focused on information gathering and analysis of how EU member states conduct pharmacovigilance activities and what good practice looks like.

SCOPE has project teams concentrated on five aspects of pharmacovigilance activities: adverse drug reaction (ADR) reporting, signal management, risk communication, quality management systems, and lifecycle pharmacovigilance.

The project team focusing on adverse drug reaction (ADR) reporting, led by Halmed – the medicines agency in Croatia –held a two-day training session in London on October 2016. It was attended by 70 pharmacovigilance staff from 20 countries. Topics covered included telephone reporting; web-based reporting; how to carry out comparisons of data from different reporter groups; medication error reports; additional monitoring; duplicate detection; measuring and auditing quality of reports; and how to effectively raise awareness of ADR reporting systems through campaigns.

Dr Júlia Pallós, head of Biomedical Division and Pharmacovigilance and a PRAC delegate for the National Institute of Pharmacy in Hungary, said: "The scale of presented subjects and discussion was very large, covering both methodological and practical aspects of ADR reporting. The workshops connected to each item gave further benefit to the audience, which consisted of mainly pharmacovigilance assessors."

The participants were taken through the different methods of ADR reporting, with a particular focus on telephone reporting and how to deal with difficult calls, with practical examples being provided. They also heard how SCOPE has developed a web-based form that is E2B compliant and available for member states to adopt.

The presenters from the national ADR centres in Croatia, UK, Romania, and Lareb in the Netherlands were joined by Sieta de Vries, a postdoctoral researcher from the University of Groningen, who spoke about ADR reporting in the context of the opinions and preferences of patients.

"For me as a researcher, it was very useful to hear about the current practices and experiences of national centres in dealing with suspected ADR reports," Sieta de Vries said. "To further improve reporting by patients, it is important to increase awareness among patients about how they can report ADRs to the national centres and to provide patients with information about what happens with their reports."

This was complimented by François Houÿez from the patient organisation Rare Diseases Europe (EURORDIS), who provided further information on patients' needs when reporting side effects.

The audience were also taken through the stages of planning, running, and evaluating ADR awareness campaigns. SCOPE has reviewed a number of campaigns run at a national level, as well as the materials and methods used. This helped in the development of a guidance document on how ADR centres can adopt the methods for increasing reporting levels in their countries.

The presenters explained that the training being delivered is derived from a series of "Best Practice" guidance documents that will soon be available on the SCOPE website. There will also be e-learning modules for National Competent Authority (NCA) staff and an e-learning package for healthcare professionals.

In addition, there are a series of animated or interactive posters that were used in an EU-wide social media campaign in November 2016 to raise awareness about national ADR reporting systems. The idea was that each NCA that joined the campaign should use Facebook, Twitter, and other social media platforms to inform people about the importance of reporting, and point them towards their national ADR system.


One of the graphics used in SCOPEs EU-wide social media campaign.

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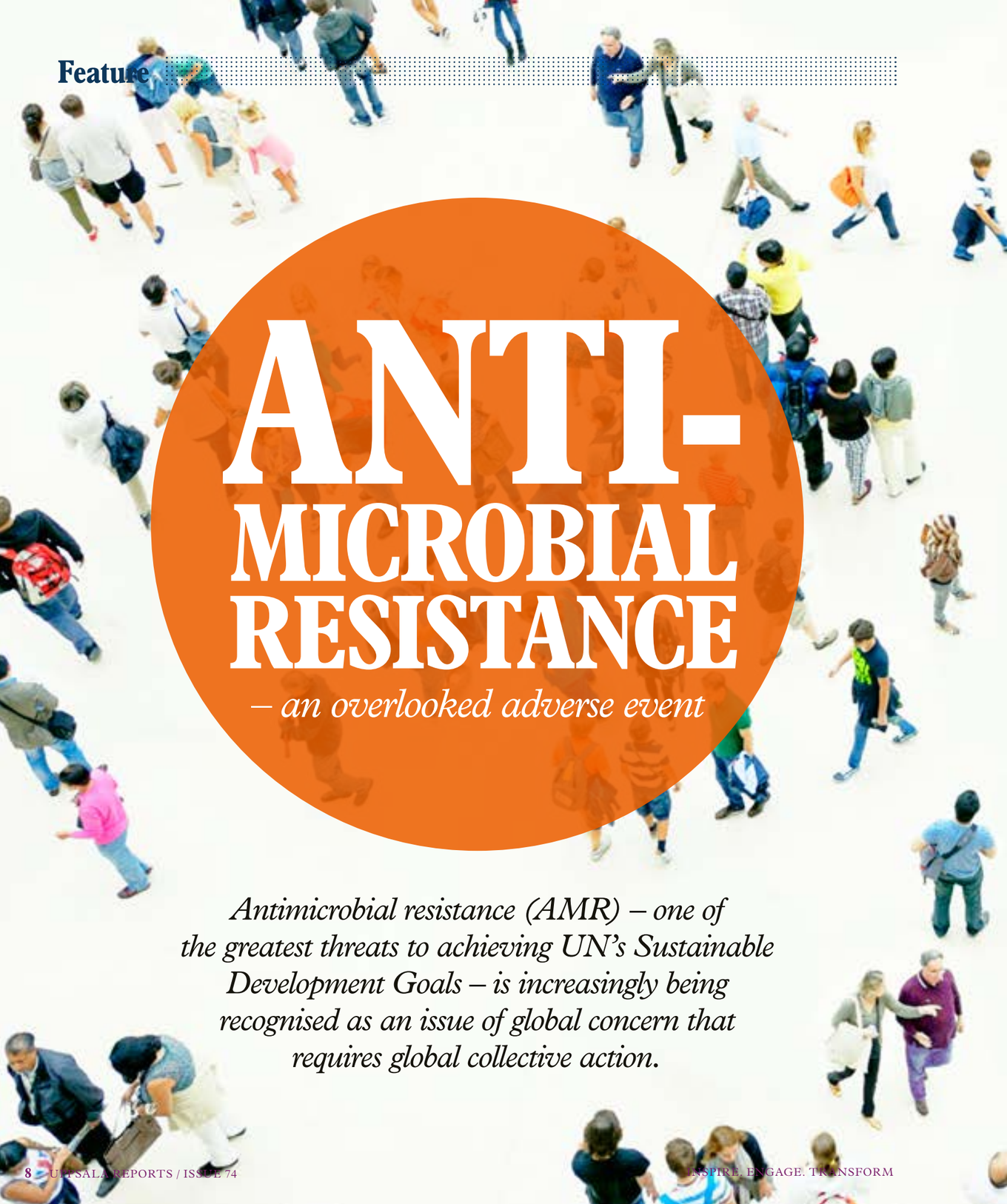

# ANTI-MICROBIAL RESISTANCE

*– an overlooked adverse event*

*Antimicrobial resistance (AMR) – one of the greatest threats to achieving UN's Sustainable Development Goals – is increasingly being recognised as an issue of global concern that requires global collective action.*





INSPIRE. ENGAGE. TRANSFORM



**IF AMR REMAINS UNCHECKED,** the progress achieved by modern medicine in the past 70 years is at serious risk of coming undone. Already today more than half a million deaths annually are attributable to antimicrobial resistance – a number projected to rise to 10 million in 2050 if no action is taken.

Solutions to contain this issue need to reflect the broad ecological nature of AMR, which require a multi-sectorial response, including management of the medicines' pathway from the manufacturing facility to the patient's bedside. Assuring quality, safety, and effectiveness of antibiotics need to go hand-in-hand with data generation on antibiotic use, resistance levels, and patients' access to effective antibiotics. All of this is needed to ensure the highest possible attainable health standards for everyone, and to inform policymakers on which interventions to prioritise in order to better manage AMR. As more data is generated to reveal the magnitude of the problem, it shows that the post-antibiotic era may already have begun.

Every year, 214,000 newborn sepsis deaths are estimated to be directly attributable to bacteria that are resistant to available antibiotics. That is roughly one third of all neonatal sepsis deaths. In the last years, antibiotic resistance has started to compromise the effectiveness of carbapenems – a last-line class of antibiotics used against serious bacterial infections. According to a study from the Southeast Asian region, more than 75% of Acinetobacter isolates, 30% of Klebsiella isolates, and 10% of E. coli isolates displayed resistance to carbapenems. Of particular concern is the increasing prevalence of carbapenem-resistant Enterobacteriaceae (CRE), as mortality rates in patients with CRE infections are high.

Another study done in health facilities in the African region detected 100% resistance to ampicillin in Klebsiella sepsis isolates. High-income countries likewise are being affected, as exemplified by at least 23,000 people dying each year as a direct result of infections caused by bacteria that are resistant to antibiotics solely in the United States.

## CROSS-CUTTING NATURE OF AMR NEEDS BROADER SET OF ACTORS

AMR has been neglected for many years, but it has finally begun to attract the necessary attention by the general public and among decision makers. AMR reaches beyond health and healthcare and is equally a serious concern in agriculture, animal health, and for the environment. This cross-cutting nature of the issue means that it has direct consequences for our social and economic development.

In 2015, countries adopted the Global Action Plan on Antimicrobial Resistance at the World Health Assembly, as a blueprint and guideline for the development and implementation of National Action Plans on Antimicrobial Resistance. Recognition of the threat AMR poses to the successful fulfilment of the Sustainable Development Goals propelled the topic to the level of Heads of States at the United Nations General Assembly in September 2016. Following HIV/AIDS, non-communicable diseases, and Ebola, AMR is only the fourth health issue to ever be brought up at the General Assembly as a matter of urgent consideration. The Political Declaration that all UN Member States subsequently adopted calls for coordinated, global action and includes a proposal to establish an ad hoc inter-agency coordination group.

**"Already today more than half a million deaths annually are attributable to anti-microbial resistance – a number projected to rise to 10 million in 2050 if no action is taken."**

The combination of the cross-cutting nature of AMR and recent political developments underline the need to involve actors that previously haven't been directly engaged with the topic. The increasing political and technical attractiveness of AMR can be helpful for this broader engagement, but that may not be enough. Means of implementation to turn words into action are essential. A few AMR-specific initiatives have been announced, such as the Fleming Fund set up by the UK government, but none are yet in operation.

## ENSURING SUSTAINABLE ACCESS TO EFFECTIVE ANTIBIOTICS

Since 1987, no new class of antibiotics has been discovered. Lack of profitability and major scientific bottlenecks has meant that pharmaceutical companies have withdrawn in big numbers from the anti-infectives research and development (R&D) field. Moving away from the current patent-based innovation model and designing incentives and investment strategies that can help overcome the scientific and financial bottlenecks is urgently needed, but is currently subject of intense debate by key stakeholders.

New approaches are needed not only in R&D, but also in the way we manage antibiotics. Environmental pollution from antibiotic production sites, substandard quality of antibiotics, and unnecessary use ➤

**"As more data is generated to reveal the magnitude of the problem, it shows that the post-antibiotic era may already have begun."**

in human medicine and livestock production are just some of the drivers of AMR, which needs to be addressed. Antibiotic stewardship measures need to be considered and developed at every step of the antibiotic lifecycle – from development, to production, to use. Such measures need however to be balanced carefully against the need to ensure universal access to effective antibiotics for all in need. Some populations still haven't even entered the antibiotic era. It is estimated that half of the one million deaths in children under 5 years of age from pneumonia every year could have been averted had they had access to the necessary antibiotics.

Within health systems, antimicrobial stewardship programmes aiming to minimise unnecessary use of antibiotics and limit the spread of resistant bacteria need to be anchored within an integrated strategy for drug safety monitoring. Such programmes include training of doctors, pharmacists, and others handling antibiotics to do the necessary benefit–risk assessment, as well as to use standard treatment guidelines to decrease irrational use of antibiotics.

Likewise, data generation on AMR on resistance levels and antibiotic use, but also the availability of antibiotics, will require context-specific new ways of thinking to fill existing significant knowledge gaps. In addition, increasing in-country technical expertise is crucial – particularly in resource-poor settings – to conduct pilot studies to inform countries' situation analyses.

### THE ROLE OF PHARMACOVIGILANCE IN AMR MANAGEMENT

Disproportionally greater reporting on antimicrobial treatment failure can be an indication of two major public health issues: presence of antimicrobial resistance and/or medicines of poor quality. The complexity emerges with the latter being a direct driver of the former. Detection of observed-to-expected ratios of reported clusters of adverse events can be an enabling factor in identification of resistance spread patterns in the respective area.

Use of poor quality medicines containing sub-therapeutic doses of the active pharmaceutical ingredient can express itself clinically with expected antipyretic effect while prolonging the illness period. Such medicines often fly under the radar of the pharmacovigilance reporting system while driving bacterial resistance. Pattern-interpreting algorithm analysis therefore needs to carefully account for antimicrobials of poor quality that can contribute to statistical bias.

This and other approaches in data generation can help bridge the knowledge gap in antimicrobial surveillance. Pharmacovigilance tools can support the WHO's efforts to strengthen the evidence base through enhanced global surveillance and research coordinated via the recently established Global AMR Surveillance System. Pharmacovigilance systems in all high-income countries and in many low- and middle income countries can directly assist and inform both policies and medicines regulatory processes when developing a National Action Plan on AMR.

Pharmacovigilance data collection and regulatory strengthening therefore has a crucial role to play to catalyse the urgently needed systemic and cultural change in how we can manage and use antibiotics to ensure their effectiveness and longevity for generations to come.


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**ReAct - Action on Antibiotic Resistance** is an independent global network for concerted action on antibiotic resistance. They aim for profound change in awareness and action to manage the interacting social, political, ecological and technical forces that drive the rising rate of resistant human and animal infection and the rapid spread of resistance within and between communities and countries. Their vision is a world free from fear of untreatable infections.

www.reactgroup.org





# Harmonising global sharing of patient safety data

*The "Simplified E2B Guide for Primary Reporters" aims to overcome some of the barriers that health authorities may face in submitting adverse drug reaction reports to the global database VigiBase.*

**ONE MIGHT THINK THAT** under-reporting from health authorities, i.e. national centres (NCs), to VigiBase, the WHO global individual case safety reports (ICSRs) database, is due to a lack of willingness to share patient safety data globally. It is quite the opposite. NCs are striving to add their national safety data to VigiBase, to boost the value of global pharmacovigilance data. The challenges for NCs are how to easily and efficiently collect national patient safety data, and ultimately how to allow for an easy and efficient sharing of that data. Electronic data captured from sources that utilise existing standards might be a solution. Standards are, however, often perceived to be complex – as we will see they don't have to be.

In most countries, paper-based reporting is still the core method for reporting suspected adverse drug reactions (ADRs) to medicines.

However, more sophisticated and electronically developed reporting solutions (e.g. mobile apps and online reporting) are rapidly evolving. No matter how sophisticated the collection process is, if it is not harmonised with global standards available for pharmacovigilance information, failure to share data globally will remain the harsh reality.

The document "Simplified E2B Guide for Primary Reporters" can help any electronic reporting solution to create and transfer safety data in a harmonised way, using the international ICH E2B standard.

"The [guide] is a very comprehensive and focused document on the main concepts of E2B R2," Stéphanie Bodin-Pärssinen said after reviewing the document. Bodin-Pärssinen, director of the QPPV office at UCB Biopharma SPRL. Quality Assurance and one of the partners in the WEB-RADR project, continued: "The xml structure, codelists, formats et cetera are illustrated through graphical representations and very valuable examples."

"This constitutes a fantastic introduction to the ICH E2B R2 standard for IT personal or vendors unfamiliar with pharmacovigilance safety reporting and also for pharma-covigilance staff willing to know more about the technical aspects of the ICSR transmission," she said.

Most NCs are already capable of handling ICSRs according to these standards, either through a vendor, or home-built systems, or through the widely adopted VigiFlow system. The NCs' needs are different and international standards can be utilised in several different ways. There is no one-size-fits-all solution in place, and standards can be introduced step by step, starting with simple primary re-porting scenarios and continuing all the way to full fledged data-exchange workflows with pharma industry.

Taking into account the international dimension of ADR reporting and the need to achieve harmonisation and high quality between all parties involved, ICSRs should be submitted electronically as structured data with the use of controlled vocabularies. In respect of the content and format of electronic ICSRs, all involved parties are encouraged to adhere to internationally agreed ICH-guidelines and standards. To interpret and implement these comprehensive guidelines and standards is, however, complex and time consuming. The aim of the guide is to make the essential parts of those complex standards reachable for everyone, thereby facilitating international data exchange.

Please feel free to contact UMC in an early planning stage when developing data-capture systems to avoid non-compatibility of data sharing.


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**Advantages with ICH E2B format:**

- Improves the ability to efficiently exchange, process and validate ICSR data:
  - according to predefined business rules
  - proper handling of follow-up reports
- Facilitates sharing of pharmacovigilance information to organisations who need it (i.e. pharmaceutical companies, public health programmes, regional pharmacovigilance centres, WHO Global ICSR database etc.):
  - not language dependent, thanks to the usage of codes and lexicon tables for most fields
  - may also include verbatim text as used by the primary reporter or an accurate translation of it
- Decreases lagtime from occurrence of a medicine-related adverse event
- Facilitates aggregation of safety data for analysis
- Allows minimising resources required for data (re-)entry activities at NC level

**WHO IS FRANÇOIS HOUŸEZ …**

… director of Treatment Information and Access, and policy advisor at the European Organisation for Rare Diseases (EURORDIS). Mr Houÿez has been working as a patient advocate since the early 1990s. Among other things, he is also involved in the IMI-WEB-RADR project, and is advisor to the SCOPE Joint Action Advisory Group.





# Patient perspectives on pharmacovigilance

*When do **patients** accept more risk than regulators, and what are the communication barriers between healthcare professionals and consumers of medicines? Uppsala Reports sat down with the European patient advocate **François Houÿez** for a Q&A on patients' **concerns** regarding pharmacovigilance.*

**HOW CONCERNED ARE EUROPEAN PATIENTS ABOUT SIDE EFFECTS?**

Safety issues are probably the main concern for patients starting a new treatment. There are patients who differ from the general patient population, who have such a severe disease that the risk they take with the medicine may be less important than the expected benefit, given what happens if their condition is left untreated. But even in this population I think side effects is a main concern.

For example, in 1997 patients who had started an highly active antiretroviral treatment for HIV several years prior discovered in large numbers that they'd undergone body-shape changes and gained weight. It was later called HIV-related lipodystrophy, but when it was first discovered nobody knew what it was. It hadn't been detected in clinical trials, because it takes time before it occurs. And then many patients started to interrupt their treatments even though they knew it was life-saving, because they didn't know what was happening to them. So they made their own benefit–risk assessment; the benefit was to control HIV replication, but the risk was completely unknown because the doctors didn't even know what these body-shape changes were.

So I think that the risk can become the main concern, even with these life-saving medicines. It's a permanent re-evaluation by the patient of their own benefit–risk, depending on how they feel and what condition they have.

**HOW DO THE PRIORITIES OF REGULATORS AND HEALTHCARE PROGRAMMES DIFFER FROM THOSE OF PATIENTS?**

What we've learned from working with regulators and healthcare professionals is that they're not people working in isolation who are indifferent towards what happens to the patient. On the contrary, they're too obsessed by the possible harm to patient, and sometimes there's a risk that a potentially effective medicine is not authorized due to the perception the regulators may have of the side effects. This is why we welcome the efforts by regulators to elicit patient preferences, to consult with more patients, and use techniques where patients themselves weigh the benefit and risk of a new medicine. How patients work through these issues can inform the regulator's actions the day they make a decision.

We did an interesting exercise at the European Medicines Agency (EMA) where we used one of these techniques to say what we thought of an anti-cancer product. The healthcare professionals sat in one room, and patients and consumers in the other room, and both groups did the same exercise. The patients were discussing one of the side effects, which was the risk of sudden death. The cancer in question emerges in a quite old population, and the representatives for the elderly said that this risk isn't really a problem in very old populations; the risk of sudden death is easier to live with than drawn-out agony and a lot of pain. So they graded this adverse drug reaction as very low. In comparison, the healthcare professionals spent the entire exercise discussing sudden death, because for them it was horrible, and they couldn't even finish the exercise because they were still debating the sudden-death risk. This highlights the need to have different opinions to make the best decision. ➤

**"I think that the risk can become the main concern for patients, even with these life-saving medicines."**

Better communications between healthcare professionals and patients is needed.

Photo: Shutterstock

**"If we don't change this cultural dilemma, then the boring package leaflet will never become a document that patients will want to read."**

**IS THERE ENOUGH INFORMATION ABOUT PHARMACOVIGILANCE AND ADVERSE SIDE EFFECTS AVAILABLE TO PATIENTS?**

There is a lot of information, the problem is how to bring it to those who need it, and that's where we need to be very imaginative. There is a lot of information on the EMA website and on the websites of the national competent authorities. There are tools where patients can receive warnings, and some communication campaigns on specific issues. Sometimes there are campaigns that invite people to report adverse drug reactions. But these efforts are usually not continued, the campaign runs only one time and it's not repeated. They need to be repeated again, and again, and again.

We hope that new tools, like for example the WEB-RADR mobile application – where people can sign in and receive information on the medicines they've listed – can establish a two-way communication with regulators where the public can be informed when there is a recall, a new warning, or any new information regarding safety. And this is what we're starting to see with the first users of the mobile app, where only a few people are using the app to report side effects, but all downloaders are using it to receive safety information on the medicines they've listed.

**WHAT ARE THE BARRIERS TO PROVIDING THE PUBLIC WITH BETTER INFORMATION?**

In general, the national competent authorities don't have the necessary expertise in communication and how to target a population. To just post a message on their own website cannot be considered real communication.

I once showed UMC's information music video Take&Tell at workshop for qualified persons for pharmacovigilance (QPPVs). Someone made an interesting comment – she said that: "This video is excellent, it does what it wants to do, it engages the public, and there are many other messages where we need to create such tools. But as soon as we propose easy-to-read material with a nice graphic design that appeals to patients, regulators reject it, because if it looks too nice then it becomes promotional material."

I don't know to which extent this is true, but I've heard and I've seen very nice and well-developed educational material submitted to regulatory authorities and rejected because it was considered "too nice". If we don't change this cultural dilemma, then the boring package leaflet will never become a document that patients will want to read.

**WHAT CAN PATIENTS DO TO CONTRIBUTE TO BETTER MEDICINES SAFETY DATA?**

In the same way that Marketing Authorisation Holders have to have a QPPV, we would like to see a contact person for pharmacovigilance in all patient organisations – someone who's been appointed on request from the regulator. That person should be the one to, for example, receive safety alerts, press releases or copies of the healthcare professional letters – and then be responsible to work with a communications colleague to disseminate the information to others in the organisation. But they should also prepare reports, queries, and research questions to pass on to pharmacovigilance experts, when they've received questions, concerns, reports or analysis of social media results within their group. We think that this could be an interesting way to engage these organisations, officially and with an official recognition. We need to make these interactions more visible to the population, so that others will want to get engaged in pharmacovigilance as well.

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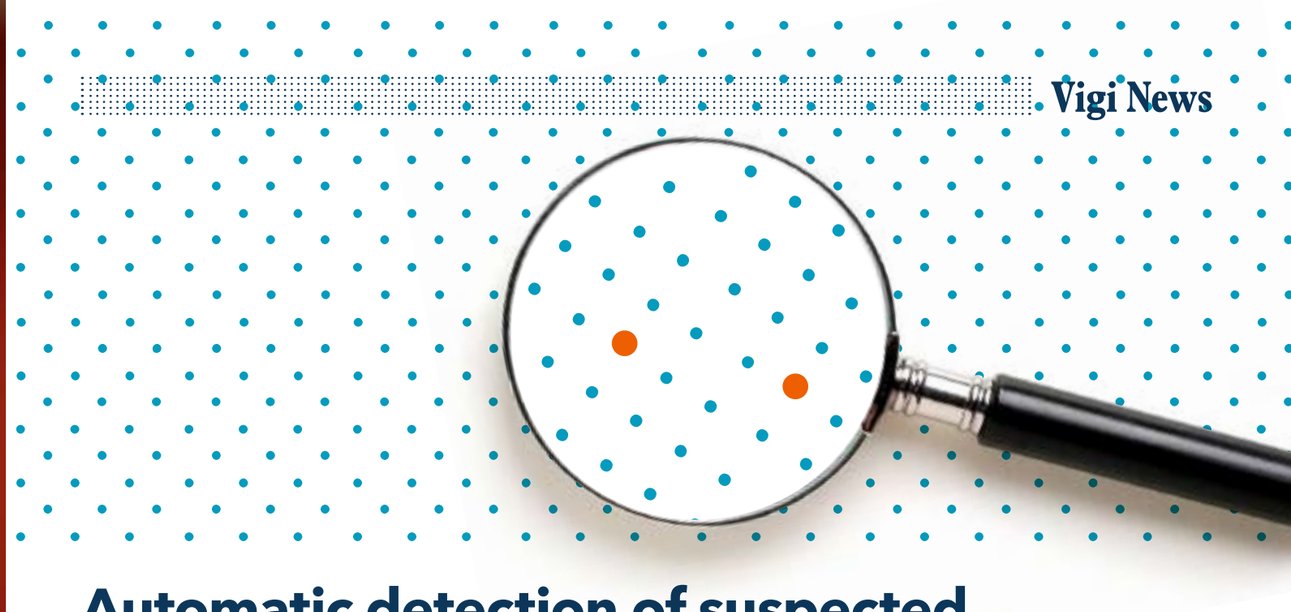

# Automatic detection of suspected duplicates in VigiLyze using vigiMatch

*Duplication of adverse drug reaction reports in VigiBase causes several problems, such as interference with complex computational methods used for signal screening and time wasted on manual work; the new algorithm vigiMatch helps to reduce duplicates.*

**A NEW ALGORITHM** developed by UMC researchers to help in the detection of duplicates in VigiBase is now ready for routine use. vigiMatch will be implemented in VigiLyze in Janaury 2017, and will mean that all reports that are suspected duplicates are hidden by default, and only the reports with the highest vigiGrade completeness score are shown. The suspected duplicates are also excluded from the statistics view and the data mining tab. Reports that have suspected duplicates are indicated by a double arrow in the list of individual case safety reports (ICSRs). In the user settings however, one can select to use the full dataset, which includes suspected duplicates in the statistics and data mining tabs.

With over 14 million reports currently in VigiBase, the WHO global ICSRs database, a manual approach to weeding out duplicates is not feasible. vigiMatch uses a statistical model that scores pairs of reports, taking into account the amount of matching and mismatching information:

- Blank fields are ignored, matches are rewarded, and mismatches are penalised.
- For numerical fields, vigiMatch rewards a close match, although with a lower score.
- The algorithm takes into account how likely it is to get a match by pure chance, so that a match on a very common drug yields a lower score than a match on a more unusual drug. The same principle applies for all other fields.
- Correlations are considered so that if, for example, two drugs are usually reported together, the score is reduced if a report pair matches on those two drugs.

The scores received for each individual field are added together to obtain a total score for the report pair. For a report pair to be automatically flagged as suspected duplicates, the score needs to reach above a certain threshold based on the expected number of duplicates in VigiBase.

There are several reasons why a report could be duplicated. Reports could be sent by multiple caregivers of the same patient as well as by the actual patient. Often the pharmaceutical companies are required to submit a report for any adverse reaction they learn about, and reports often contain drugs from different companies, which can result in many duplicates of a single underlying case. Duplication can also arise due to errors when transferring the reports between different systems and databases. Since reports of the same underlying case can come from multiple different sources, it means that the reports are usually not identical. Differences can arise from typos, variability when coding drugs and adverse reactions, as well as uncertainty in the available case information. This makes it harder to detect if two reports actually describe the same underlying case.

vigiMatch does a good job at identifying possible duplicates; it has even been shown to outperform rule-based duplicate detection. However, reports that are not duplicates but otherwise related (e.g. same patient, different issue) are difficult for the algorithm – and even humans – to handle. It can also miss some duplicated reports.

vigiMatch is an aid to reduce duplicates, but in the end it is up to each national centre to determine which suspected duplicates should be officially merged.

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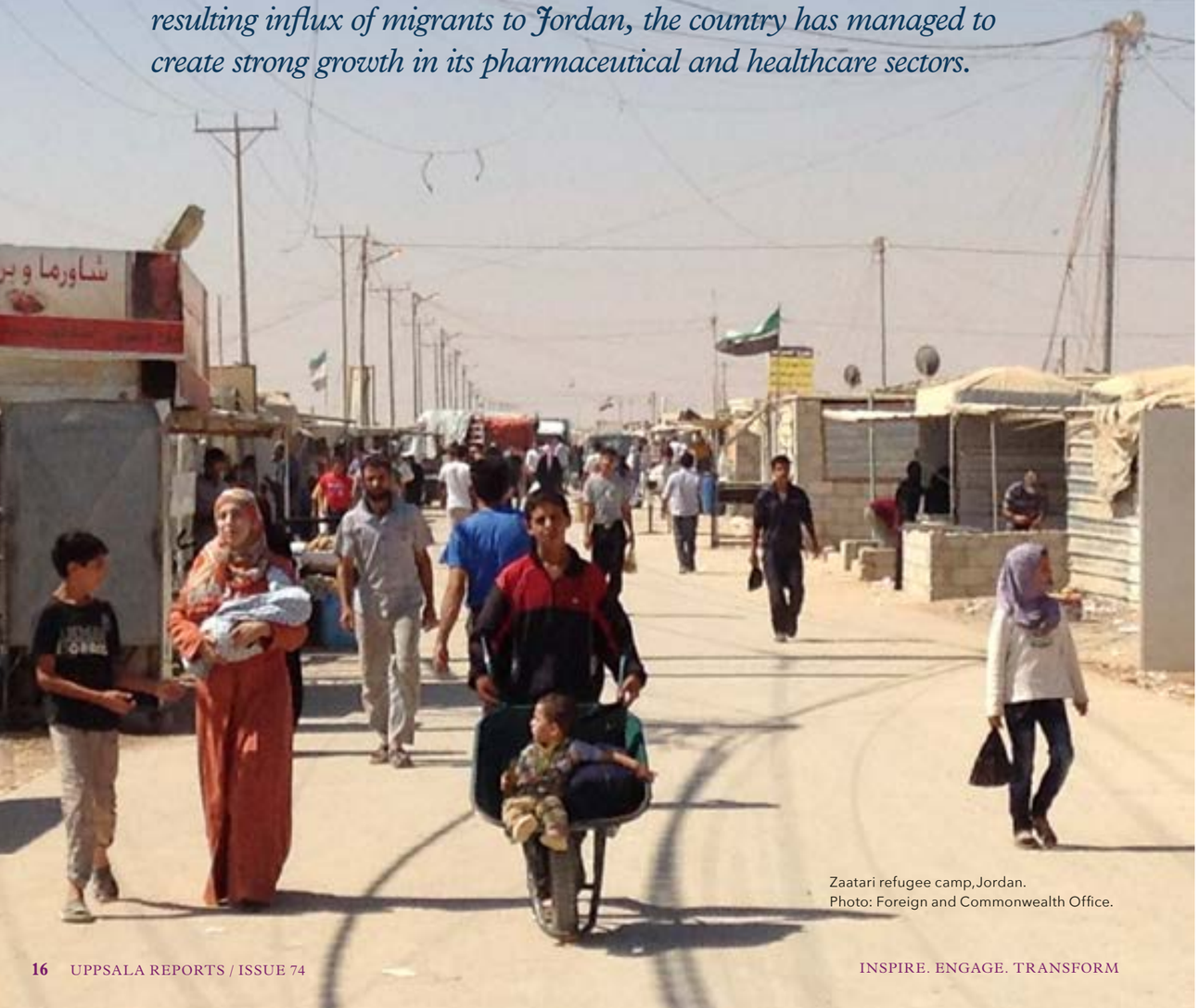
READ MORE: Tregunno, P. M., et al., Performance of Probabilistic Method to Detect Duplicate Individual Case Safety Reports. Drug Safety. 2014.

# Jordan's medical sector grows despite regional instability

*In spite of long-lasting geopolitical unrest in the region and the resulting influx of migrants to Jordan, the country has managed to create strong growth in its pharmaceutical and healthcare sectors.*



Zaatari refugee camp,Jordan.
Photo: Foreign and Commonwealth Office.





**THE FIRST INTERNATIONAL** congress arranged by the Jordan Food and Drug Administration (JFDA) took place in the country's capital Amman in October 2016, covering topics on how to mobilise investments in a medical sector facing complex challenges, and characterising the role of regulatory institutions in the Middle East and North Africa region.

The two-day conference attracted around 600 participants from 27 countries. They shared their perspectives and presented future directions for a pharmaceutical industry and healthcare sector that are complicated by the unstable political situation in the region.

Bordering Syria, Iraq, Israel, the West Bank and Gaza Strip, and Saudi Arabia, Jordan has remained one of the few stable countries among its neighbours. Being located in the midst of a region plagued by conflicts has impacted the country's economy in different ways and has shaped its various industries to adapt to the waves of migration from the West Bank and Gaza Strip, Iraq, and Syria.

Over the last few years, Jordan has coped with these external strains and managed to maintain economic stability despite rising socio-economic tensions and the hosting of a large number of people displaced from neighbouring countries.

**TO COME TO TERMS** with the challenges that political instability and its effect on the economy poses, authorities have undertaken significant adaptations in policies to cope with the current conditions and enhance financial growth, through improving competitiveness and to stimulate good governance. In particular, the pharmaceutical industry has become a strategic sector for investments and with its continued good outlook for growth it has become a key sector in the country's economy.

The unique role of the pharmaceutical industry and the healthcare sector in Jordan and in the region was evident at the opening session of JFDA's 1st International Congress in Amman. The conference highlighted the medical requirements of current and future generations living in Jordan, and the need for an efficient pharmaceutical and healthcare sector. Harmonisation between the neighbouring countries to manage the shift to a more specialised healthcare that focuses on post-conflict care is also needed, as is the ability to adequately respond to changes arising from the political context in the region.

Hayel Obeidat, Director General of Jordan FDA, President of the 1st International Congress of JFDA, speaking during the opening session discussion panel. Photo: JFDA

**THE JORDANIAN PHARMACEUTICAL** industry has expanded rapidly over the past 50 years, and to date there are 16 registered local pharmaceutical companies in the country. The sector has developed into an export-driven industry delivering 81% of production to markets in more than 60 countries at an affordable cost, out of which 90% of the production is delivered to other Arab countries, underlining the need to establish a harmonised pharmaceutical regulatory framework for the industry.

Economically, Jordan has benefitted from being a geographical hub for trade between Europe and the Middle East. The country also has an advantage in its highly educated labour force, which provides the neighbouring Gulf countries with human capital through Jordanian migrant workers. The influx of displaced people settling and working in the country also provides a larger population that could contribute to the domestic work force.

Decades of migration have increased demand on the pharmaceutical sector, and the regional lack of access to medicines and healthcare presents challenges in meeting those demands.

As many of the displaced people from neighbouring countries often come from a middle-income background, the proportion of chronic, non-communicable diseases increases. This also calls for a shift in the type of healthcare that's provided. There is an increased demand for long-term care in areas such as cardiac and hypertensive treatment, diabetes, psychiatric disorders, and war trauma rehabilitation.

**"The pharmaceutical industry has become a strategic sector for investments and with its continued good outlook for growth it has become a key sector in the country's economy."**

A key survival characteristic of the Jordanian pharmaceutical industry and health sector has been to respond quickly to external conditions and having a proactive, agile regulatory and legislative framework to stimulate cooperation and mobilise capital in a region facing novel healthcare needs in a time of political turbulence.

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# The changing faces of device safety

*Many aspects of device regulations are under revision globally. The status of revision implementation varies between regions, but increased expectation for manufacturers to be more proactive than reactive when marketing safe and effective devices remains constant.*

**MANUFACTURERS ARE OBLIGED** to provide evidence of the safety, efficacy and benefit throughout the device lifecycle. This includes data from clinical trials prior to marketing, and establishing Post-Marketing Surveillance (PMS) systems to monitor device performance; data from published literature are required.

At first glance this may appear to be just an increased burden to manufacturers. But proactive literature monitoring for evidence of device performance in the real world is more than just regulatory compliance. Effective data-gathering may help reduce time and costs to market and improve technical design, the likelihood of reimbursement, and overall reputation as a responsible manufacturer. Collectively, this may help gain an edge in this competitive and innovative industry.

Regulation essentially protects the market from ill-designed, inadequate or unsafe devices, and encourages production of good quality products that fulfil a medical need. Real-world data are important because they are created in less restricted environments than in clinical trials, and are gathered from wider patient populations. Real-world data also provide an insight into the performance of a device in the hands of consumers with a range of skills. Demonstrating device performance based on expert opinion is no longer acceptable; it is crucial to provide evidence, some of which is found in the scientific literature.

**GATHERING REAL-WORLD DATA** during the research stage provides a landscape view to help designers identify market gaps and appropriate predicate devices; the latter also determines what regulatory pathway needs to be followed (e.g. with or without predicates).

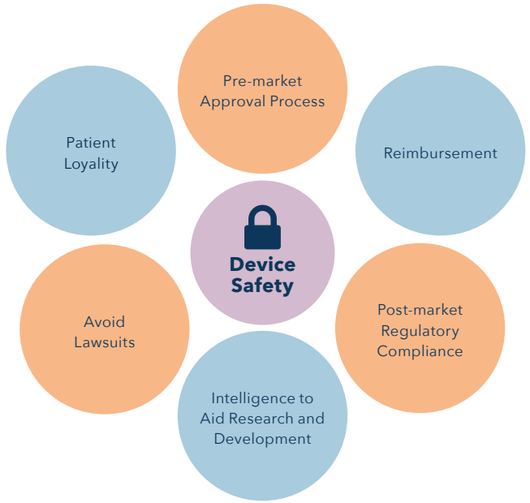
PMS systems require manufacturers to gather evidence for own and similar devices. These data are used to update various regulatory reports including, the technical document, Periodic Safety Update Reports, and can also be used for ongoing signal detection and risk mitigation.

Literature monitoring can provide performance data to help demonstrate device benefit–risk over existing treatments. If positive, the likelihood of market entry is increased. If negative, it will save the time and costs of pursuing a fruitless project. Proving superior benefit will ensure a device remains on the market and enhances reimbursement potential, an important aspect of marketing success.

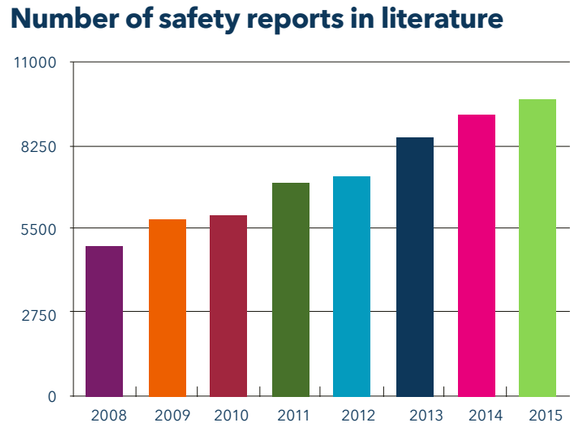
Historically, some medical devices have not performed as expected (e.g. transvaginal mesh and metal-on-metal hip prostheses). These devices were originally considered "not high risk", so the regulations at the time did not require comprehensive clinical evidence of safety prior to release, or strict post-market performance monitoring. Consequently, several similar devices with fault potential were released in relatively rapid succession into a wide patient population. Decades later, some manufacturers still have to budget for million-dollar payouts in lawsuits and litigation fees.

It could be easy to look back and blame, but it is more appropriate to take responsibility and look forward to successful, reliable medical devices that will enhance the lives of many. Taking responsibility includes establishing robust, auditable PMS systems; this means searching public literature, which is a huge task if the processes are unfamiliar. Searches need to be broad enough not to miss pertinent information; this introduces an exaggerated triaging task. Identified, relevant articles require globally recognised, uniform tagging to allow appropriate, efficient analyses of the data.

If devices follow the same trend as drugs, it is highly likely that the amount of publically reported device safety data will increase over the next few years. According to the AdisInsight Safety database, the number of drug safety reports published has doubled between 2008 and 2015.




The wide-ranging benefits of literature monitoring for device safety




Based on information taken from the AdisInsight Database adisinsight.springer.com

**CONSUMER EXPECTATIONS ARE ALSO INCREASING.** They demand value; commonly, a low-cost or a discounted product. As a result, manufacturers outsource and offshore production, and encounter a greater number of authorities to gather data for. Alternatively, device designers may "de-innovate" a product (i.e. produce a subsequent more basically designed device with the functionality required by healthcare professionals and patients, but delivered at a lower cost). Being aware of real-world performance and user experiences for own and competitor devices may assist improvement of design iterations resulting in a device that will satisfy the functional requirements and financial constraints of consumers.

There is no doubt that the revised regulations for medical devices are for the good of the industry, nor that this increased demand for responsibility in proving the benefit clinically and economically of a device will increase the workload of the manufacturer and potentially require additional resource. However, being proactive and sensitive to consumer needs and experiences could lead to opportunities for the release of additional devices, and wider global market penetration. Importantly, it demonstrates responsibility and a willingness to act in the best interest of patient safety, and this can only enhance the reputation of the devices industry as a whole.

**Wendy McNeely**
Product Development Specialist,
Adis Business Intelligence

READ MORE: www.springer.com/gb/adis/the-changing-faces-of-device-safety

Hussain Al Ramimmy, Director of Pharmacovigilance & Drug Information, DGPA&DC Oman. Photo: Oman organiser

# Annual meeting draws pharmacovigilance experts to Oman

*The 39th annual meeting of the WHO Programme for International Drug Monitoring drew around 150 pharmacovigilantes from nearly 60 countries to Oman in 2016.*

**A SPIN OF THE GLOBE,** and the annual meeting touched down again in November 2016; after Brasilia, Rome, Tianjin, and New Delhi, the national pharmacovigilance centre (NC) representatives set their compasses for the ancient Arabian coastal city of Muscat in the Sultanate of Oman. For the first time, the WHO Programme for International Drug Monitoring (WHO PIDM) met on the Arabian Peninsula.

With the Minister of Health of the Sultanate of Oman and other senior dignitaries present, the Director-General of Pharmaceutical Affairs & Drug Control, Dr Mohammed Hamdan Al Rubaie, opened proceedings by setting out his centre's achievements.

In the Eastern Mediterranean region, there are 11 member countries, where Morocco was the first to join in 1992 and Afghanistan the latest in 2016. Oman is a member country since 1995 and has made great progress in strengthening their safety surveillance system in the last few years, for example by transforming their organisational structure, adding resources, arranging training workshops for healthcare professionals, and raising public awareness. Oman is currently contributing the highest number of reports per million inhabitants of all countries in the Eastern Mediterranean region.

**THE ANNUAL NC MEETINGS** provide a unique opportunity to share information, exchange experiences and to learn from each other. Depending on its location, the meeting naturally attracts staff from centres nearby, so this year Arabic countries and those in the Eastern Mediterranean region came out in force – including fresh faces from Libya and Qatar, and old friends from Morocco. At the closing session the Iraqi representative reported to everyone from a productive round-table, where representatives from the regional countries that were present at the meeting had explored potential regional collaboration in patient safety.

While the WHO PIDM meeting invites its members to a face-to-face gathering only once a year, the programme's work continues even when colleagues are far apart. Ideas floated during the few days of the meeting are fleshed out and explored by the WHO Collaborating Centres and individual NCs in the intervening months. Exchanging ideas and comparing day-to-day issues with colleagues from other countries is always a vital formal – and informal – function of the meeting; many of the barriers to improved monitoring and better patient safety are similar all over the world.

**UMC'S HEAD OF GLOBAL SERVICES,** Anki Hagström, gave a presentation on developments in adverse drug reaction reporting and global statistics over the past year. In 2016, the number of individual case safety reports (ICSRs) in VigiBase has climbed to more than 14 million, and the number of full member countries to 125.

Topics which were eagerly discussed last year were treated to further in-depth examination, either with updates from experts leading projects, or in smaller working group settings where common cause can be fashioned for continuing action in the future.

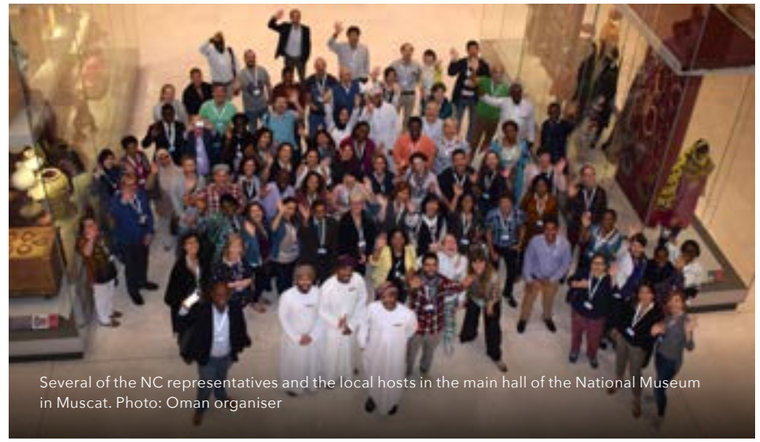
The 39th meeting was organised by the Safety and Vigilance section at WHO, the local NC and the WHO Country Office in Oman, and welcomed over 150 pharmacovigilance staff from nearly 60 countries.

At the close a special tribute was paid to UMC's WHO programme expert Sten Olsson, who attended his last WHO PIDM meeting before his retirement in early 2017; he has attended as a UMC spokesperson all but once since the first meeting in 1978.

In 2017 the meeting will land a few degrees south in Uganda. Until then all the project work – as well as the routine work – will continue behind the scenes at NCs worldwide, at WHO headquarters in Geneva, at UMC in Uppsala, and at the other WHO Collaborating Centres in pharmacovigilance.

**Global Services**
vigibase@who-umc.org





Several of the NC representatives and the local hosts in the main hall of the National Museum in Muscat. Photo: Oman organiser

Dr Manal Younus, head of the NC in Iraq, presents a poster. Photo: Oman organiser

# LATIN AMERICA *in* FOCUS

*Uppsala Monitoring Centre embarked on a* ***multi-destination tour*** *to Latin America in September 2016, visiting the FIP congress in* ***Argentina,*** *the ISoP–UMC training course in* ***Peru,*** *and the International Pharmacovigilance Meeting of the Americas in* ***Panama.*** *The team also visited national pharmacovigilance centres (NCs) of the WHO Programme for International Drug Monitoring (WHO PIDM) and other institutions in these countries, as well as in* ***Costa Rica, Guyana, and Uruguay.***





SAN JOSÉ

## Costa Rica's "Good pharmacovigilance practice" regulation

UMC's Elki Sollenbring with pharmacovigilance training course participants in San José.

**THE "GOOD PHARMACOVIGILANCE PRACTICE"** regulation was announced in January 2016 in Costa Rica and sets out the functions and responsibilities that must be fulfilled by each of the stakeholders in the national pharmacovigilance system. Despite the short time since the release it has garnered great interest and attracted involvement, especially from pharma companies. The rate of individual case safety reports (ICSR) sent by different stakeholders has increased. Training and dissemination has been performed at several sites, including the Medical Sciences School (UCIMED) and the University of Costa Rica (UCR).

In September 2016, UMC's Elki Sollenbring was invited to talk about the WHO PIDM during the launch of the new regulation, and to speak at a pharmacovigilance training course for healthcare professionals.

**Xiomara Vega**
Head, National Pharmacovigilance Centre Costa Rica

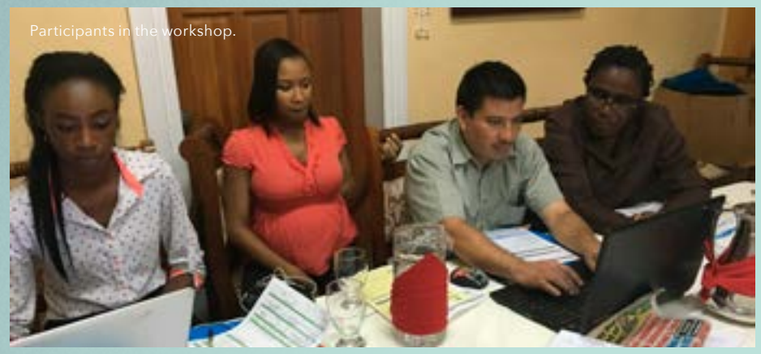
MONTEVIDEO

## Reviewing reporting methods in Uruguay

**UMC VISITED THE MINISTRY OF HEALTH** in Uruguay in September 2016, to attend a meeting focusing on the WHO PIDM and Take&Tell. The visit also focused on the national centre unit's pharmacovigilance work in the country, and its challenges and objectives. The possibility to better utilise VigiFlow and the use of eReporting were explored during the visit. These tools would allow the fulfilment of two fundamental objectives: the reporting to the centre following the current regulations, and the transfer of reports on to VigiBase, so that all countries in the WHO PIDM can access this critical information.

**Salome Fernandez**
Head, National Pharmacovigilance Centre Uruguay

UMC's Elki Sollenbring with Salome Fernandez and Maria Viera from the NC in Montevideo.


Participants in the workshop.

GEORGETOWN

# Guyana aims join the WHO PIDM in 2017

**GUYANA'S NATIONAL** regulatory authority – the Government Analyst Food and Drug Department (GA-FDD) – decided to establish a national pharmacovigilance centre in 2013. To support this process, a training workshop was held in September 2016.

The workshop was coordinated by the Pan-American Health Organization (PAHO) in Guyana and the GA-FDD, with support from the Ministry of Public Health (MoPH), and involved staff members of the GA-FDD and other stakeholders. The workshop focused on increasing healthcare professionals' awareness of pharmacovigilance, and on how to run an NC. The facilitators – Dr Shanthi Pal from WHO, Dr Gurumurthy Parthasarathi from JSS University in India, Ms Elki Sollenbring from UMC, and Ms Leticia Megias Lastra from WHO – introduced the audience to the subject.

GA-FDD staff were also taken through the rigours of establishing, operating, and maintaining an NC. According to the plan of action to establish the centre, which was prepared during the workshop, the centre should start operating by April 2017 and join the WHO PIDM – at least on the level of associate member – during the year.

With the establishment of Guyana's centre it is hoped that reports on adverse drug reactions will be made on a regular basis beginning with a pilot project in two hospitals, and that this information will be used to develop greater and more effective regulatory oversight on prescription drugs in the country.

The process of establishing and maintaining an effective NC will be an ongoing exercise, so the Guyana centre foresees a future need to gain and enjoy the invaluable support of various stakeholders. Moreover, the need for capacity building and ongoing training of GA-FDD staff cannot be overstated. Employing a quality management reporting system to run the centre is important, as is the need to ensure that a monitoring and evaluation system to measure the impact of the centre's activities over time is created.

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BUENOS AIRES

# World congress in Argentina

**STEN OLSSON,** UMC's WHO programme expert, gave a presentation at the 76th FIP World Congress of Pharmacy and Pharmaceutical Sciences in Buenos Aires in late August 2016. Mr Olsson's talk opened a half-day session on the role pharmacovigilance may play in improving and better understanding patient adherence.

**WHILE IN BUENOS AIRES,** the UMC team also visited the Argentinian NC, where the delegation had in-depth discussions with the local pharmacovigilance experts about challenges and solutions to issues that they may face in their work.


UMC staff together with the Argentinian NC team. Photo: UMC





LIMA

# The first ISoP–UMC course in Latin America

**THE 3RD** ISoP–UMC Pharmacovigilance Training course took place in Lima in early September. It was not only the first time an ISoP–UMC course was organised in Latin America, but also the first time UMC was involved in such a course in this part of the world. 69 participants from 11 countries in the region took part in the three-day course, which focused particularly on casualty assessment, signal detection, and risk communication. The majority of the presentations were delivered in Spanish – with real-time translation services provided to those who needed it – and having access to several Spanish speaking lecturers and was well appreciated by the attendees.

The participants were representatives from regulatory agencies, the pharma-industry, academia, and hospitals, and the open learning environment offered a rare opportunity for pharmacovigilance experts across different sectors to come together and exchange ideas and experiences.


The attendees and lecturers at the ISoP course. Photo: UMC

**IN CONNECTION TO** the stay in Peru, UMC also took the opportunity to visit the NC in Lima. The Peruvian centre's efficient use of VigiFlow could be used as a role model for other centres in the region; Their database of roughly 40,000 individual case safety reports is shared in it entirety with the WHO PIDM, through VigiFlow.


UMC's Sten Olsson and Paula Alvarado with ISoP's previous president Prof Hervé Le Louet. Photo: UMC

PANAMA CITY

# Three stops in Panama

**THE JOURNEY TO** Panama in September took the UMC team to several destinations, most notably the three-day International Pharmacovigilance Meeting of the Americas, organised by PAHO. The meeting's first day opened its doors to around 120 participants, both from Panama's regional pharmacovigilance centres and representatives from 14 countries in the Regional Network of Pharmacovigilance Focal Points in the Regulatory Authorities. The second and third day of the meeting was open only for members of the regional network.


UMC's Elki Sollenbring shows NC staff how to use VigiLyze. Photo: UMC

**THE UNIVERSITY OF PANAMA** invited UMC's Elki Sollenbring to give a lecture about the WHO PIDM to over 100 pharmacist students, while the UMC team were in the country. The university is the first in the country to incorporate pharmacovigilance into its curriculum.

**THE UMC DELEGATION** also visited the national centre in Panama City – a relatively young centre that became a full member of the WHO PIDM in 2016, after joining as an associate member in 2005. While there, UMC's Elki Sollenbring and Heloísa Conesa showed the NC team how to use VigiLyze and other important tools provided by UMC.

READ MORE: "The growth of drug safety networks in Latin America", page 26.

**Reporting on the events in Argentina, Peru, and Panama was made by:**


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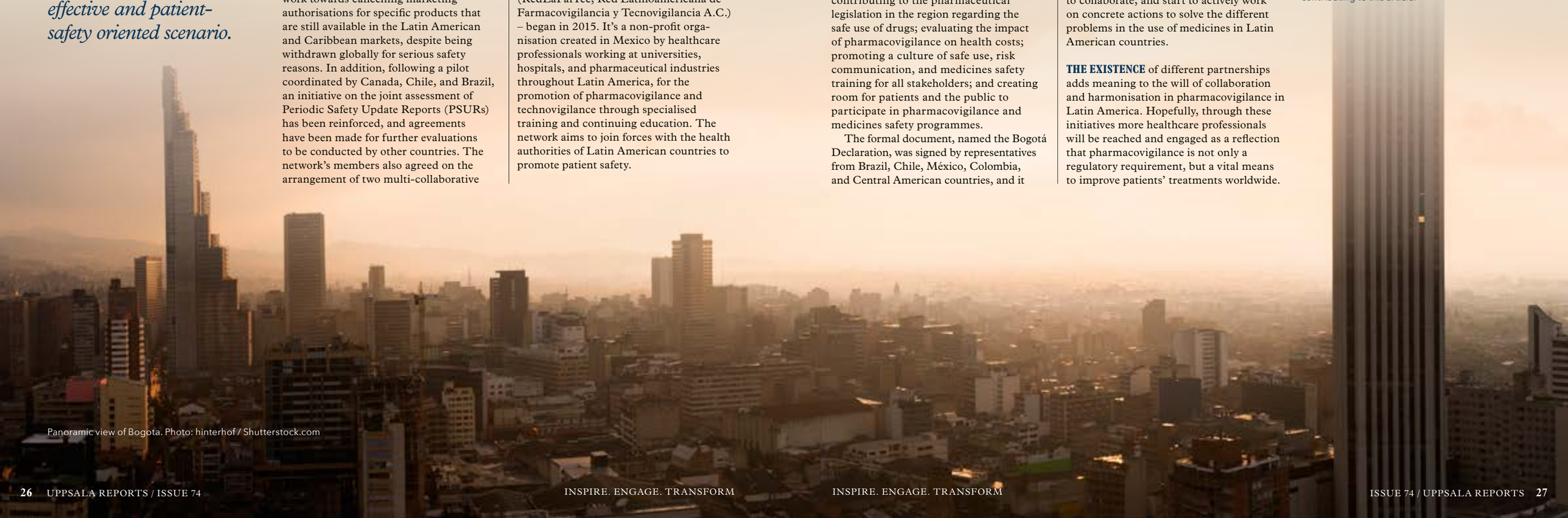
# The growth of drug safety networks in Latin America

*Over the past few years, many initiatives to boost pharmacovigilance and medicines safety communication have been launched in Latin America, in order to exchange experiences and shift to a more effective and patient-safety oriented scenario.*

**SINCE 2012,** the Regional Network of Focal Points in the Regulatory Authorities, moderated by the Pan American Health Organization (PAHO), has worked on the dissemination of safety communications, alerts, and other information generated within and outside the Americas. Additionally, through a permanent communication scheme, monthly virtual meetings, and at least one annual face-to-face meeting, the network has developed multiple initiatives to strengthen medicines regulation that benefits the safety of patients in the region.

Moving forward, countries will work towards cancelling marketing authorisations for specific products that are still available in the Latin American and Caribbean markets, despite being withdrawn globally for serious safety reasons. In addition, following a pilot coordinated by Canada, Chile, and Brazil, an initiative on the joint assessment of Periodic Safety Update Reports (PSURs) has been reinforced, and agreements have been made for further evaluations to be conducted by other countries. The network's members also agreed on the arrangement of two multi-collaborative projects on active surveillance of new medicines for the treatment of hepatitis C and multidrug-resistant tuberculosis (MDR-TB). Finally, an important initiative is also in progress regarding the electronic bridging of national adverse drug reaction (ADR) databases and VigiBase, the WHO global ICSR database; currently, Chile is working on the transmission of their reports of adverse events following immunisation (AEFIs).

**ANOTHER SIGNIFICANT INITIATIVE** – the Latin-American Network of Pharmacovigilance and Technovigilance (RedLaFarTec, Red Latinoamericana de Farmacovigilancia y Tecnovigilancia A.C.) – began in 2015. It's a non-profit organisation created in Mexico by healthcare professionals working at universities, hospitals, and pharmaceutical industries throughout Latin America, for the promotion of pharmacovigilance and technovigilance through specialised training and continuing education. The network aims to join forces with the health authorities of Latin American countries to promote patient safety.



Panoramic view of Bogota. Photo: hinterhof / Shutterstock.com





INSPIRE. ENGAGE. TRANSFORM

Latin America

**"The existence of different partnerships adds meaning to the will of collaboration and harmonisation in pharmacovigilance in Latin America."**

**MORE RECENTLY,** during the 3rd Symposium of the ISoP Latin-American Chapter in Bogotá in August 2016, the Colombian Pharmacovigilance Association (Asociación Colombiana de Farmacovigilancia) led an initiative to create a space to discuss solid actions to further their main concern: the safer use of drugs and the development of pharmacovigilance in Latin America.

The participants concluded that the strategic areas to integrate within the countries should be: unifying and contributing to the pharmaceutical legislation in the region regarding the safe use of drugs; evaluating the impact of pharmacovigilance on health costs; promoting a culture of safe use, risk communication, and medicines safety training for all stakeholders; and creating room for patients and the public to participate in pharmacovigilance and medicines safety programmes.

The formal document, named the Bogotá Declaration, was signed by representatives from Brazil, Chile, México, Colombia, and Central American countries, and it will give impetus to unify different players such as regulatory and health authorities, healthcare professionals, healthcare service providers, pharmaceutical industry, healthcare organisations, academia, and most importantly patients and the public.

"The goal is to be able to count on organised working groups, with multiple participants working together to achieve specific improvements that demonstrate the importance of pharmacovigilance, both in patient safety and in the optimisation of resources", said Dr Carlos Maldonado, president of the Colombian Pharmacovigilance Association.

Anyone who is interested in contributing to the proper and safe use of medicines, and the development of pharmacovigilance, can join the Bogotá Declaration published on the website of the Colombian Pharmacovigilance Association in both Spanish and English. Anyone can demonstrate their interest in participating, choose a strategic area in which they want to collaborate, and start to actively work on concrete actions to solve the different problems in the use of medicines in Latin American countries.

**THE EXISTENCE** of different partnerships adds meaning to the will of collaboration and harmonisation in pharmacovigilance in Latin America. Hopefully, through these initiatives more healthcare professionals will be reached and engaged as a reflection that pharmacovigilance is not only a regulatory requirement, but a vital means to improve patients' treatments worldwide.

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RedLaFarTec: www.redlatamfvtv.org

Colombian Pharmacovigilance Association: www.asofarmacovigilancia.org
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Thanks to Heloísa Conesa and Elki Sollenbring, both pharmacovigilance specialists at UMC, for contributing to this article.

# Local needs in focus at ISoP's Latin American symposium

*Pharmacovigilance training at universities, medication errors, and risk management plans took centre stage when ISoP's Latin American chapter gathered for its third symposium in Colombia in August 2016.*

**GLOBAL DEVELOPMENTS IN** safer use of medicines should be adapted to local population's characteristics and drug markets. Pharmacovigilance must be locally performed and implemented, strategies for preventing drug associated risks should take each country's health system features into account, as well as its population's medical, environmental, and cultural characteristics.

Pharmacovigilance concepts and tools should be expressed in local languages in order to be accurately and effectively communicated to specific or wider public audiences; Latin American countries need at-home pharmacovigilance meetings and trainings to allow participants to fluently express their thoughts and experiences. In addition, as many clinical practitioners, pharmacists, and academics in the region have low incomes, these activities – especially the educational ones – should ideally be free of charge or affordable for academics or independent health professionals.

On this basis, the International Society of Pharmacovigilance's (ISoP) Latin American chapter, under the chairmanship of its president Prof Luis Alesso, has been organising regional symposia since 2014. The third symposium of the chapter was held in Bogotá, Colombia, in August 2016, with a scientific agenda coordinated by Raquel Herrera Comoglio.

Aiming to promote exchange and discussion between professionals, students, regulators, and industry around local realities and challenges, the scientific programme focused on three important topics for patients and public health: pharmacovigilance teaching at universities, medication errors, and risk management plans.

Academics from Colombian, Brazilian, and Argentinean universities shared their vision about the central role educating healthcare professionals can play in increasing spontaneous reporting and raising awareness about the magnitude of adverse drug reactions. Educating healthcare professionals is also one of the key strategies to diminish the occurrence of medication errors, which cause a substantial part of all adverse drug reactions.

Pharmacovigilance development and regulations around the world are largely driven by the most influential regulatory agencies – for example the European Medicines Agency, the US Food and Drug Administration, and others requiring risk management plans (RMPs) or minimisation strategies from marketing authorisation holders (MAHs). In order to get reliable results, these activities must take each country's particular needs, drug utilisation patterns, and healthcare system into account. Latin American national centres require RMPs – both in national and transnational companies – which should be designed and implemented according local features, not merely be a replica of those issued in Europe and the US. As has been shown for example with isotretinoin, measures proposed by RMPs cannot reach its objectives even in countries where they are originally conceived. In regions or countries where it's difficult to implement such controls or the drug market is not completely regulated, the efficacy of these strategies may be reduced, and its assessment can be impracticable or unreliable.

Moreover, in order to be effective, communication strategies should be tailored to patients' culture and social contexts, and conveyed in the most effective and locally suitable way. This complex and multiple-level topic was discussed by representatives from three national regulatory agencies of the region – Colombian INVIMA, Brazilian ANVISA, and COFEPRIS in Mexico – and Health Canada. An active round-table discussion on communication strategies – focusing on reaching the right audience with the right information in a timely fashion, measuring effects, and challenges – closed the session.

Besides patients' suffering, adverse drug reactions cause a wide range of illnesses, and even disabilities and deaths, impacting the health system's economic burden. Awareness of health professionals is central, and all partners – academia, regulators, industry representatives, media, and patients – should actively contribute to a safer use of medicines.

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READ MORE: www.isoponline.org/chapters/latin-america





# Meet Annie and Mac – the new pharmacovigilantes on the block

*Aimed at readers aged 9-13 and those with a beginner's knowledge of English, "Annie & Mac's adventures" follows the lead characters as they explore different aspects of side effects and safe medicines.*

**THE PHARMACOVIGILANCE COMIC** book – Uppsala Monitoring Centre's (UMC) new communication project – was developed to reach young minds and give children important information about medicines safety.

"Children are great teachers and have the capacity to influence their communities. By giving them early access to information we are tapping into their capacity to drive change," Paula Alvarado, the head of Global Communications at UMC, said.

Through the pages of the comic's first issue, we're taken through an action-fuelled chapter where Annie and Mac set out to stop the evil Count Erfeit from producing and selling fake medicines. This is followed by colourful activity pages, and the issue ends with a chapter where Annie irritates her entire family as she explains how side effects happen by pretending that her parents and brother are different body parts.

The project's lead writer is Fredrik Brounéus, pharmacist and author, who has written several books for children and young adults, including *Drugs and Bugs – a small book about medicines*.

"We went through quite a few protagonists and sidekicks before Annie and Mac stepped into the picture. She is inquisitive and brave, and Mac is an eagle in the body of a hummingbird. Together they make the perfect team to tackle important medicines safety issues," Mr Brounéus said.

The illustrator is Paul Crumpacker, a designer and artist from the US who lives in Wuhan in central China. "It was very fun to get to know Annie and watch her grow and change through designing and drawing her. I can't wait to see what she does in the future," he said.

UMC plans to test the comic in different countries and then discuss a distribution plan with those interested. After an initial pilot phase, UMC will translate the comic into a few other languages, and expand the cast of heroes to include lead characters from different parts of the world, in order to properly reflect the diversity of the global pharmacovigilance community. In 2017, a second issue of the comic will be published.


**Interested?**
For more information on the process, contact UMC' head of global communications Paula Alvarado on: paula.alvarado@who-umc.org

# Sten Olsson elected new president of ISoP

*At ISoP's annual meeting in India in October 2016, it was announced that UMC's WHO Programme Expert Sten Olsson has been elected to the post of president.*

**MR OLSSON, ONE OF THE THREE** original founders of UMC, is set to retire from UMC in early 2017, after 39 years in the organisation. "Instead of preparing for a quiet retirement from UMC, I'm now fully charged with the challenge of making the International Society of Pharmacovigilance (ISoP) a dynamic, supportive, and visible organisation," he said.

"As pharmacovigilance expands geographically and in its scope, it is essential that ISoP also expands its coverage and membership services, while maintaining its essence of minimising the risk of harm for individual patients," he said.

Besides his responsibilities at ISoP, Mr Olsson will also run a consultancy firm focusing primarily on matters relating to the establishment of pharmacovigilance systems and how to assess them, particularly in resource-limited settings. He can be reached on stenolssonpv@gmail.com or on Twitter at @StenOlssonPV.

**Colourful UMC bike helmets** were produced for participants in the 2016 Uppsala Forum. They've found their way all over the world and one of them is to been seen frequently on the roads of the northern Thai province of Chiang Rai, on the head of Nana Yaw Osei Bediako, a Ghanaian student at Mae Fah Luang University.

**In October 2016** a group of specialists from the Russian regulatory agency Roszdravnadzor visited UMC. During a two-day seminar, UMC covered data processing tools, statistical methods of signal detection, coding of ADR reports, causality assessment, and other topics of interest. The Russian team also gave a presentation on the state and future of their pharmacovigilance system. The country is preparing to implement a new Eurasian Economic Union pharmacovigilance regulation, which is harmonised with the EU GVP guidelines. This mandates the participation in the WHO PIDM, which will help to increase Russia's contribution to VigiBase and assure regular interaction with UMC.

## Maldives 125th member of WHO PIDM

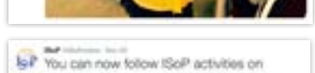
**IN OCTOBER 2016** the national pharmacovigilance centre of the Maldives submitted their first batch of individual case safety reports (ICSRs) to VigiBase, using VigiFlow. The Ministry of Health and Family of the Republic of Maldives applied for membership of the WHO Programme for International Drug Monitoring (WHO PIDM) in March 2011, and have now become the 125th full member country of the programme.





## Join the conversation on social media!








# Pharmacovigilance Meetings 2016

**16-27 January 2017**
### 3rd Asia Pacific Pharmacovigilance Training Course
Mysore, India · JSS University & Uppsala Monitoring Centre (UMC)
**www.jsspharma.org**
**@UMCGlobalSafety**

**23-25 January 2017**
### DIA Pharmacovigilance and Risk Management Strategies Conference
Washington D.C., USA · Drug Information Association (DIA)
**www.diaglobal.org**
**@DrugInfoAssn**

**15-16 February 2017**
### Back to Basics in Pharmacovigilance
Fareham, UK · Drug Safety Research Unit
**www.dsru.org/trainingcourses**
**@DSRUDrugSafety**

**22-23 February 2017**
### Towards Professional Excellence in Pharmacy Practice
Muscat, Oman · Ministry of Health
**www.pharmacareconference.om**
**@7thpcc**

**6-8 March 2017**
### Advanced Pharmacovigilance
London, UK · Management Forum Ltd
**www.management-forum.co.uk**

**2-4 April 2017**
### ISPE Mid-Year Meeting
London, UK · International Society for Pharmacoepidemiology (ISPE)
**www.pharmacoepi.org**

**19-21 April 2017**
### Congrès annuel de la Société Française de Pharmacologie et de Thérapeutique
Rouen, France · Société Française de Pharmacologie et de Thérapeutique
**www.congres-sfpt.fr**

**27 April 2017**
### An Essential Overview of Pharmacovigilance
London, UK · Management Forum Ltd
**www.management-forum.co.uk**

**3-5 May 2017**
### Medical Aspects of Adverse Drug Reactions
London, UK · Drug Safety Research Unit
**www.dsru.org/trainingcourses**
**@DSRUDrugSafety**

**8-19 May 2017**
### 19th International Pharmacovigilance Training Course
Uppsala, Sweden · Uppsala Monitoring Centre (UMC)
**www.who-umc.org**
**@UMCGlobalSafety**

**8-19 May 2017**
### 11ème Cours Francophone de Pharmacovigilance
Rabat, Morocco · Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM)
**www.capm.ma**

**25-26 May 2017**
### ISoP Mid-Year Training Course
Bangkok, Thailand · International Society of Pharmacovigilance (ISoP)
**www.isoponline.org**
**@ISoPonline**

## Uppsala Monitoring Centre courses 2017

**16-27 January 2017**
### 3rd Asia Pacific Pharmacovigilance Training Course
Mysore, India · JSS University, UMC

**8-19 May 2017**
### 19th International Pharmacovigilance Training Course
Uppsala, Sweden · Uppsala Monitoring Centre

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Uppsala Monitoring Centre

WHO Collaborating Centre for International Drug Monitoring

Uppsala Monitoring Centre (UMC) is an independet non-profit foundation and centre for international service and scientific research. Our vision is a world where all patients and health professionals make wise therapeutic decisions in their use of medicines. Our mission is to support and promote patient safety through effective global pharmacovigilance practise.