The Pharmacovigilance Bulletin

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Annual meeting draws Pharmacovigilance Experts to Kampala 2017

Pharmacovigilantes from nearly 60 countries will be converging in Kampala for the 40th annual meeting of the WHO Programme for International Drug Monitoring

EDITORIAL

Welcome to this latest issue of our Pharmacovigilance Bulletin. The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products based on communications received from our esteemed reporters in Uganda and from the international drug safety alerts. In this issue, we let you know why doctors should actively be involved in soliciting and reporting of all adverse events. We have updated you on our upcoming pharmacovigilance event what the whole world will converge in Uganda to deliberate on Pharmacovigilance

If you have any comments or feedback on any of the articles in this bulletin, we would be pleased to receive them at www.nda.or.ug

Further information on adverse reactions may be obtained from the National Pharmacovigilance Centre,

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With best wishes

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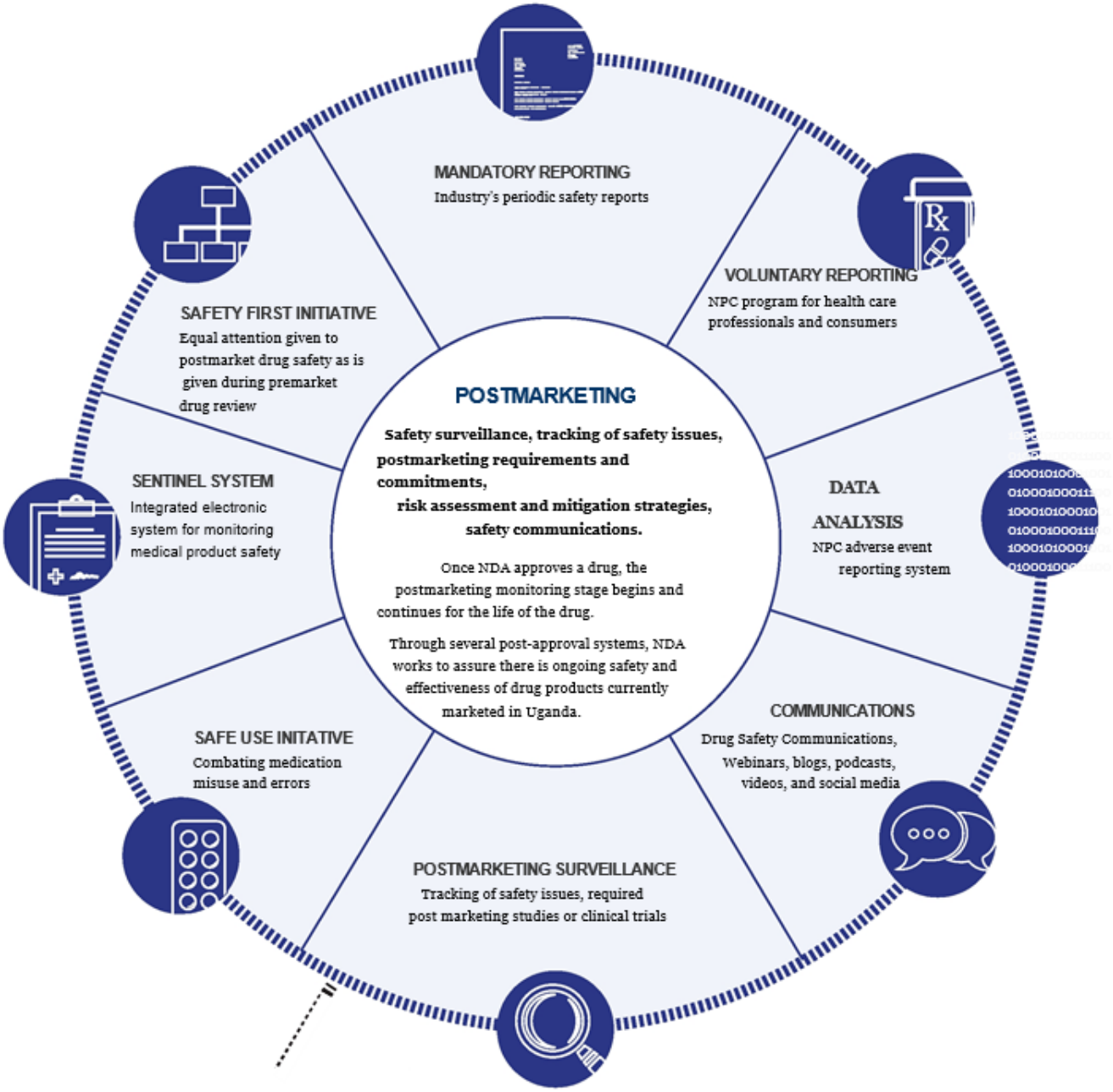

Case report: *Cycloserine induced Libido*

Case Presentation

A31-year-old African man reported to his doctor about a social inconvenience associated with an increase in sexual urge and erection following ingestion of Cycloserine I000mg. He had history of pulmonary MDR-TB and was on treatment with oral Cycloserine 1000mg od daily, levofloxacin 1000mg od, Ethionamide 1000mg and Pyrazinamide 2g daily. This patient was not on any other medication apart from HAART. He was not taking any dietary supplements or herbal medication. He was neither using alcohol nor other recreational drugs.
His CBCs are all normal. Renal function tests are normal. Around the time of the complaint, he had slightly elevated direct and total bilirubin, and GGT. The other LFTs and liver enzymes were normal. Unfortunately, blood levels of the drug were not assessed.
On presentation, Dr Sharon Namiiro of Mulago hospital reported that his clinical examination was unremarkable and without signs of drug use.

Initially this patient was initially taking 750mg, but when he gained weight, this was adjusted to 1000mg, and this was when the complaint started. He started noting continuous libido whenever he took his medicines.
When the drug was reduced to 750mg daily the patient's condition improved. The adverse drug reaction was assessed based on the Naranjo Algorithm where it scored 5 with a conclusion of (probably related)

Discussion

The available data allows for a broad association of Cycloserine with increased libido. The demographics, medical history and personal history of this patient did not suggest any underlying reduction in testerone. The time sequence of the start of Cycloserine and onset of the event is consistent with drug- induced libido. This is further supported by the dose- response effect. It could not also be attributed to altered metabolism as the LFT were normal. Although no rechallenge was attempted, the rapid improvement of after reduction in strength of Cyloserine (i.e. positive dechallenge) suggests an association of the high libido with the use of the drug. Other patients on the same drug did not report this events given the associated embarrassment but one day when we were training peer counselors after completion

Conclusion

Our opinion is that a relationship between the drug and the prolonged high libido which reduced with reduction in the strength of Cycloserine is plausible, and prescribers and users of cycloserine should be alert to the possibility of such adverse reactions. This case will be reported to the manufacturer of the drug

Communicating Drug Safety: A Global Public Interface

A. Etonogestrel implants (Nexplanon®) Reports of device relocating to vasculature system and lung

The United Kingdom. The MHRA has issued advice on the use of etonogestrel (Nexplanon®) implants to minimize risk of implants reaching the lung via the pulmonary artery.

Nexplanon® is a long-acting contraceptive implant containing the active ingredient etonogestrel. Nexplanon® is usually effective for three years.

For maximum effectiveness Nexplanon® needs to be correctly implanted by someone who is trained to fit it. The number of reports of Nexplanon® implants in the vasculature received by the licence-holder is estimated to be approximately 1.3 per million implants sold worldwide.

The MHRA has advised that: if an implant cannot be palpated at its insertion site in the arm, it should be located as soon as possible and removed at the earliest opportunity. It is also advised that chest imaging is performed, should this occur. Correct subdermal insertion reduces the risk of these events.

Evidence from literature shows that implants found in the vasculature can become endothelized into the pulmonary artery. If they are located early enough it is possible to remove them by an endovascular procedure. Women should therefore be shown how to locate the implant immediately following insertion and advised to check the position of the implant frequently for the first few months

B. Bromhexine-containing cough and cold medicines: Risk of allergy and skin reactions

Australia. The Therapeutic Goods Administration (TGA) has advised that product information for all bromhexineproducts (including generics) should contain information on the small risk of severe allergic reactions and severe skin reactions. The current package insert for the brand, Bisolvon®, already includes a warning regarding anaphylactic reactions and skin reactions.
A number of over-the-counter cough and cold medicines contain bromhexine as a mucolytic.

As of 19 February 2016, 34 cases of hypersensitivity reactions, 10 cases of anaphylactic/anaphylactoid reactions, and five cases of severe cutaneous adverse reactions (SCARs) had been reported to the TGA.

A definite link to bromhexine in 29 of these cases could not be made because: they involved products with multiple active ingredients or excipients such as benzoates which can also cause hypersensitivity; or there were other confounding factors.

The TGA reviewed this issue following a review by Europe's Pharmacovigilance Risk Assessment Committee (PRAC) that confirmed the risk of severe allergic reactions and SCARs associated with bromhexine- and ambroxolcontaining medicines. Subsequently, product information for these products was updated with warnings of these potential adverse events.
The TGA has found that similar warnings to those being implemented in Europe are appropriate for bromhexinecontaining

medicines marketed in Australia.

(See WHO Pharmaceuticals Newsletter No.2, 2015: Risk of allergy and skin reactions with the use of ambroxol and bromhexine expectorants in the EU)
Reference:
Medicines Safety Update, TGA, Vol. 7, No. 3, June 2016 (www.tga.gov.au)

C. Benzoyl peroxide Risk of wide-spread swelling

Japan. The MHLW and the PMDA have announced that the package inserts for benzoyl peroxide preparations (Bepio® and Duac combination gel®) have been updated to include the risk of wide-spread swelling as a precaution.

Benzoyl peroxide is indicated for acne vulgaris. It is available as a single agent or in combination with clindamycin (Duac combination gel®)

A total of seven cases of cutaneous symptoms with the use of benzoyl peroxide have been reported in Japan. Of these, a causal relationship could not be excluded in six cases.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reports on the cases of erythema and swelling spreading to the entire face and neck will be added as a precaution to the package insert.
Reference: Revision of Precautions, MHLW/PMDA, 5 July 2016 (www.pmda.go.jp/english/)

D. Diclofenac Risk of gastrointestinal stenosis and obstruction

Japan. The MHLW and the PMDA have announced that the package inserts for diclofenac preparations (Voltaren® and Rectos®) have been updated to include the risk of gastrointestinal stenosis and obstruction as clinically significant adverse reactions.
Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) and used for relief of pain and anti-inflammation.

A total of five cases of gastrointestinal stenosis or obstruction associated with the use of diclofenac have been reported in Japan. Of these, a causal relationship could not be excluded in four cases (one case was for a condition not included in the approved dosage and administration). In addition, the company core datasheet (CCDS) has been updated.

Following an investigation of available evidence and advice from experts, the MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 5 July 2016 (www.pmda.go.jp/english/)

Opinion

Mobile tech meets medicines safety

Imagine yourself waiting at the bus stop or in Mulago 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. The above reality is something that can 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

What could mobile technologies provide that cannot be delivered via traditional channels such as online web reporting? According to experts, 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, 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.

Where mobile tech meets medicines safety

NPC is investigating how mobile technologies can be utilized to collect and leverage important medicines

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.

Adverse reaction report for October 2016-December 2016

1.0 Background

The spontaneous reporting system (SRS) which is passive in nature is still the main method for collecting information on drug related issues. This is true even with several epidemiological methods being proposed and utilized to collect safety information for drugs. The National Pharmacovigilance Centre at the National Drug Authority of Uganda is responsible for ensuring that the medicines used in the country are safe, by establishing systems for collecting, collating and evaluation of information relevant to the risk benefit balance of medicinal products. The centre uses spontaneous reporting to get signals that are strengthened later through active methods. This report primarily highlights the individual case reports received in the period October to December 2016.

2.0 Reporting, Collation and Analysis of Individual Case Reports (ICRS)

A total of 146 individual case reports were received at the National Pharmacovigilance centre. Reports were received from various districts as shown in figure 1 while figure 2 shows the reports coming from district or referral hospitals and other specialized treatment centers that are not public facilities.

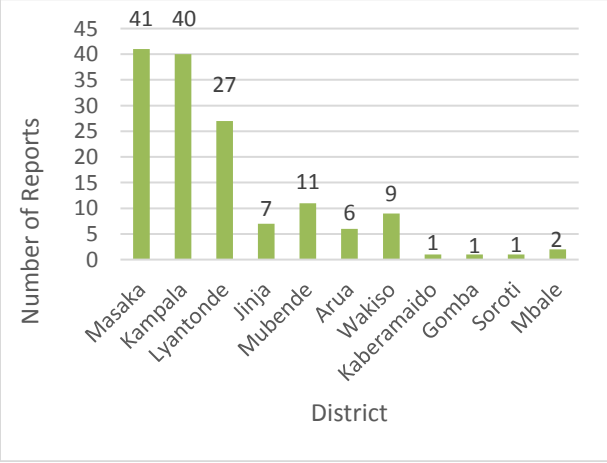

Figure 1. Graph showing the number of reports received from each district.

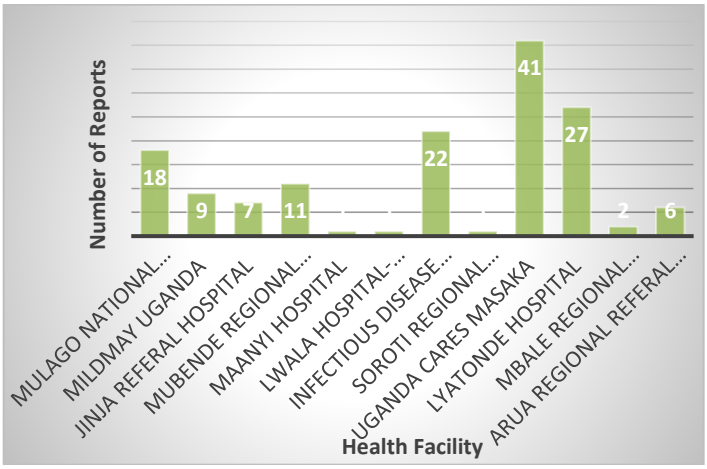

Figure 2 Facilities that submitted ADR Reports

2.1. Suspected drugs reported

In Uganda, patients have access to a number of drugs for a wide range of illnesses presented to a healthcare provider. In this reporting period, it is Tenofovir that was reported most by health workers as suspected to be the cause of adverse drug reactions with 46 cases (31.5%) but also was considered as potential suspect in 17 (11.6%) case reports (i.e reports where there is no isolated suspected drug in a combination of multiple drugs regimen). Zidovudine, Efavirenz and Kanamycin which is used in management of MDR-TB, were among the most reported drug to have caused serious reactions. Other suspected drugs that were reported on are represented in the figure 3 below with their respective frequencies.

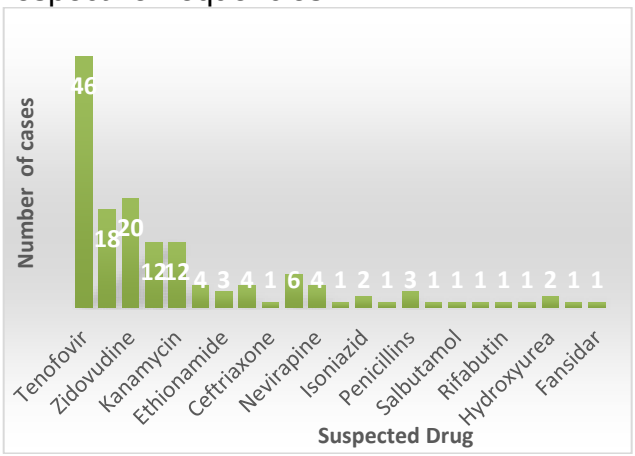

Figure 3 Suspected drugs and the attributed Number of individual case reports

2.2 Reported Reactions

Although majority of the reactions reported are expected with the exception of 2 cases (excessive libido attributed to cycloserine and cardiovascular disease attributed to Zidovudine), 39 cases (27%) were serious. The serious cases involved death, hospitalization, disabling reactions and life threatening reactions.

Table 1 below shows the different reactions attributed to various drugs.

Drug	Most prevalent reaction.
Tenofovir	Increase serum creatinine with other symptom (34 cases) Fanconi syndrome (2 cases) Osteomalacia (5 cases)
Tenofovir/Lamivudine. (Combination with no drug specified)	Renal impairment (2 cases) skin reactions (15 cases)
Zidovudine	Anaemia(15 cases) Peripheral Neuropathy(3 cases) lipodystrophy grade III(1 case) Cardio Vascular Disease(1 case)
Efavirenz	CNS effects. (4 case) Skin reactions (7 case) Gynaecomastia (2 case)
Kanamycin	Hearing impairment(12 cases)
Cycloserine	Hallucinations/psychosis (3 cases). Increased libido (1 cases
Ethionamide	GITsymptoms (Nausea,vomiting,epigastric pains).(2 cases)
Pyrazinamide	Hepatotoxicity(1 case)
Ceftriaxone	hypersensitivity(1 case)
Cotrimoxazole	Steven Johnson Syndrome(1 case)
	Severe skin reactions (5 cases)
Nevirapine	Skin reactions (4 cases)
Depoprovera	Prolonged bleeding(1 case)
Fansidar(S/P)	Macular papular rash (1 case)
Isoniazid	Hypersensitivity skin reactions(Vesicular lesions)(2 cases)
Acyclovir	Severe dermatitis(1 case)
Penicillins	Hypersensitivity (2 cases)
Tetanus Toxoid	Steven Johnson Syndrome(1 case)
Salbutamol	Croup (1 case)
Whole blood.	Urticaria (1 case)
Rifabutin	Hepatotoxicity.(1 case)
Carbamazepine/Pregabaline	Ulcerated lips and tongue(1 case)
Atazanavir/Ritonovir	Jaundice(1 case)
Hydroxyurea	Neutropenia(2 cases).
MDR-TB regimen (Ethionamide/ linezolide/ levofloxcin/ Bedaquiline)	Death(2 cases)

3.0 Signal Detection and Generation.

Tenofovir based regimen and Fanconi Syndrome (case reports)

Tenofovir Disoproxil Fumarate (TDF) based ART regimens is currently used as preferred first line or second line combination in HAART in Uganda. The National pharmacovigilance center has received several reports (40 cases) indicating fanconi syndrome related to the use of Tenofovir.

Patients with Fanconi Syndrom are reported to present with Proteinuria, raised plasma creatinine, hypokalaemia, hypophosphataemia, and glucosuria in absence of diabetes. Clinical symptoms include Generalized body pain/weakness (54.5%), joint pains (63%), limb/bone pains (lower back pain (18%), Limping gait -difficulty in movement (54 %), Paresthesia (18.2%)

Recommendation

We recommend close monitoring of patients started on TDF containing ART regimens and educating/encouraging the patients to report to the health workers once they experience any of the clinical symptoms mentioned above. Symptoms resolve once TDF is withdrawn

What is Pharmacovigilance?

According to the WHO, Pharmacovigilance is the science and activities relating to the de tection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

The National Pharmacovigilance Center

Regulatory authorities all over the world are facing an increased demand for patient welfare and safety. This, is why the National Drug Authority Phramacovogilance Center (NPC) is continuously collecting and evaluating information on all pharmaceutical products marketed in Uganda.

In pursuit of this function, NPV is taking all appropriate measures to:

1. Encourage physicians and other healthcare professionals to report the suspected ad- verse reactions to NPC.
2. Necessitate the pharmaceutical companies to systematically collect information on risks related to their medical products and to transmit them to NPC.
3. Provide information to end-users through adverse drug reaction news bulletins, drug alerts and seminars.

WHAT TO REPORT? (You do not need to be certain, just suspicious!)

NPC encourages the reporting of all suspected adverse reactions to medicines, including vaccines, OTC medicines, herbal, traditional or alternative remedies. ADRAC particularly requests reports of:

*ALL suspected reactions to new drugs (see drugs of current interest, front page)
*ALL suspected drug interactions
*Suspected reactions causing
•Death
•Admission to hospital or prolongation of hospitalisation
•Increased investigations or treatment
•Birth defects

Reports of suspected adverse drug reactions are best made by using the NDA reporting form which is available at the hospital or from the website:

Reports can also be submitted electronically, by going to the NDA website
http://www.nda.or.ug

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

This Pharmacovigilance 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-fueled chapter where Annie and Mac set out to stop the evil Count Erfeit from producing and selling fake medicines. This is followed by colorful 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 side-kicks 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.

Would you like to participate? Visit us at NDA