SEPTEMBER 2016 ISSUE 73

UPPSALA REPORTS

COVERING THE WORLD OF PHARMACOVIGILANCE

The rapid access dilemma

Uppsala Forum • Africa needs true partnerships • Few resources for PV in Sierra Leone • Assessing pharmacovigilance activities Mobile tech • Women & risk • UMC's training courses 2016

THE MAGZINE FROM UPPSALA MONITORING CENTRE

Uppsala Monitoring Centre

Director´s message

IF YOU LIVED IN AN AREA where there is widespread endemic disease – would you want your child to benefit from the latest and best vaccines against the diseases that could seriously harm, or even kill them? If your elderly mother or father had cancer, would you want them to be treated with the latest and best chemotherapy to delay its progress? I would, and I'm far from the only person who thinks like this. The demand for rapid access to new, effective medicines has become a global public health issue, and a matter of political and scientific urgency.

So maybe we should not be surprised that no one is cheering when we say, "Hang on – haven't we forgotten something here? What about safety?" Our traditional methods take time, often too much time, and time is precious when millions of people are waiting, impatiently, for sometimes life saving treatments.

On the other hand, if patients feel that they are being subjected to what is effectively an experiment, will they support the new options and our efforts to speed them along? What additional resources will health professionals need to ensure that the benefits to their patients outweigh the potential harms?

How do we see to that effective safety monitoring is a facilitator and not a bottle-neck in the delivery of new and more effective therapy? I believe the answer to this problem, and to many of the well-known inadequacies of safety monitoring, lies in a new, flexible, responsive, agile pharmacovigilance. Regulators are talking about 'adaptive pathways' as the new regulatory approach: a shift away from one-off marketing authorisation towards iterative safety monitoring and evaluation throughout a medicine's whole life cycle.

But can we really reform the ponderous processes of pharmacoviglance? And what do I mean by agile pharmacovigilance?

The origin of the concept of 'agile development' comes from the IT world. According to Wikipedia, "Agile software development is a set of principles for development in which requirements and solutions evolve through collaboration between self-organizing, cross-functional teams. It promotes adaptive planning, evolutionary development, early delivery, and continuous improvement, and it encourages rapid and flexible response to change.".

"How do we see to that effective safety monitoring is a facilitator and not a bottle-neck in the delivery of new and more effective therapy?"

All we need to do is to change 'software' to 'pharmacovigilance' in the description; the principles are the same. The devil, as always, is in the detail. How do we move from theory to implementation of agile pharmacovigilance?

First, how can we change mind-sets and practices? How can we build a genuine, robust social contract in which all stakeholders are ready and willing to take some risks with the promise of greater benefits? How can we engage everyone in active, rapid monitoring and evaluation of new treatments?

Second, how can we apply agile work processes and relationships throughout the whole life of medicines, from development to trial to marketing to therapeutic use?

Third, how can we manage the collection and interpretation of increasing volumes of information on individual patients including data from wearable devices and patient stories? How do we know that the data we collect is relevant? How can we protect privacy?

These complex and challenging questions were discussed at the recent Uppsala Forum organised by UMC. For those of you who weren't able to attend, a meeting report will be made available. Do read it, and let me know what you think are the next steps we should take!

This message is a slightly edited version of my Uppsala Forum introduction.

Marie Lindquist

Marie Lindquist, Director

Uppsala Monitoring Centre

UPPSALA REPORTS *Covering the world of pharmacovigilance*

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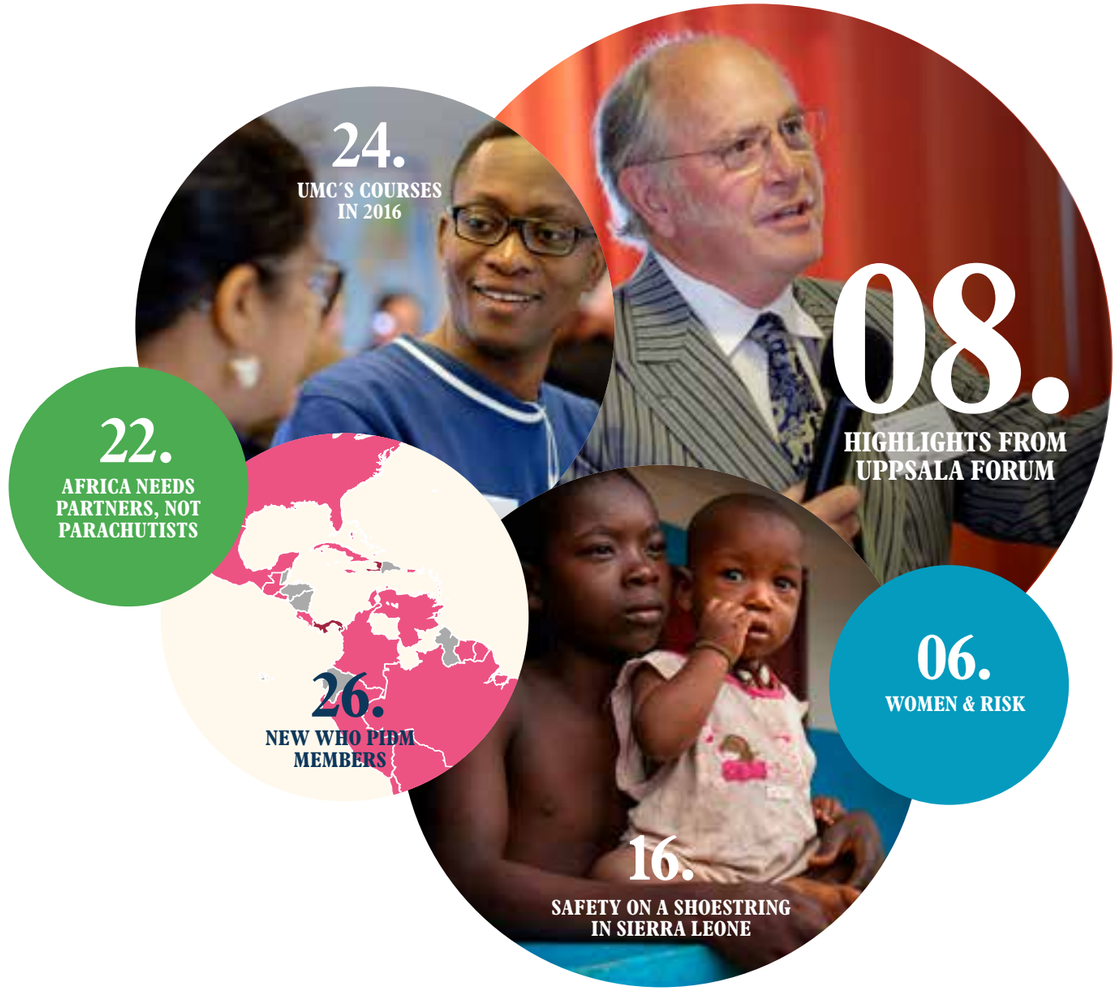

ANTIGUA

Harmonising pharmacovigilance in Central America

*The recently passed **technical regulation** on pharmacovigilance and the establishment of a regional adverse drug reaction database pushes **drug safety** forward in Central America and the Dominican Republic.*

A WORKSHOP FOR the validation of the Central American Technical Regulation (RTCA) on Pharmacovigilance was held in Antigua, Guatemala in October last year. 15 delegates from different ministries of health and social security institutions in Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama and the Dominican Republic – all members of the Regional Technical Group of Pharmacovigilance (GTRFV) – attended the event.

Participants from the Council of Ministers of Health of Central America and the Dominican Republic (COMISCA), the Spanish Agency for Medicines and Health Products (AEMPS), and the Pan-American Health Organization (PAHO), were also in attendance; as were representatives from the Spanish Agency for International Development Cooperation (AECID) and the System of Central American Integration (SICA).

"During the activity they analysed the arising opportunities to develop a consensus proposal for the regulation of medicines that includes internationally recognized recommendations and regulatory guidelines," an AEMPS press release stated.

All work was coordinated by COMISCA, which has provided technical assistance in the process of transferring the Spanish database of suspected adverse reactions, FEDRA, to the Central American FACEDRA database.

During the workshop, the draft for the proposed technical regulation was finalized, after seven months of discussions between GTRFV members. The foundation for the FACEDRA database, modelled on FEDRA, was also established. The database will allow every national centre access to the information system, upload their individual case safety reports (ICSRs), and share their reports with other stakeholders. FACEDRA will also be equipped with an output module that will periodically send the ICSRs collected in Central America to Uppsala Monitoring Centre's VigiBase® database.

The approval of the technical regulation fulfils one of the objectives set between COMISCA and the AEMPS regarding the provision of support to the Subregional Pharmacovigilance Programme of Central America and the Dominican Republic (reported in Uppsala Reports 56).

During the XII International Meeting of Pharmacovigilance in the Americas, which took place from 11-13 November 2015 in Medellín, Colombia, the Antigua workshop was presented. Mariano Madurga Sanz and other speakers set out the results of the collaboration. At the close of the Medellín meeting, the Focal Point Network of Pharmacovigilance, coordinated by PAHO, was informed about the actions taken and future steps.

During COMISCA's XLIII Regular Session, held in El Salvador on 11-12 December 2015, the RTCA on pharmacovigilance – which was developed in the regional health sector – was approved. Its acceptance for the SICA economic sector is awaited.

As a part of the implementation process of the Medicines Strategy for Central America and the Dominican Republic 2015-2017, this is a further step towards the harmonisation of regulations in the region, which in turn may increase the likelihood of interested nations in the region joining the WHO Programme for International Drug Monitoring.

Participants in the workshop on pharmacovigilance in Central America and the Dominican Republic. Photo provided by organizer.

COMSICA: Consejo de Ministros de Salud de Centroamérica y República Dominicana
FACEDRA: Farmacovigilancia Centroamericana de Reacciones Adversas
GRTFV: Grupo Técnico Regional de Farmacovigilancia

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ASMARA

Government support and media attention boost medicines safety in Eritrea

Media coverage during and after the East African Advanced Course on Pharmacovigilance and Risk Management, in Asmara, Eritrea in April was so extensive that medicines safety became a topic of national discussion, and adverse drug reaction (ADR) reporting increased from about 120 to 160 per month.

While it was running, the course was the subject of a 30-minute national TV programme every evening and was reported in Tigrigna and English in the daily newspapers. Media interest continued for several weeks after the course.

"The media attention really brought medicine safety to the attention of the population," said Mulugeta Russom, Head of Pharmacovigilance in Eritrea. "We've had many people approaching us to ask about their medicines, and professional awareness of pharmacovigilance has really gained ground."

The course was attended by 81 participants from 17 countries and was led by local and foreign experts. Feedback from participants suggests that they regarded the course as a great success in supporting the development of medicines safety and patient safety practice in East Africa.

Eritrea became a full member of the WHO Programme for International Drug Monitoring in 2012 and adopted an ambitious national medicines safety plan in 2014. This includes the integration of pharmacovigilance into all public health programmes and the curriculum of the School of Pharmacy. Around 95% of all health professionals are trained in pharmacovigilance, and a total of 85 journalists have attended courses.

"We've had many people approaching us to ask about their medicines, and professional awareness of pharmacovigilance has really gained ground."

Eritrean Pharmacovigilance team from left to right: Merhari Zeregabr, Merhawi Debesai, Mulugeta Russom, Elsa Mekonnen, Dawit Tesfai, Selamawit Ghebrehiwet, Aziza Afendi.

With specific responsibility for advocating and overseeing patient safety, Medical Therapeutic Committees have been established in sixteen hospitals and on-site ADR monitoring projects have been initiated at hospitals and clinics, especially those concerned with HIV/AIDS and TB.

"Consumer reporting is our next priority," said Russom. "We are collaborating with Eritrean Telecommunication Services to establish a free call ADR reporting system and, internally, are working to introduce an SMS ADR reporting system, compatible with VigiFlow®." Both of these projects are supported by Global Fund.

Apart from the evident enthusiasm and skill of the pharmacovigilance team at the National Centre, one reason for the success of medicines safety in Eritrea is the unwavering support from the government. One powerful demonstration of this was the presence of the Minister of Health, H.E. Amina Nurhussien, throughout much of the course. The WHO Representative in Eritrea, Dr. Josephine Namboze also participated.

Mulugeta Russom with UMC´s Sten Olsson on the road to Asmara.

Eritrea's national pharmacovigilance centre now has a five-year strategic plan (2016-2020) to optimize systems following the recent course. They intend to maintain their position as one of the leading reporting countries in Africa and to continue the development of effective pharmacovigilance in Eritrea and the region.

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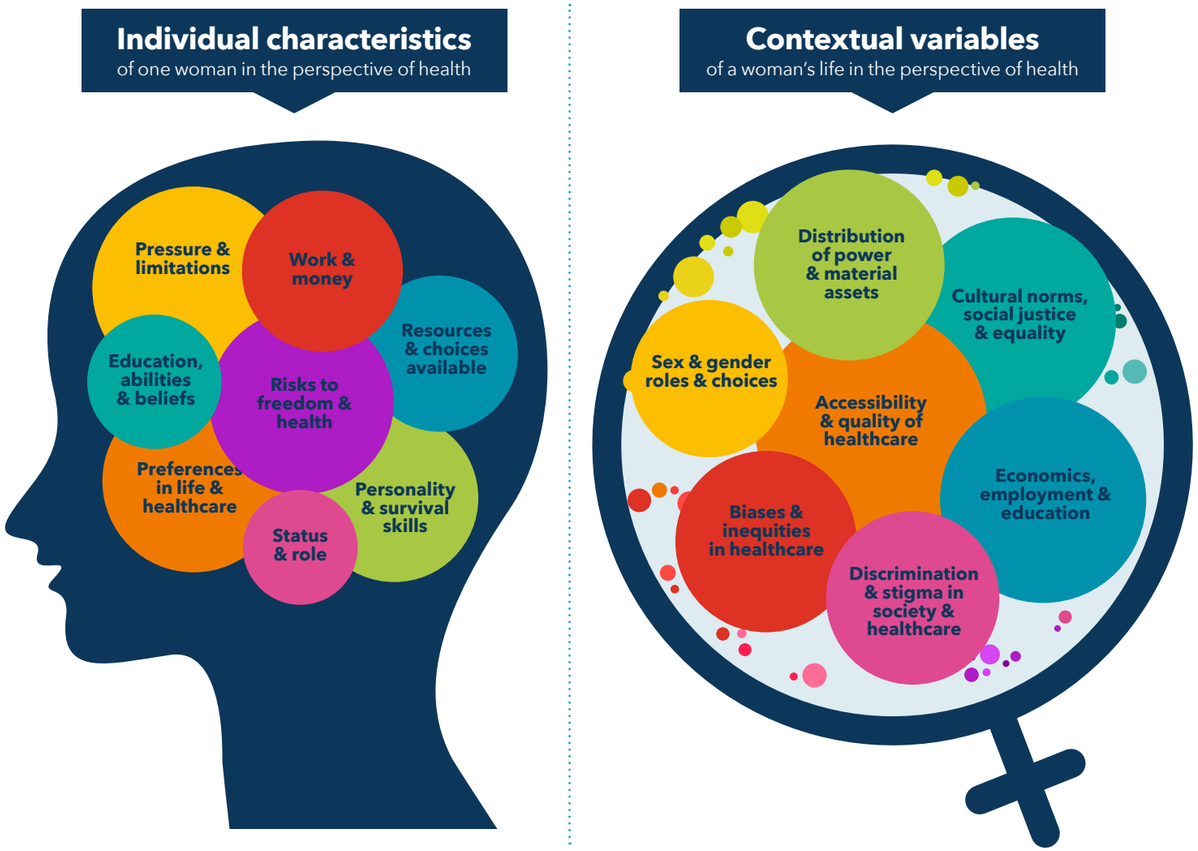
A WHOLE NEW GAME

Risk communication for women

*The diagnosis and treatment of **women's health** concerns, and the risk communication accompanying them, must take account of the immense internal and contextual **complexity** of women's lives; particularly of the disadvantage and oppression they often suffer as a result of **male-dominated** societies.*



WHEN CONSIDERING risk communication for women, there are three primary considerations that are specific to women´s lives, that need to be taken into account:

FIRST, IN ILLNESS, the risks women face go far beyond the significant risks of diagnosis and therapy; medical practice in general, and risk communication in particular, must respect, acknowledge and respond effectively to the complexity of women's lives and the multiple risks they face, and find solutions that precisely meet their wishes, preferences, priorities and needs.

SECOND, THE DISEASES, conditions and unique risks that are endured by women are mediated by multiple, powerful variables determined by gender, social constructs, health systems and personality that often stand between women and the just and equitable delivery of healthcare and may compromise diagnosis and treatment.

THIRD, FEW PATIENTS demand attention from their clinicians or ask more than one or two questions; the complexity of women's lives is rarely manifest in the clinical encounter. Women's symptoms (especially pain) are often misperceived, misdiagnosed, disparaged or ignored even though they may relate to serious, underlying causes and to multiple personal and contextual risk factors.

This material is an abstract of a poster presented at Evidence Live 2016, Oxford, UK and EACH 2016, Heidelberg, Germany.

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READ MORE: Harrison-Woolrych, Mira (ed.), *Medicines for Women*, Chs 18–19, Adis, 2015.

OXFORD

Chasing evidence-based medicine

Every patient hopes that their diagnoses and treatments will be based on something more substantial than the preferences, habits and whims of doctors; that, at best, evidence will be at the heart of decisions in all medical consultations and in the work of regulators.

We all know, however, that things often fall far short of the ideal. Evidence Live is an annual conference, sponsored by the British Medical Journal (BMJ) and the Centre for Evidence-Based Medicine at Oxford University, United Kingdom, to examine such questions. It brings together some of the best known names in the field, such as Ioannidis, Spiegelhalter, Montori, Goldacre, Glasziou, Jefferson, McCartney, Aronson, and Gøtzsche, and more than 300 health professionals, researchers, academics, patients, and other interested parties.

This year's meeting explored some of the major issues about quality of evidence that burden medical practice. Gross flaws in research design and evidence and the absence or manipulation of data have led to patients being harmed; the lack of critical appraisal skills in professionals and the public results in weak or false claims gaining currency or valid results being ignored or dismissed; impressive new medicines and techniques – such as methylphenidate and breast-cancer screening, for example – gain momentum and lead to over-diagnosis, over-treatment and unnecessary harm to patients, alongside their benefits.

In relation to this, 'slow medicine' in Italy and 'prudent healthcare' in Wales were showcased as examples of a new, international movement to maximize the benefits of healthcare and to reduce harm and cost through more discriminating, moderate practice.

THE CONTROVERSIAL NOTION that evidence is, in fact, coercive and authoritarian ('prescriptive') was raised. This formed part of the debate about patients' priorities and needs, particularly their wish to have rich information about the options available to them, in formats that meet their needs, and the opportunity to make deliberate, considered choices in partnership with their health professionals. A wide range of modern resources to assist professionals and patients in the search for wise guidance was presented, including The Cochrane Library, The James Lind Library, the web page www.testingtreatments.org, The Ottawa Hospital Decision Aids, apps and websites, information graphics and comics, and many more.

A lot of clever people – many of whom attended the conference – are working hard to reduce the confusing, sometimes impenetrable and unreliable, mass of medical information currently available, and to produce systems, materials and tools that will genuinely help patients make wise decisions that they will not regret.

AMONGST THE 60 POSTERS on display at the Evidence Live conference in Oxford was one from Uppsala Monitoring Centre: *A woman is not like a man: Why risk communication for women is a whole new game*, based on Bruce Hugman's research published in "Medicines for Women" in 2015. The poster was designed by Karin Rask, a member of UMC's Global Communications Team.

The poster was commended by participants for both its design and content. One woman commented: 'I think it is fantastic that you are championing these issues as a male. The poster manages to capture, and clearly present, a considerable amount of information in an accessible manner. It has given me food for thought certainly. Particularly about how some (many) of the issues women face are the product of male-developed services. As a female working for a healthcare research collaboration, it will encourage me to raise gender related issues more readily with my colleagues.'

The poster's topic of risk communications for women is presented in summary on the page opposite.

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UPPSALA FORUM 2016

Prof Ralph Edwards, senior advisor at UMC. Photo: UMC

The rapid access dilemma: Speed or safety?

*The road to **faster access** to novel medicines is lined by regulatory challenges, clinical uncertainties, and **health risks** to patients. At Uppsala Forum in May, pharmacovigilance experts discussed these and other topics relevant to **medicines and patient** safety today.*

CUTTING DOWN THE CLINICAL TRIAL and approval time of a new medicine and getting it out on the market faster can mean the difference between sickness and health for severely ill patients. This is particularly the case for diseases against which there are no effective therapy available.

Fast-track approval of medicines can offer timely relief of symptoms in people who may have few or no other options. But in a worst-case scenario, a pharmaceutical product that has been fast-tracked through the clinical trial and approval process can cause unforeseen side effects to patients.

At Uppsala Monitoring Centre's (UMC) research conference Uppsala Forum, hosted in its namesake city in Sweden in May, a body of international experts sought to address what role the pharmacovigilance community can and should play in contributing to the safety of novel medicines when fast access is of paramount importance. Other areas of discussion related to the conference's main focus included topics such as medicines safety in resource-poor settings, monitoring mass deployment of medicines, drug repurposing, patient advocacy, emergency vaccine development, and pharmacovigilance impact assessment.

The diverse national and professional backgrounds of the gathered speakers and attendees contributed to a cosmopolitan atmosphere where contrasting ideas and experiences both challenged and complemented each other. Many voices spoke in favour of faster delivery of new therapeutics to the market, while some were reluctant to make concessions to today's stringent regulatory requirements. Many strong opinions and well-backed arguments – representing research, academia, regulatory agencies, patient advocates, and industry actors – were heard during the two days of the forum.

Uppsala Forum

Dr Andrea Marzi from NIAID with UMC's Jennifer Wall and Dr Pia Caduff. Photo: UMC

"Time is precious when millions of people are waiting impatiently for sometimes life-saving treatments."

FIRST TO THE STAGE was UMC's CEO and director Dr Marie Lindquist, who delivered the opening remarks and gave an agenda-setting presentation on the need for a new medicines safety paradigm. The demand for quicker access to medicines is prevalent all over the world, where adequate treatments aren't readily available to patients. In this light, it is hardly surprising that concerns regarding the monitoring of adverse drug reactions are not at the top of the agenda in global efforts to get medicines to market faster, Dr Lindquist said – particularly as post-marketing safety surveillance and the data collection it depends on is a slow process. However, Dr Lindquist said, the urgency for new therapeutics "must be weighed against the dangers of exposing large populations to medicines for which there is very limited information on their effects." She concluded that the solution lies in a responsive, flexible and agile pharmacovigilance.

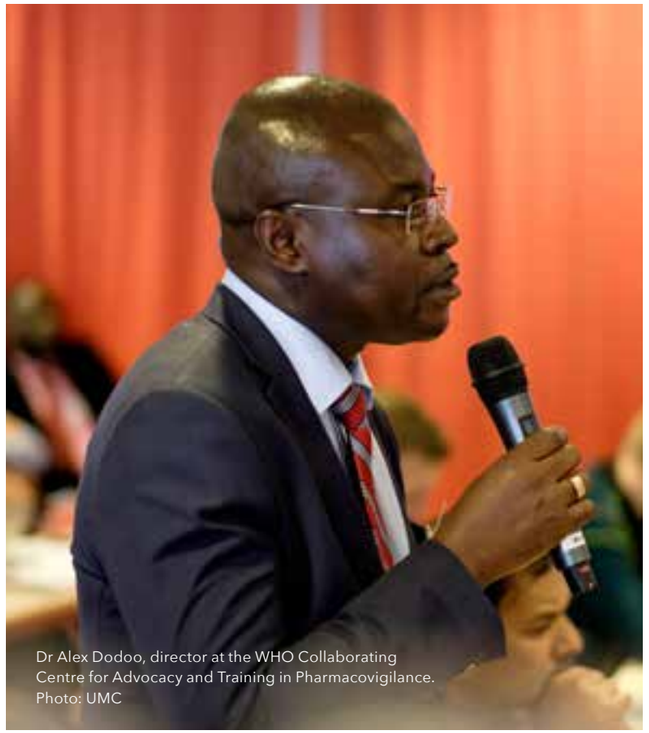
In the following presentation by Alex John London, professor of philosophy and director of the Center for Ethics and Policy at Carnegie Mellon University in the US, the audience heard more about the ethical aspects of an accelerated approval of medicines. Prof London acknowledged the validity of arguments in favour of rapid access, such as fairness, anti-paternalism, and reasonable risk, but argued that the key product of a translational process is not a pharmaceutical product itself, but rather the information that is gained from the process.

The next talk offered hands-on experience of carrying out pharmacovigilance in a resource-poor setting: **Wiltshire Johnson**, registrar and CEO at the Pharmacy Board of Sierra Leone, shared his experiences from ➤

READ MORE:

Read Wiltshire Johnson's article "Safety on a shoestring in Sierra Leone" on page 16.

INSPIRE. ENGAGE. TRANSFORM



Dr Alex Dodoo, director at the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance. Photo: UMC

mass administration of antimalarials in Sierra Leone – a nation where patients outnumber physicians 50,000 to one – during the Ebola outbreak.

Dr Noel Southall, following on Mr Johnson's talk, focused his presentation on drug repurposing, and outlined some of the benefits and risks of using already approved medicines or discarded clinical candidates to treat new diseases.

In the afternoon, six speakers shared an hour to present five-minute Rapid Fire presentations over a broad range of topics, such as the study of molecular structures to predict severe adverse drug reactions, the value of VigiBase in real-time surveillance to the influence exposure variables have on safety issues during the post-approval period.

The last talk of the day was given by the Paris-based patient advocate François Houÿez, director of Treatment Information and access and policy advisor at the European Organisation for Rare Diseases (EURORDIS). Houÿez discussed patient reporting and patients' access to structures and organisations that monitor adverse drug reactions. EURORDIS, a part of the **WEB-RADR** project, works to develop smartphone apps for patient reporting and information sharing, and Houÿez presented some of the features and planned developments of the apps.

READ MORE:

Read more about WEB-RADR in "Where mobile tech meets medicines safety" on page 20.

READ MORE:

Read A. Hoegberg, "Andrea Marzi puts Ebola under the microscope", Uppsala Reports 72, May 2016, Uppsala.

"Do you deny patients the benefits of these particular treatments on behalf of them being not cost-effective, or do you deny other patients cheaper and more far-reaching healthcare programmes?"

THE CONFERENCE'S SECOND and last day opened with virologist **Dr Andrea Marzi,** staff scientist at the National Institute of Allergy and Infectious Diseases (NIAID) in the US, who provided insights into the development of the live-attenuated Ebola vaccine VSV-Ebov. Dr Marzi´s talk focused primarily on pre-clinical research and development but she also put the vaccine's journey and its ultimate purpose into context by sharing her experiences from running Ebola diagnostics out of a field lab in Liberia during the West African outbreak, and drawing examples from a subsequent ring vaccination trial that was carried out in Guinea using the VSV-Ebov vaccine.

After Dr Marzi's presentation, Prof Ralph Edwards, senior advisor and former director of UMC, and Dr Alex Dodoo, director of Ghana's WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, took to the stage to hold a debate on real-time, real-life drug surveillance. The debate garnered a lot of input from the audience and forum speakers, contributing to an engrossing discussion about various aspects of pharmacovigilance and the balance between the sometimes mutually exclusive demands on novel medicines to be both quickly accessible and safe.

Dr Gerald Dal Pan, director at US FDA's Center for Drug Evaluation and Research, took over after the debate, delivering a detailed presentation on various methods for assessing the efficiency of pharmacovigilance activities; The ultimate purpose of these assessments is to determine which methods are most successful and where efforts should be focused.

When discussing rapidly released medicines, the question of increased cost and who should reimburse it must also be considered, a topic that was covered by pharmacoeconomics professor Dyfrig Hughes from Bangor University in Wales, UK. His talk outlined the principles of health economics, where the cost of rapidly released medicines for rare diseases – which is quite high and benefits a few, often severely ill, patients – is juxtaposed to other healthcare needs that may benefit a larger scope of a population. "Do you deny patients the benefits of these particular treatments on behalf of them being not cost-effective, or do you deny other patients cheaper and more far-reaching healthcare programmes?" Prof Hughes pondered.

Rounding up the conference were two industry perspectives from Janssen Pharmaceuticals. Medical advisor Andreas Palmborg spoke about the challenges a manufacturer may face when delivering accelerated

The Rapid Fire speakers from right to left: Dr Agnes Kant, Alexandra Pacurariu, Dr Rebecca Chandler, Dr Jing Bao, Tomas Bergvall, and Dr Brian Edwards.

release HIV medicines. Ingela Larsson, cross sector country safety team lead of the Baltics and Nordic region at Janssen, delivered the final talk, discussing how marketing authorisation holders can support the infrastructures needed with accelerated release of medicines.

THE LAST PERSON to capture the attention of the audience was UMC's senior researcher Dr Ola Caster, who in his closing remarks ended the conference by revisiting the main points of conversations that had taken place during the two days.

Providing a yes-or-no answer to the hotly debated question of whether the benefits of faster access to medicines outweigh the risks proved difficult, he noted. However, the forum attendees gave a general impression of wishing for a quicker process only when the circumstances mandate it. Specific medical needs or the absence of other treatments, for example, could warrant fast-tracking a treatment. This should be combined with an effort to create a safe rapid access process, for example by improving pharmacovigilance practices for novel medicines with a poorly understood safety profile, or collecting additional data for the specific situations when medicines approved under a fast track procedure are deployed.

Dr Caster closed with words that aptly captured the spirit of the forum: "I would like to remind us that we who have gathered here are tremendously privileged in that our professional roles give us the ability to work for change, to work for improvements that can lead to benefits to patients – children, women and men – all over the world."

"We who have gathered here are tremendously privileged in that our professional roles give us the ability to work for change, to work for improvements that can lead to benefits to patients."

READ MORE:

Read Gerald Dal Pan's article "Measuring the impact of pharmacovigilance" on page 14.

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Measuring the impact of pharmacovigilance

*Over the years, many approaches to evaluating and managing the **risks** of medicines have been developed; by **assessing** the outcomes of these pharmacovigilance activities, resources may be focused on **high-impact** efforts.*

THE PAST 50 YEARS have seen the emergence of pharmacovigilance as an important public health activity. While early efforts centred on the collection and evaluation of individual case safety reports, current efforts examine both individual cases as well as population-level assessments of the effects of medicines.

Modern pharmacovigilance embraces many disciplines, such as medicine, pharmacy, pharmacology, epidemiology, toxicology, informatics, and risk management, to name a few. Pharmacovigilance activities have now a global reach. Over the years, regulatory requirements concerning pharmacovigilance have increased in many countries and regions. At the same time, industry, regulators, pharmacovigilance centres and academics have developed many approaches to evaluating and managing the risks of medicines. While these approaches may vary from country to country or from region to region, they all seek to improve patient care and patient safety.

IN VIEW OF THE BROAD RANGE of current pharmacovigilance activities, it is reasonable to ask which of those activities are most effective at achieving their goals, and which are less effective at doing so. The practical value of assessing the impact of pharmacovigilance activities is that, ideally, it can allow resources to be directed toward those activities that have high impact and away from those that have little (or even negative) impact. These impact assessments might examine how pharmacovigilance centres assess the safety of medicines, the actions regulators take to address safety concerns, and the risk minimization efforts that the health system puts in place to improve patient care and patient safety.

To this end, the Pharmacovigilance and Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) published in January 2016 the PRAC strategy on measuring the impact of pharmacovigilance activities, which outlines a multi-year plan to assess systematically pharmacovigilance activities, with a focus on four key areas: effectiveness of risk minimisation actions; effectiveness of specific pharmacovigilance processes; enablers of effective pharmacovigilance including stakeholder trust and engagement; and method identification and development.

The US Food and Drug Administration (FDA) has also begun to examine the impact of certain pharmacovigilance activities. In the area of assessing the impact of safety signal generation and evaluation, FDA has shown that spontaneous reports are responsible for over 50% of all safety-related labelling changes – a finding that underscores the importance of these reports.

FDA has also demonstrated that it is often difficult to determine the manufacturer of the specific product a patient took, when there are both brand and generic versions of the product available. In a review of 2,500 individual case safety reports for five antiepileptic drugs, FDA found that the specific manufacturer could not be identified in about 84% of cases. This number is unacceptably high, and calls for increasing efforts to capture accurate manufacturer information.

In collaboration with a visiting fellow from the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), FDA assessed the impact of scheduled post-marketing summary safety analyses on regulatory actions. These safety analyses are in addition to the bi-weekly screening of the FDA Adverse Event Reporting System (FAERS) database of spontaneous adverse event reports and other safety monitoring activities. While the safety analyses were completed for 300 products, they contributed to only 2% of the labelling changes for these products; it was concluded that they provide only marginal value over other pharmacovigilance activities.

IN THE AREA OF RISK MANAGEMENT, FDA has assessed the extent of patient knowledge of key risks of the medicines that they had been prescribed. To do so, data was summarized from patient knowledge surveys that FDA required the manufacturers to conduct for 66 products with a Medication Guide, a type of FDA-approved patient labelling. The threshold for acceptable knowledge was defined as when 80% or more of survey respondents correctly answered questions about the primary drug risk. Of the 66 surveys, only 20 (30.3%) achieved the 80% threshold. The conclusion was that there needs to be improvements in medication information directed toward patients.

Assessing the impact of pharmacovigilance activities is a relatively new area, and will require the development of robust methods to achieve its goals. One important aspect of methods development will be to assess the impact of pharmacovigilance activities on actual patient outcomes, and not simply on intermediate endpoints, such as process indicators or regulatory actions. Multidisciplinary collaboration will be necessary to achieve these goals.

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READ MORE:

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Photo: robertonencini / Shutterstock.com

Safety on a shoestring in Sierra Leone

*In Sierra Leone, where **patients outnumber physicians** 50,000 to one and where the vast majority of the population doesn't have access to **essential medicines,** the national pharmacy board battles numerous challenges to spread the practice of pharmacovigilance.*

FOR BARE-BONES ACCESS to healthcare, the World Health Organization (WHO) says a country needs at least 23 medical practitioners including doctors, nurses, pharmacists, and midwives per 10,000 people. Shortage of health professionals is a problem that spans across sub-Saharan Africa, but it is particularly a serious concern in Sierra Leone, where a lack of medical practitioners correlates with some of the worst health outcomes in the world.

In a country where health resources are very limited, funding a pharmacovigilance system to monitor the safety of products that are barely available to the majority of the population comes last on the list of other competing priorities, such as fighting infectious diseases, improving access to life-saving medicines, and providing basic healthcare delivery services.

This scenario illustrates the challenges of conducting pharmacovigilance in an environment where medicines are not even available or, when available, are mostly self-medicated and/or not prescribed properly due to inadequate diagnostic facilities, health workforce, and infrastructure.

THE ROLE OF HEALTH CARE professionals is crucial in pharmacovigilance. However, in Sierra Leone, they are few and often have many patients to attend to with little time to fill an adverse drug reaction (ADR) form to report a suspected ADR. The physician/pharmacist to patient ratio is 1:50,000. The nurse to patient ratio is twice that for the doctor/pharmacist to patient ratio. This allows little time for health care professionals to detect and record ADRs.

An unpublished study that was done by the National Pharmacovigilance Centre (NPC) of the Pharmacy Board of Sierra Leone (PBSL) in collaboration with the WHO country office in Sierra Leone showed that healthcare professionals may be unwilling or uncomfortable reporting ADRs with treatments out of fear of litigation for professional errors or liabilities.

Distribution and availability of ADR reporting forms in all health facilities across the country can also be a challenge in riverine and hard-to-reach areas that have few or little access to information and communication technologies. In some cases, where some of these facilities get the ADR forms, there are usually long delays before the reports are received at the NPC, and in the overall information sharing.

PUBLIC HEALTH PROGRAMMES (PHPs) such as the malaria, HIV/AIDS, TB-Leprosy control programmes are key actors in pharmacovigilance. Traditionally, PHPs in Sierra Leone focus on expanding access to treatment to achieve the goals of preventing or treating diseases in the population. Many of these PHPs use and distribute large quantities of vaccines and medicines, and sometimes in the form of mass drug administration, often without much consideration to safety monitoring. Thanks to the intense diplomacy and advocacy strategies employed by the NPC, these programmes have started integrating pharmacovigilance into their activities.

A success story is the collaboration between the NPC and the National Malaria Control Programme (NMCP), which resulted in the change of a treatment regimen. The NPC actively participated in pharmacovigilance monitoring during mass drug administration of over 5 million doses of artesunate-amodiaquine in two cycles during the peak of the Ebola outbreak, by going into the communities and searching, finding, identifying, referring, and managing adverse events. The adverse reactions that were collected and analysed by the NPC led to changing first-line treatment of malaria from artesunate-amodiaquine to artemether-lumefantrine.

In a similar manner, due to the Pharmacy Board of Sierra Leone's 'pharmaco-advocacy' with the HIV/AIDS and Expanded Programme for Immunization (EPI) control programmes, the collaboration between these institutions has been greatly enhanced. The NPC is now receiving more AEFIs reports from the EPI programme, and pharmacovigilance units and focal persons have been identified and trained in over 40 antiretroviral therapy treatment sites. This collaboration with EPI was further strengthened when the WHO vaccine safety department in Geneva came to assess the vaccine pharmacovigilance system of the programme, considering the potential introduction of novel Ebola vaccines post licensure.

ANECDOTAL EVIDENCE SUGGESTS that a large part of the population in Sierra Leone uses or is dependent on traditional medicines, seeking help from traditional healers rather than from formal health facilities. This is done either by choice or due to limited access to essential medicines, especially in rural and remote areas, or because of the cost involved and the dearth of trained healthcare professionals.

Moreover, the common perception in the general population is that natural remedies are, by their very nature, free from adverse reactions. The therapeutic remedies used in traditional medicine are also poorly characterized, which makes causality assessment and analysis of adverse incidents very complicated. Integrating pharmacovigilance in traditional medicine practitioners' activities is key. In this light, the Pharmacy Board of Sierra Leone has established a complementary and alternative medicines department to foster collaboration with herbal medicines practitioners.

THIS YEAR, THE PBSL will introduce requirements for marketing authorization holders (MAHs) to have Qualified Persons for Pharmacovigilance (QPPV), who will put functional pharmacovigilance systems in place in order for them to assume responsibility and liability for their products. Such a requirement will strengthen the pharmacovigilance system and bring Sierra Leone's medicines safety in line with international best practices.

Other measures that the NPC has undertaken include updating the ADR reporting form to capture lack of effectiveness/therapeutic failure and medication errors, and developing a patient reporting form to promote and encourage consumer reporting. Pharmacovigilance training has been introduced in the undergraduate curriculum for pharmacists in Sierra Leone's only medical training school. An online ADR reporting system was recently established with technical support from Uppsala Monitoring Centre, which will soon be accessible on the Pharmacy Board's website as an easy-access, user-friendly reporting tool for healthcare professionals and consumers. Additionally, this year the NPC has employed medical doctors and pharmacists as clinical regulatory pharmacovigilance officers stationed at regional health facilities, to support the regional pharmacovigilance centres to enhance medicines safety activities in their respective health facilities.

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WHO guideline aims to tackle medication errors

In WHO's publication on failures in medical treatment processes, pharmacovigilance centres are offered guidance on the identification, management and prevention of medication errors.

AS MEDICATION ERRORS (MEs) fall within the scope of pharmacovigilance, the WHO has published "Reporting and Learning Systems for Medication Errors: The Role of Pharmacovigilance Centres", which sets out terminology, tools and methods that pharmacovigilance centres should implement when they deal with MEs.

The guideline raises awareness about the centres' role in managing and preventing medication errors, and aims to strengthen the centres' capacity to identify and analyse this type of error so as to minimise harm to patients. In addition, the guideline is intended to stimulate cooperation between national pharmacovigilance centres and patient safety organizations.

MEs are not always visible to practitioners and are then reported as adverse drug reactions (ADRs). Different methods have been proposed in the guideline which could be applied to identifying MEs through the individual case safety reports (ICSRs) that are sent to the centres.

The centres could improve their ICSR reporting form with elements that are relevant for identifying and differentiating MEs from ICSRs, and for assessing the preventability of MEs. The P method – where P stands for preventability – was developed to this end, and can be applied to any reported adverse event once a reasonable link between the event and the suspected drug has been validated by a causality assessment.

THE P METHOD, developed by the WHO Collaborating Centre for Strengthening Pharmacovigilance Practices (CAPM) in Rabat, Morocco, is systematically used to assess preventable adverse drug reactions through reported ICSRs. The Moroccan experience has inspired some national pharmacovigilance centres, such as those in Iran and Croatia, to use the P method to evaluate the rate of preventable ADRs in their database.

An identified medication error should be analysed in terms of the harm caused to the patient, the stage of their occurrence in the medication use process, the medication problem, and the therapeutic groups that have a higher risk to cause harm to the patient.

Reports of MEs that have caused serious harm should be analysed in order to understand the contributory factors and root causes, which requires an understanding of human errors and human factors. Contributory factors are those that influence the performance of individuals whose actions may affect the delivery of safe and effective care to patients, and may be considered to either influence a medical error or to actually cause it.

The objective behind having pharmacovigilance centres collect MEs is to detect recurrent errors, so that risk minimization actions (RMAs) can be put in place. Several examples of prevention strategies have been outlined in the guideline to help pharmacovigilance centres launch RMAs. These actions should be undertaken in collaboration with all stakeholders who are involved in medication error issues.

FOR THE BENEFIT OF PATIENTS, pharmacovigilance centres should collaborate with institutions and organizations that are completely or partially involved in patient safety promotion, or in collecting, analysing and preventing medical errors in their countries. Such partnerships are essential to develop further tools and methods to prevent medicine-related adverse events.

Implementing this guideline is a great opportunity for pharmacovigilance centres to join efforts to reduce the occurrence of MEs. Sharing experiences and findings will be easily done through the pharmacovigilance network and thus allow the centres to show their valuable contribution to the enhancement of patient safety.

The issue of medication errors is a priority to CAPM; the centre contributes to decreasing related risks through RMAs carried out together with the Moroccan health authorities. Collaborative initiatives from all stakeholders engaged in tackling MEs are encouraged and will be strongly supported to ensure patient safety.

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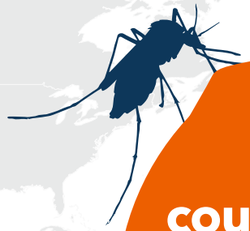
READ MORE: World Health Organization, *Reporting and learning systems for medication errors: The role of pharmacovigilance centres,* Paris, World Health Organization Press, 2014.



September 2016

Outbreak counter measures

As more and more cases of microcephaly, central nervous system malformations, and Guillain-Barré syndrome (GBS) occur, the global health community are scrambling to put more counter measures on the market.

55

MOSQUITO-BORNE
55 countries – 46 in the Americas, two in Africa, and seven in the Western Pacific Region – have reported a first outbreak of mosquito-borne Zika virus since 2015.

PERSON-TO-PERSON
12 countries – in the Americas, Europe, and Western Pacific Region – have reported evidence of person-to-person transmission of Zika virus, probably through sexual contact.

PHASE 1
Two DNA vaccines are in Phase 1 clinical trials, with dozens of candidates still in the non-clinical phase.

5

POSSIBLE ENDEMIC
Five Asian nations have reported a *possible* endemic transmission or evidence of local mosquito-borne Zika infection in 2016.

HARDEST HIT
In Brazil 1,857 cases of microcephaly and/or CNS malformations potentially associated with Zika virus have been counted. In contrast, Colombia – the second hardest hit country – has counted 38 cases.

IN A SITUATION REPORT from September, WHO listed 72 countries that have reported locally transmitted mosquito-borne infection, person-to-person transmission, and possible endemic transmission or evidence of local mosquito-borne Zika infection.

As Zika virus continues to spread, several different vector control options are used or under investigation. Traditional measures to manage mosquito populations include limiting the breeding grounds for the vectors by removing and cleaning out water containers of all sizes and preventing stagnant water, using larvicides in water, and using mosquito spray indoors. Recommended personal protection is to wear clothing that minimizes skin exposure to bites, applying mosquito repellent products to the skin, and using window and door screens and air conditioners indoors, as well as insecticidal mosquito nets.

New vector control tools are also being examined. Two that are are considered for carefully monitored pilot deployment are microbial control of human pathogens in adult vectors, where the introduction of a strain of symbiotic Wolbachia spp. bacteria (wMel) into Aedes aegypti populations reduces the mosquitoes' ability to transmit arboviruses to humans; and mosquito population reduction through genetic manipulation, using a transgenic strain of Aedes aegypti engineered to carry a lethal genetic system. Mosquitoes carrying the gene die before functional adulthood.

Different Zika vaccine candidates are under investigation. In WHO's Vaccine Pipeline Tracker – a spreadsheet available online – they have listed 29 vaccine candidates for Zika virus, out of which two DNA platform vaccines begun Phase 1 clinical trials in July. Studies for the candidate GLS-5700 by GeneOne Life Science/Inovio Pharmaceuticals are estimated to be completed in November 2017. The other candidate, VRC ZIKV DNA created by the Vaccine Research Centre (VRC) at the National Institute for Allergy and Infectious Disease (NIAID) is estimated to reach completion in December 2018. The other 27 vaccine candidates are still at the non-clinical stage.

MICROCEPHALY & GBS
As of September, 20 countries and territories have reported microcephaly and other central nervous system (CNS) malformations potentially associated with Zika virus infection or suggestive of congenital infection. Additionally, 18 countries and territories worldwide have reported an increased incidence of Guillain-Barré syndrome (GBS) and/or laboratory confirmation of a Zika virus infection among GBS cases.

Sources: www.who.int/emergencies/zika-virus
Situation report: www.who.int/emergencies/zika-virus/situation-report
Vector control: www.who.int/csr/resources/publications/zika/vector-control
Vaccine tracker: www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet

IMAGINE YOURSELF WAITING at the bus stop or in a hospital waiting room. In the good old days, people were reading books, newspapers or just relaxing while waiting. Over the past few years, however, this scenery has shifted dramatically. Nowadays it's hard to find anyone awake who is not using their smartphone. The phone is always at hand, for example during dinner parties when discussions about the height of the Eiffel Tower or the size of Sweden is abruptly interrupted by someone googling the answer on their smartphone.

The above reality is something that can and should also be used to improve pharmacovigilance; There are enormous possibilities to collect information from all kinds of resources, but also to get information out to those who need it, when they need it.

One ongoing project aiming to explore these opportunities is the WEB-RADR project. The project has two parts: one is about monitoring/mining social media streams as a new way of finding drug related safety information, while the other is more specifically about using mobile technologies for reporting safety concerns.

So why has the importance of data collection and information spreading increased? To start with, patients and healthcare professionals are much more used to searching for information online – and they expect to find the answers. Many are also getting used to sharing information in different types of social media forums, both general and more specialized forums. Moreover, the simplified access to medicines via web channels challenges the traditional way of data collection and risk communication (previously often communicated to healthcare professionals in "dear doctor" letters and leaflets).

Scientifically, there is also an increased need for more information. With a drive towards shortened development processes to get drugs on the market earlier to benefit both patients and generate income earlier, there is an increased need to capture traditional "post-marketing" information as part of the safety evaluation of new drugs.

WHAT COULD MOBILE TECHNOLOGIES provide that cannot be delivered via traditional channels such as online web reporting?

At the research conference Uppsala Forum in May, François Houÿez, director of Treatment Information at EURODIS, which is also a part of the WEB-RADR consortium, put forward some of the benefits of mobile technologies. According to Houÿez, there are a number of things a mobile device can bring to reporting of adverse events: pictures taken by camera, bar-code scanning for identification of medicines, geographical location (for SSFFC detection), health data collected via wearable technology, weather information (that could help explain respiratory issues for example), voice recordings, and so on. Voice recordings especially, that translate speech to text, is something that could really speed up and simplify the process of describing the event reported.

BUT WHY WOULD ANYONE wish to report an adverse event via a mobile app? Most patients report very rarely. Healthcare professionals should report more frequently, but what is in it for them? The answer to this is that the reporting functionality must be bundled with functionalities that are of use to the reporter. Interviews with users revealed that reporters generally would like to get information back, such as reporting statistics, targeted news about the drug they take, and feedback on the reporting they do.

Magnus Wallberg and Hussain Talib Al Ramimmy from Oman's Ministry of Health discuss a WEB-RADR app at a course in Uppsala, Sweden. Photo: UMC

"Patients and healthcare professionals are much more used to search for information online – and they expect to find the answers."

The initial app developed in the WEB-RADR project has focused on the latter parts – sending information back to the reporters – and kept the reporting functions simple, without including more advanced features such as pictures and so forth. The reason to not include all features is that the project tries to keep to existing reporting standards, such as E2B, in order to be able to use existing processes as far as possible, while at the same time ensuring that the app itself is interesting to install. Later in the project it is planned to upgrade to the forthcoming E2B (R3) standard. This will allow more information to be embedded in the reports, but it will also require that the receiving systems at the involved authorities can handle this additional information.

E2B is the international standard used to transfer information about adverse events. The standard is quite elaborate and complex, so parallel to the WEB-RADR project a "Simplified E2B guide for primary reporters" as well as a guide for transferring such data to authorities have been developed.

Presently, the WEB-RADR project has delivered three smartphone apps available for iOS and Android. The authorities behind those apps are the Dutch pharmacovigilance centre Lareb, Croatia's health authority HALMED, and the UK regulator MHRA.

MUCH REMAINS TO BE DONE before it will be as natural to look up drug safety information and report drug-related issues on our mobile devices as it is to google the height of the Eiffel Tower during dinner, at the bus stop, or in the hospital waiting room. The apps being developed in the WEB-RADR project will not take us all the way there, but they are important steps on the road.

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Two new apps launched in 2016

LAREB APP FOR REPORTING AND INFORMATION

In January, the Netherlands Pharmacovigilance Centre Lareb launched their side effects app "Bijwerkingen" ("Side effects"). The uptake was good and in the few weeks following the launch the number of downloads was quite high. However, it is a challenge to keep promoting the app and increase its uptake.

The app is both an information and a reporting app. The ratio of downloads to reports is about 250, so only 1 out of 250 users report, indicating that it might mainly be used as a source of information. So far, its use for reporting is almost equally split between patients and healthcare professionals. The reports received seem to be of good quality, but further evaluation of them within the WEB-RADR project is planned for later in the year.

CROATIAN APP LINKS TO VIGIFLOW

Croatia's Agency for Medicinal Products and Medical Devices (HALMED) presented their mobile application for reporting suspected adverse drug reactions in May. The app not only lets users report, but also view reporting statistics for all medicines, and select particular medicinal products from the agency's Medicinal Products Database and get updates about their safe use.

The app aims "to additionally strengthen the involvement of patients and healthcare professionals in the monitoring of safe use of medicinal products by enabling a simple and direct way of ADR reporting via smartphones," a HALMED press release stated. The HALMED app is directly connected and automatically sends reports to the UMC tool VigiFlow®, which the Croatian authority uses to manage their Individual Case Safety Reports (ICSR).

Linda Härmark
Head of Innovation at the Netherlands Pharmacovigilance Centre Lareb, contributed the Lareb app update.

READ MORE:
www.lareb.nl
www.halmed.hr/en

Health research in Africa needs INTERNATIONAL PARTNERS, NOT PARACHUTISTS

*The sub-Saharan **research community** needs true international **partners** to help build regional scientific capacity – not "parachutists" who conduct research on the continent without **sharing** the results, argues Professor Alex Dodoo at the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance in Ghana.*

IN THE ARTICLE "Partnerships, Not Parachutists, for Zika Research", published by Heyman et al in the New England Journal of Medicine, the authors lamented the lack of data and virus sharing amongst the scientific and public health community in relation to Zika research.

Touching on the recent Ebola pandemic, the authors stated inter alia that "West Africa became a playground for researchers" – a phrase that will ring true to several researchers in sub-Saharan Africa. Similar sentiments have been expressed by other researchers who, especially during the Ebola outbreak, called for some form of research and development ethics that require capacity-building of local researchers and regulators for Ebola in particular, and all other interventions in general.

AFRICA DOES NOT have a strong health force for health research. WHO and other groups have worked over the years to improve capacity and some progress has been made. However, several capacity-building initiatives are donor-driven, focusing on the needs and interests of the donor with some assumption that donor-led approaches represent the best interest of the countries involved.

In nearly all such cases, some consultation takes place, but even a casual chat with any leading scientist or policymaker in Africa will reveal the unease they feel when they are invited to a meeting with a pre-set agenda. Given the boundaries within which funding is provided, the local professional can hardly be considered to have been truly consulted. As one such individual mildly put it, "it is like downloading a free programme from the Internet and being asked whether you agree to the conditions of use". Click no and that is the end. Invariably, we all click yes, despite any reservations we may have or any desire for progress we would have shared, had we been given the opportunity.

COUNTRIES IN SUB-SAHARAN Africa need partners to build stable and lasting infrastructure for safety monitoring of existing and new medicines and vaccines. They need technical assistance and they need adequate financial support both for targeted programmes as well as unrestricted financial support to enable them to innovate and create programmatic systems for monitoring the safety of products in their local environments.

As stated previously, some infrastructure has been built in Africa for clinical research and safety surveillance. The focused efforts of WHO and Uppsala Monitoring Centre to create a sustainable medicines safety hub in Africa in the form of the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, hosted at the University of Ghana, and the emergence of the African Collaborating Centre for Pharmacovigilance (ACC) are good examples of what can be obtained when true partnerships are built. The ACC is fully African-led and provides much-needed pharmacovigilance leadership on the continent.

"They need technical assistance and they need adequate financial support both for targeted programmes as well as unrestricted financial support to enable them to innovate and create programmatic systems for monitoring the safety of products in their local environments."

In the area of clinical trials, the European and Developing Countries Clinical Trials (EDCTP) platform built four regional Networks of Excellence for clinical trials, trained 14 PhDs, 44 Master of Science graduates; in addition, over 1,000 Africans have been educated in Good Clinical Practice, Good Clinical and Laboratory Practice, IT, and laboratory techniques. Not surprisingly, EDCTP's efforts have directly led to 38 peer-reviewed publications and upgraded infrastructure at 40 research sites.

WHAT SHOULD SOME of the essential elements of genuine partnerships in health research in Africa be? At the very least, there should be an understanding of the complete environment in which African researchers work and the challenges they face: power outages, poor Internet connectivity, low wages, political interference, lack of basic infrastructure, and so forth. Linked to this understanding should be empathy and a genuine desire to support, collaborate, and cooperate to ensure that sustainable systems are built based on the needs and priorities of Africa. This should be done with a view to ensure adherence to global standards and with continuous engagement with the international community, especially in the area of data sharing.

Sub-Saharan Africa needs help, but this help should be provided in a mature framework that involves mutual respect, cooperation, and understanding. The helpers must be true partners who will feel the pain of Africa, rather than parachutists who come in, grab what they want, and disappear forever taking the knowledge gained with them.

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READ MORE:
Partnerships, Not Parachutists, for Zika Research
David L. Heymann, M.D., Joanne Liu, M.D., and Louis Lillywhite, M.B., B.Ch. N Engl J Med 2016.

UMC's 2016 pharmacovigilance courses in retrospect

Group photo of course participants and some UMC staff at the 18th International Pharmacovigilance Training Course in Uppsala. Photo: UMC

Uppsala Monitoring Centre's ***renowned*** *global pharmacovigilance courses have attracted* ***participants*** *from every corner of the world to events in Sweden and India in 2016.*

THE SCIENCE OF pharmacovigilance is a global endeavour that becomes stronger the more organisations and individuals are involved in it. Uppsala Monitoring Centre (UMC) recognises that building solid, regional pharmacovigilance capacities is a key component in the world-wide effort to improve medicines safety. With this goal in mind, UMC draws on the expertise and experience of its staff and external pharmacovigilance professionals to put together the agenda of its pharmacovigilance training courses.

The course in Uppsala, Sweden – labelled the International Pharmacovigilance Training Course – has shared insights into medicines safety-related issues for 18 years. The Asia Pacific Pharmacovigilance Training Course – in its second year – was launched in collaboration with JSS University's College of Pharmacy in Mysuru, India, in order to create more learning opportunities and cutting the cost of travel and time for pharmacovigilance professionals in the Asia Pacific region.

THE COURSE IN MYSURU, this year organised between 18-29 January, follows the original course concept that's been developed in Uppsala over so many years. The idea behind the course is to offer pharmacovigilance training that is relevant to the region, that combines UMC's global perspective and scientific and technical excellence with the public health qualities offered by the local partner – JSS University.

Dr G. Parthasarathi, the principal of JSS College of Pharmacy and dean of JSS University's Faculty of Pharmacy, emphasized the regional flavour of the Mysuru event. "This course is modelled after the one in Uppsala, but at the same time we have more experts coming from the local region, and the knowledge-sharing comes from their own experiences from real-life situations and Asia-specific problems," he said. "We're trying to build a competence that meets global requirements, while keeping the local needs in mind," he continued.

This year, participants from India and its immediate neighbour countries, as well as from South East Asia and Africa, attended. The faculty consisted of specialists from UMC, JSS, US pharmacopeia, the European Medicines Agency (EMA), the Pharmacovigilance Programme of India (PvPI), the Indian pharmaceutical industry, Lareb – the Dutch WHO Collaborating Centre in pharmacovigilance, and the University of Queensland in Australia. The main part of the course took place in the charming campus of the JSS College of Pharmacy, accredited to be one of the ten best pharmacy colleges in India.

One of the special features of the Mysuru course is the immediate access to JSS Hospital and its model for integration of pharmacovigilance into clinical pharmacy practice and patient management. A study visit to this environment encourages discussions around practical implementation of pharmacovigilance in a low- and middle-income country setting, and around issues of managing patients affected by medicines-related harm.

THIS YEAR'S INTERNATIONAL Pharmacovigilance Training Course took place in Uppsala between 16-27 May, and hosted participants from over 20 countries across the globe.

The lecturers came from UMC, as well as from WHO Collaborating Centres in pharmacovigilance – namely Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM) in Morocco, and Lareb in the Netherlands. Expert speakers from WHO's Safety and Vigilance team, the pharmaceutical industry, and the scientific community were also present.

"The organization of the course was excellent, UMC staff were very warm and helped me to feel at home though I was thousands of miles away," Onome Thomas Abiri, a course participant from Sierra Leone, said. "The course content was super rich, thorough, and relevant to my practice of pharmacovigilance, and the tutors presented the materials in a way I call pharmacovigilance made simple," Abiri said.

The open exchange of thoughts and ideas in a group of 30 participants from 20 different countries offers a unique opportunity for both participants and lecturers to learn more about the struggles and challenges each country face in pharmacovigilance. Learning from each other's experiences adds an extra dimension to the knowledge foundation that the participants build up throughout the two-week course, and solutions to country-specific problems take shape in real-time through the participants' classroom conversations.

The course offers an environment that stimulates ideas for what the next step forward should be, and initiates collaborations and exchanges of ideas that may pave a path toward safer medicines for all.

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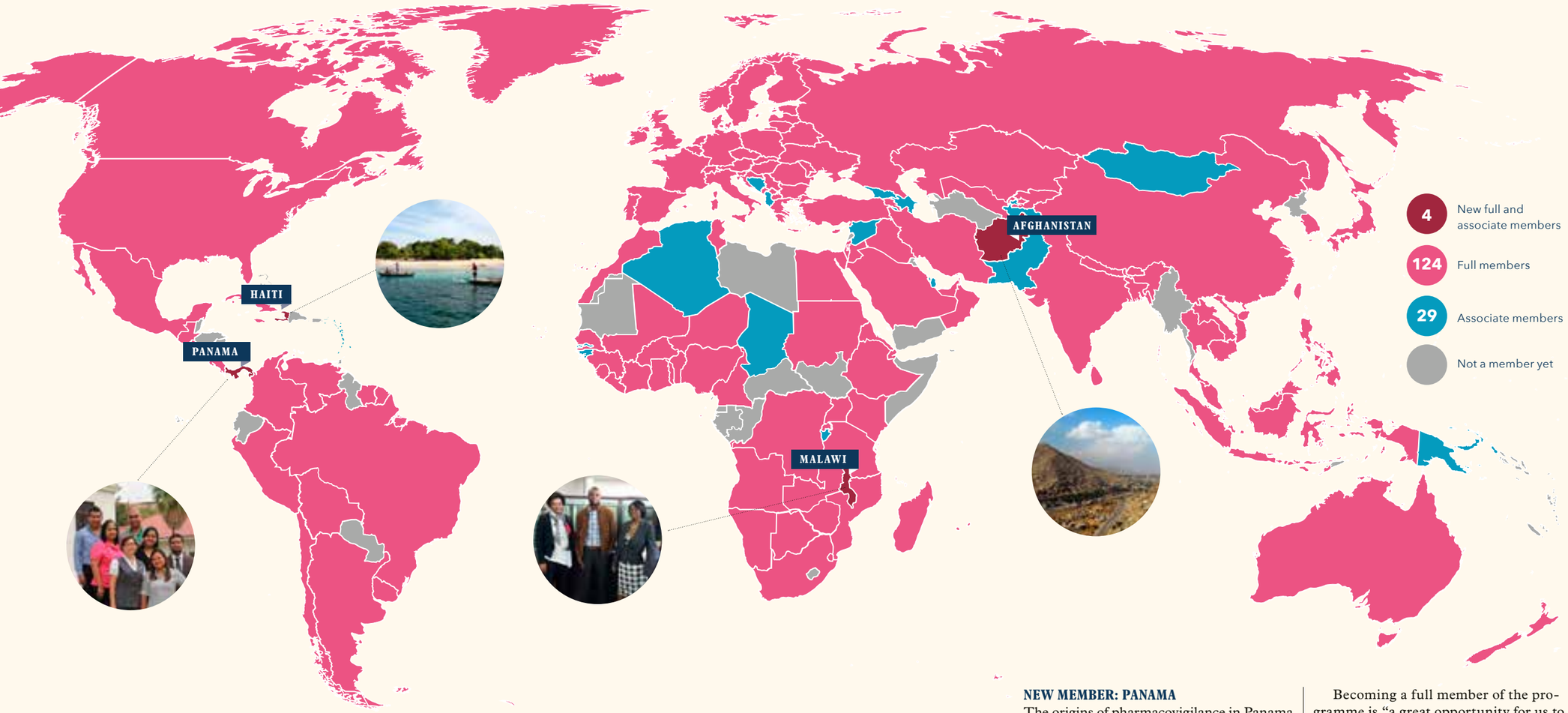
WHO PIDM



WHO Programme for International Drug Monitoring

NEW MEMBERS

Since the beginning of the year, two new full members and two associate member countries have joined the WHO Programme for International Drug Monitoring (WHO PIDM), bringing the total to 124 full and 29 associate members.

NEW MEMBER: PANAMA

The origins of pharmacovigilance in Panama date from 1998, and in 2001 a National Law of Drugs was approved, which established pharmacovigilance as an activity to be developed by the National Drug Regulatory Authority (Dirección Nacional de Farmacia Drogas).

The Ministry of Health of Panama is responsible for guaranteeing the safety, quality, and efficacy of the drugs marketed, as well as to establish any new regulation for drug marketing authorizations and rational use of drugs.

Panama became an associate member of the WHO PIDM in 2005, and has made steady progress since then, including the introduction of pharmacovigilance training in the university curriculum. The country recently adopted VigiFlow® as its data management tool.

Becoming a full member of the programme is "a great opportunity for us to grow up and make pharmacovigilance stronger, always bearing in mind that we are all responsible for monitoring any drug-related problems in pro of safety patients," Mario A. Torrero at the pharmacovigilance department said.

NEW MEMBER: AFGHANISTAN

In January 2016 Afghanistan became a full member of the WHO PIDM. This encouraged the country's General Directorate of Pharmaceutical Affairs at the Ministry of Public Health to focus more on adverse drug reaction (ADR) reporting and capacity building.

Afghanistan wants to enhance its capacity to regulate the pharmaceutical sector through different mechanisms, including pre- and post-marketing surveillance of medicines. A medicines policy for the years 2014-2019 notes that pharmacovigilance encourages practising physicians, pharmacists, and nurses, as well as manufacturers and patients, to submit data to the National Centre on suspected adverse reactions, product quality issues or medication errors associated with medicines.

An assessment of ADR reporting and management conducted at six national hospitals in Kabul in 2013 showed that there was no system in place for ADR detection, reporting, and management in the country. An ADR reporting system pilot ran in four hospitals in 2014-2015, and was expanded to additional central and regional hospitals. Currently the reporting system has been established in 16 central and four regional hospitals, and 386 health professionals have been trained in pharmacovigilance.

NEW ASSOCIATE MEMBER: MALAWI

Malawi's first pharmacovigilance centre was established at the College of Medicine in Blantyre, the country's financial centre.

"As Malawi was not a member of the global drug safety monitoring community we have relied on data from other countries. Realising the disparities that may exist in the side effects that occur in different countries, we wished to introduce pharmacovigilance in Malawi to collect data relevant to the country," said the National Centre staff Ms N. Dzabala and Mrs F. Chimimba, who have received pharmacovigilance training in Uppsala and in Ghana, respectively.

The centre has started training health care professionals on pharmacovigilance practices and plan to push for the inclusion of pharmacovigilance in the curricula of medical training institutions.

NEW ASSOCIATE MEMBER: HAITI

In January 2016 WHO received an application from the Ministère de la Santé Publique et de la Population of Haiti to join the WHO PIDM. Work is underway to establish relationships with the new office in Port-au-Prince as an Associate Member of the programme.

A special thanks to Mario A. Torrero from Panama, Adbul Hafiz Quraishi from Afghanistan, and N. Dzabala from Malawi for contributing to this article.

Japan's model for post-marketing medicines safety

*Product reviews, post-marketing safety measures, and relief services are the three main **focus areas** of Japan's Pharmaceuticals and Medical Devices Agency (PMDA). The agency has recently taken steps to enhance the **effectiveness** of its post-marketing safety measures.*

IN 2001, the PMDA introduced a programme known as Early Post-marketing Phase Vigilance (EPPV), which was designed to reflect the critical importance of monitoring adverse drug reactions (ADRs) during the first six months following the approval and retail launch of a new drug. This programme requires that marketing authorization holders provide all information necessary for proper use to applicable healthcare professionals, and must also actively gather adverse drug reaction (ADR) related information during the EPPV timeframe by making periodic visits to hospitals and medical institutions.

The goals of EPPV are to promote the proper use of newly approved drugs, detect serious adverse reactions as early as possible, and prompt execution of safety countermeasures. Moreover, the EPPV programme will generate especially valuable information in cases where innovative new drugs are approved in the near future under Japan's new "SAKIGAKE" expedited review system.

"The Asia Training Center (ATC) will provide critical regulatory training for staff members of regulatory agencies."

ANOTHER POST-MARKETING safety measure implemented in Japan is drug-specific risk management plans (J-RMPs), introduced in 2013. J-RMPs are designed to facilitate the performance of necessary safety measures by evaluating the benefits and risks of drugs throughout their lifecycles. A J-RMP is a compact document comprising three elements: safety specifications, a pharmacovigilance plan, and a risk minimization action plan. EPPV is conducted under the J-RMP as part of the pharmacovigilance and risk minimization action plans.

THE MEDICAL INFORMATION for Risk Assessment Initiative (MIHARI, a word that means "guard" in Japanese), launched in 2009, is another post-marketing safety programme administered by the PMDA. The primary aim of the MIHARI project is to leverage large-scale electronic health information databases as novel sources of information to support pharmacoepidemiological drug safety assessments. The project is expected to complement the ongoing collection of spontaneous adverse event reports by adding capacity for quantitative risk estimation. The MIHARI pilot studies evaluated the system's ability to effectively conduct quantitative risk forecasting for drug products as well as the impact of regulatory safety actions.

The PMDA's MID-NET (Medical Information Database Network) project is a nationwide initiative to establish a network of databases to support the electronic healthcare data monitoring and analytical activities of the MIHARI project.

THE PMDA ESTABLISHED its "Asia Training Center for Pharmaceuticals and Medical Device Regulatory Affairs" on April 1 this year. The Asia Training Center (ATC) will provide critical regulatory training for staff members of regulatory agencies of Asian nations. The content of ATC training programmes includes information concerning benefit–risk assessment of medical products as well as post-marketing safety measures.

Lastly, the PMDA will establish a Regulatory Science Center by 2018. This centre will be involved with risk identification and simulation/modelling activities based on electronic data. The centre's activities will be conducted in close collaboration with relevant members of academia, scholarly societies, and representatives of industry from medical product companies from around the globe.

EACH OF THE PROGRAMMES and activities described above will work to ensure the integrated and efficient execution of post-marketing safety measures in Japan, and also contribute to global pharmacovigilance efforts.

Rika Wakao
Review Director, Office of Regulatory Science, Pharmaceuticals and Medical Devices Agency (PMDA Japan)

INSPIRE. ENGAGE. TRANSFORM

Database of WITHDRAWN drugs

*A **database** of medicines that have been **withdrawn** or discontinued from circulation in the global pharmaceutical market because of **adverse drug reactions** has been established.*

THE STRUCTURAL Bioinformatics Group at Charité – Universitätsmedizin Berlin, Germany, established the WITHDRAWN website, where a lot of information from this database is publicly available online.

The site claims to be complete regarding withdrawals from the US and EU markets since the 1960s. Information from other markets has been obtained from literature, public databases, and text books, but completeness is not assured. The database is updated annually and currently contains information on 578 medicines.

For each of the withdrawn or discontinued medicines the following technical information is provided:

- Chemical structure (JChemSuite)
- Therapeutic use (ATC classification)
- Acute toxicity class
- Human protein target for effect
- Information on genetic variations (SNPs)
- Type of adverse reaction
- A set of physiological pathways e.g. cytochrome P450 metabolism

The WITHDRAWN database provides several options for information retrieval. Medicines may be searched on the basis of name, classification or structure. You may also search by protein target for effect or by type of toxicity leading to withdrawal or discontinuation. The facility allows scientists involved in drug development or toxicity prediction to learn about chemical structures of medicines or their effects on human protein targets and their variability, that have caused harm to patients in the past.

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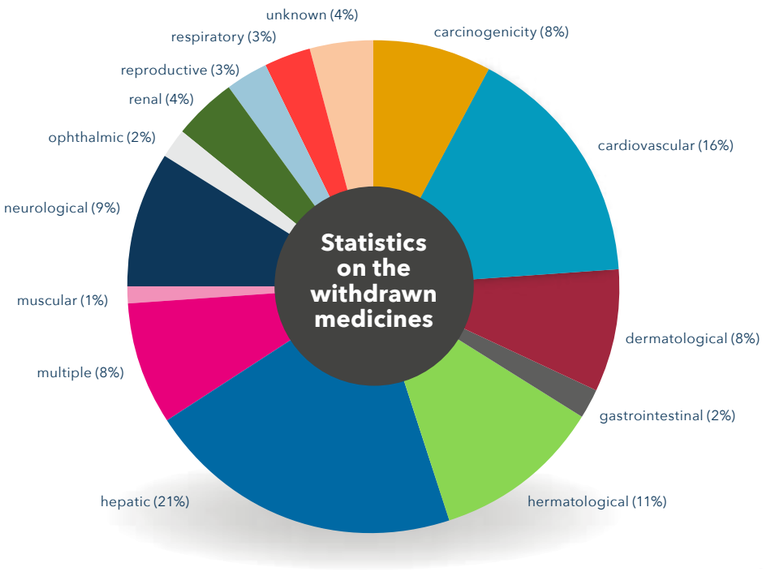
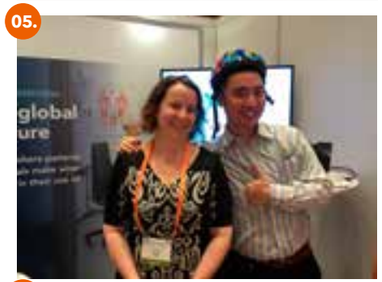
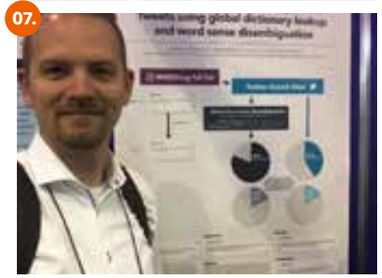
READ MORE: www.cheminfo.charite.de/withdrawn

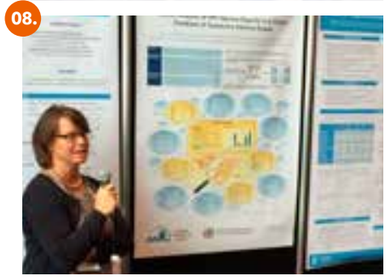
V.B Siramshetty, J., Nickel, C. Omieczynski, B-O Gohlke, M.N. Drwal, R. Preissner, *WITHDRAWN – a resource for withdrawn and discontinued drugs.* Nucleic Acid Research 2015.



01. UMC´s Bruce Hugman presented a poster at Evidence Live in Oxford, UK, in June. **02.** I ♥ coding! Attendees at the WHODrug User Group Meeting in Hamburg, Germany, in April. **03.** Dr Ola Caster gave a presentation on how to utilise VigiBase® data for regional signal detection at DIA's Annual Meeting in Philadelphia in June. **04.** Rebecca Kush, president and CEO of CDISC, and Hidetoshi Misawa, J3C chair, together with UMC's Yoko Yoshimoto Tyrefors and Damon Fahimi at CDISC Interchange Japan in May-June. **05.** UMC gave away one of its helmets in a raffle at DIA China Annual Meeting in Beijing in May. The winner was happy to try out his prize next to UMC's Anna Mattsson. **06.** One of the happy winners in UMCs raffle at ICPE Dublin. **07.** UMC´s Tomas Bergvall presented a poster at ICPE Dublin. **08.** UMC´s Dr Rebecca Chandler presented a spotlight session about HPV vaccine and POTS at ICPE Dublin. **09.** Can you spot the difference? UMC's Damon Fahimi, Anna Mattsson, and Ola Caster in Philadelphia, USA, in June – at DIA's Annual Meeting and at a charity run in connection to the event, June 2016.







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Pharmacovigilance Meetings 2016

6-9 October 2016
EACPT Focus Meeting on 'How to Assess Medicines'
Opatija, Croatia · European Association for Clinical Pharmacology and Therapeutics (EACPT)
www.eacpt-focusmeeting.eu

10 October 2016
Observational Research and Pharmacoepidemiology in Europe: Deeper insights to drive health research and discovery
Amsterdam, Netherlands · European Epidemiological Forum
http://2016-epiforum.eventify.it

12-14 October 2016
X Congreso Nacional de Farmacovigilancia
Mérida, Yucatán, Mexico · Mexican Pharmacovigilance Association (AMFV)
www.amfv.org.mx

12-13 October 2016
Assessment and Medical Evaluation of Individual Case Reports
Fareham, UK · Drug Safety Research Unit (DSRU)
www.dsru.org/courses

16-19 October 2016
16th ISoP Annual Meeting: Pharmacovigilance for a safer tomorrow
Agra, India · International Society of Pharmacovigilance (ISoP)
www.isop2016agra.org

17-18 October 2016
Risk Management and Safety Communication Strategies
Washington, DC, USA · Drug Information Association (DIA)
www.diaglobal.org

19-20 October 2016
Risk Benefit Assessment in Pharmacovigilance
Fareham, UK · Drug Safety Research Unit (DSRU)
http://www.dsru.org/courses

25 October 2016
Nordic Pharmacovigilance Day 2016
Copenhagen, Denmark · Life Science Academy
http://nordicpharmacovigilanceday2016.eventify.it

22-24 November 2016
3rd European Conference on Monitoring the Effectiveness of Risk Minimisation
Prague, Czech Republic · Drug Safety Research Unit (DSRU)
www.dsru.org/courses

23-24 November 2016
Signal Management in Pharmacovigilance
Basel, Switzerland · Drug Information Association (DIA)
www.diaglobal.org

5-9 December 2016
African Society of Pharmacovigilance 2016 meeting
Mombasa, Kenya · African Society of Pharmacovigilance (ASoP)
Info: khaemba@pharmacyboardkenya.org; pv@pharmacyboardkenya.org

6-8 December 2016
Pharmacovigilance
London, UK · Management Forum Ltd
www.management-forum.co.uk

Uppsala Monitoring Centre courses 2017

16-27 January 2017
3rd Asia Pacific Pharmacovigilance Training Course
Mysore, India · JSS University, UMC
www.jsspharma.org/online-registration-form
Register by October 1!

May 8-19 2017
19th International Pharmacovigilance Training Course
Uppsala, Sweden · Uppsala Monitoring Centre
Registration not yet open!

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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.