DrugLens NEWSLETTER

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Robust Pharmacovigilance Systems for the Local Industry

The Food and Drugs Authority (FDA) with support from the Department for International Development (DFID) organized the fifth training for Qualified Person for Pharmacovigilance (QPPV) from September 25th to October 5, 2017 for would-be QPPVs from the Local Pharmaceutical Industry. The training was followed by a one-day symposium on the topic **"Pharmacovigilance and Patient Safety"** for Managing Directors of the Local Pharmaceutical Industry.

The programmes were held in collaboration with the African Collaborating Centre for Pharmacovigilance (ACC) and the UK Medicines and Healthcare Regulatory Agency (MHRA).

The objectives of the training programme and the symposium were to:

- Train staff of the local pharmaceutical industry to set up systems and structures to ensure safety monitoring of marketed products to promote patient safety as envisaged in Section 125 of the Public Health Act 2012, Act 851.
- Promote understanding of the regulatory requirements for safety monitoring of marketed products by the Managers and Chief Executive Officers of the Local Pharmaceutical Industry and also obtain their buy-in in order to guarantee establishment of effective pharmacovigilance systems by the QPPVs.

The MHRA was represented by Dr. June Raine, the Director of Vigilance and Risk Management of Medicines and the Chair of the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA).

The Chief Executive Officer, Mrs. Delese Darko presents a certificate to a participant at the end of the 5th QPPV Training Programme, looking on is Dr. June Raine, the Director of Vigilance and Risk Management of Medicines, MHRA and Chair of PRAC, EMA

She gave a presentation to the participants of the fifth QPPV course on the topic "Establishment of Risk Management Systems for Safety Monitoring of Marketed Drugs: Experiences from the European Union" and was the Guest Speaker at the symposium where she gave a talk on "Operating Pharmacovigilance Systems to Support Safe Access to Medicines". She highlighted the need to monitor the safety of all products irrespective of the age of the molecule because old molecules could also come up with safety signals.

The Chief Executive Officer of the FDA with Facilitators and Managing Directors of the Local Pharmaceutical Industry at the Symposium

In a welcome address, the Chief Executive Officer of the FDA, Mrs. Delese Darko highlighted Ghana's achievement in medicine safety over the years and the expectation from the Managing Directors of the Local Pharmaceutical companies in setting up robust pharmacovigilance systems to the benefit of patients and consumers.

FDA's Intervention in Snakebite Management

Background

Snakebite envenoming (SBE) is a major public health problem among communities in West Africa with *Echis ocellatus* (West African carpet viper) responsible for 90% of snakebites and 60% of deaths.[1] Although the precise incidence of snakebite is difficult to determine and is often grossly underestimated, a recent study estimated over 314, 000 bites, 7300 deaths and up to 14,000 amputations occurring annually in sub-Saharan Africa.[2]

Meanwhile, envenomation from snakebites are treatable with anti-snake venom (ASV). A study in Ghana revealed that staff training, monitoring of compliance and patient education is able to reduce the case fatality rate in snakebites from 11% to 1.3%.[3]

FDA's Intervention

The Food and Drugs Authority (FDA) received 55 adverse event reports (including therapeutic ineffectiveness) from January 1, 2017 to July 13, 2017 for which the suspected products were ASVs. Investigation and causality assessment of the spontaneous adverse event reports revealed that the

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events may be due to the administration of less than the recommended dosage of the ASVs. The FDA therefore instituted additional Risk Minimization Measures (aRMMs) following recommendations made by the Technical Advisory Committee on Safety of Vaccines and Biological Products (TAC-VBP) in March 2017. The aRMMs involves training for health workers on snake envenomation, correct administration of ASVs and distribution of posters/fliers by Marketing Authorization Holders on the correct dosage of marketed ASVs. These interventions have since led to marked reduction in adverse event reports received for the ASVs.

Principles of Management of Snakebites

Therapeutic ineffectiveness to an ASV may be due to the wrong choice of ASV, use of monovalent Antivenom instead of a polyvalent one (since in most cases the type of snake causing envenomation is unknown), insufficient initial dose of antivenom, inactive antivenom or an excessive delay in administration after envenomation.

ASVs are the only effective specific treatments or antidotes for snakebite. These may be monovalent/monospecific or polyvalent/polyspecific (produced from several species of snakes).

When injected ASV neutralizes a fixed amount of venom and since snakes inject the same amount of venom into adults and children, the same dose/volume of ASV must be administered to both children and adults.[4]

It should be noted that not all bites by venomous snakes lead to venom injection. On an average of 50% of occasions, no venom is injected; this is referred to as a "dry bite".[4] ASVs will therefore not be needed in such instances. However, patients without clinical features of local or systemic envenomation should be closely observed before discharge from hospital. The time required to observe the patient with snakebite without clinical features of local or systemic envenomation in hospital before discharge is based on local protocols for the management of snakebites.

The effects of snakebite can be divided into distinct syndromes, such as Neurotoxicity, Systemic toxicity (including hypotension and shock), Coagulopathy, Rhabdomyolysis, Renal failure and Local tissue necrosis. These syndromes may vary in severity depending upon the species of snake.

Treatment of severe envenoming is a medical emergency that may require a range of medical skills, equipment, anti-snake venom and other medicines. Referral of severe envenoming should be to the highest level of care that is readily available.[4]

References

1. Nasidi, A. (2007). Snakebite as a serious public health problem for Nigeria and Africa. Available from http://www.who.int/bloodproducts/animal_sera/A.Nasidi.pdf Accessed 7 Dec 2017
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5. WHO Guidelines for the Prevention and Clinical Management of Snakebite in Africa. (2010). Available from https://www.aho.afro.who.int/sites/default/files/ahm/pages/44/AHM%2013%20Special%20Issue%20Page%20103.pdf Accessed 1 Dec 2017

SPONTANEOUS REPORTING FOR 2017

The National Pharmacovigilance Centre received 2,715 (two thousand seven hundred and fifteen) spontaneous adverse reaction reports from January to December 2017. These reports were received from Healthcare Professionals, the Pharmaceutical Industry and Patients/Consumers. The reporting for 2017 was the highest in the history of pharmacovigilance in Ghana.

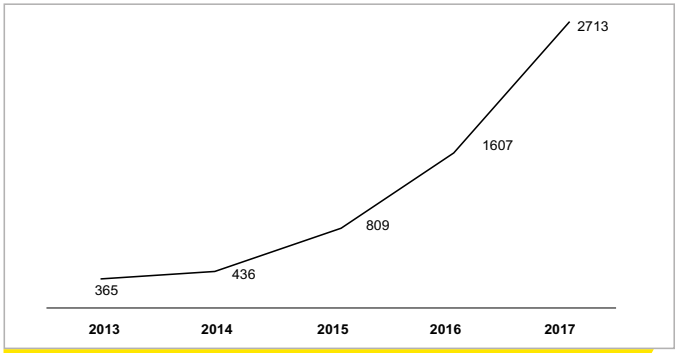

Figure 1: Number of spontaneous adverse reaction reports received in the past 5 years (2013-2017)

Out of these reports 1,026 were from the Seasonal Malaria Chemoprevention (SMC) in the Upper West, Upper East and Northern regions, 57 suspected product quality defect and 23 medication error reports.

The WHO Seasonal Malaria Chemoprevention is defined as the intermittent administration of full treatment courses of an antimalarial medicine to children in areas of high seasonal transmission during the malaria season. The objective is to prevent malaria illness by maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk. The WHO recommends SMC with sulfadoxine-pyrimethamine + amodiaquine in areas with high seasonal malaria transmission in the Sahel and sub-sahel regions of sub-Saharan Africa, where P. ***falciparum*** is sensitive to both antimalarial medicines.

Below is the analysis of 1,609 (one thousand, six hundred and nine) spontaneous reports excluding those received for the SMC, product quality defect and medication error.

Out of the 1,609 reports, 1,010 (62.8%) were from females and 534 (33.2%) from males, the gender for the remaining 65 (4.0%) is unknown.

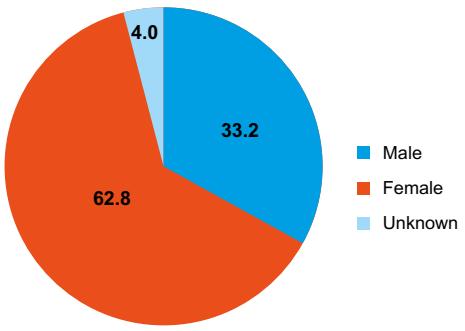

Figure 2: Gender distribution of patients who had adverse reactions

The spontaneous reports were received from different categories of healthcare professionals as shown in Figure 3.

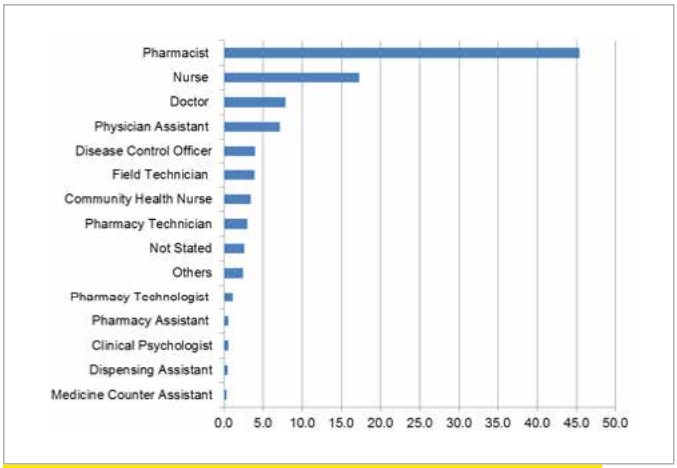

Figure 3: Percentage reporting by healthcare professionals

The top 10 medicines with the most commonly reported adverse reactions are shown in Figure 4.

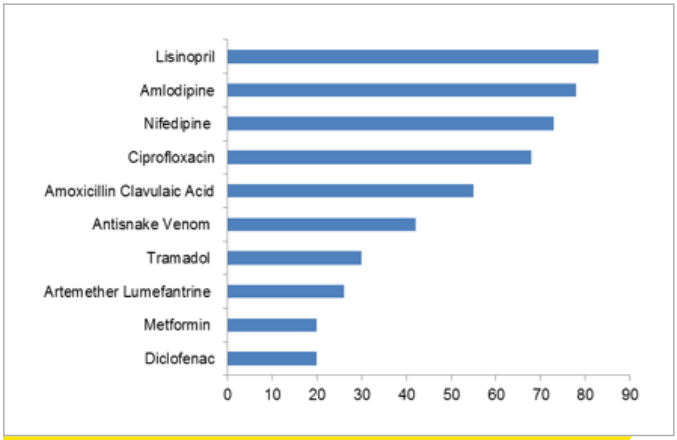

Figure 4: Top 10 medicines with the most commonly reported adverse reactions

The final outcome of the reported reactions is in Figure 5.

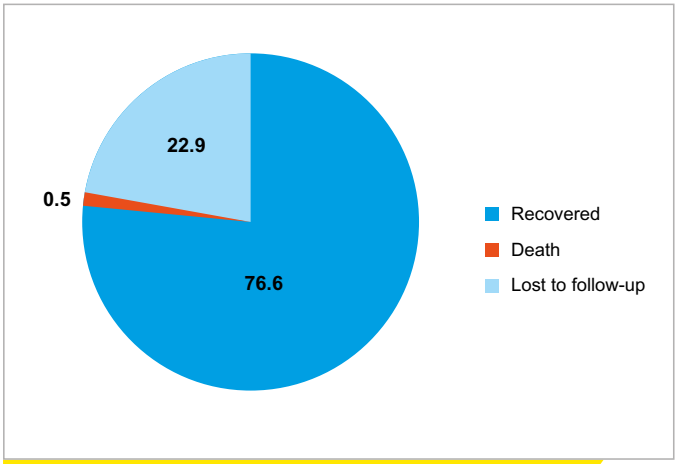

Figure 5: Outcome of the Reported ADRs

Figure 6 is the percentage contribution of all regions to the spontaneous reports received.

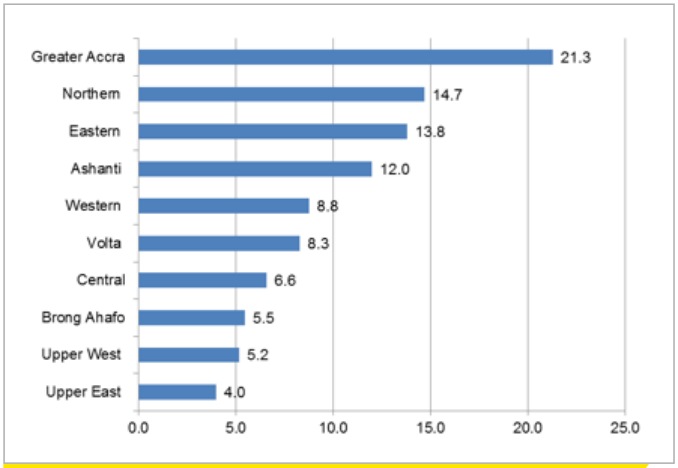

Figure 6: Percentage of Regional contribution to the spontaneous reports received

Table 1 represents the top thirty four (34) healthcare facilities which submitted reports to the National Pharmacovigilance Centre in 2017.

Table 1: **Top thirty-four reporting healthcare facilities**

FACILITY	NO. OF REPORTS	REGION
Koforidua Regional Hospital	50	Eastern
Komfo Anokye Teaching Hospital	40	Ashanti
Kwahu Government Hospital	40	Eastern
St. Martins Hospital, Agroyesum	35	Ashanti
Shai Osudoku District Hospital	35	Greater Accra
Wa Regional Hospital	33	Upper West
Jasikan District Hospital	31	Volta
Peki Dzake Health Centre	30	Volta
Agona Government Hospital	23	Ashanti
Sene District Hospital	22	Brong Ahafo
Cape Coast Teaching hospital	21	Central
Nagel SDA Memorial Clinic	20	Western
Family Care Hospital	19	Ashanti
Asamankese Government Hospital	19	Eastern
Yendi Health Centre	19	Northern
Hohoe Municipal Hospital	19	Volta
Korle Bu Polyclinic	18	Greater Accra
University Hospital, Legon	18	Greater Accra
St. Francis Xavier Hospital	17	Central
Korle-Bu Teaching Hospital	17	Greater Accra
Mamprobi Polyclinic	17	Greater Accra
War Memorial Hospital	17	Upper East
Tamale Teaching Hospital	16	Northern
New Abirem Government Hospital	15	Eastern
Ashaiman Polyclinic	15	Greater Accra
La General Hospital	15	Greater Accra
St. Dominic Hospital, Akwatia	14	Eastern
Ga South Municipal Hospital	14	Greater Accra
Goaso Municipal Hospital	13	Western
Atua Government Hospital	13	Eastern
Achimota Hospital	13	Greater Accra
Enyiresi Government Hospital	12	Eastern
Ngleshie Amanfro Health Centre	12	Greater Accra
VRA Clinic	12	Greater Accra

Pharmacists to be Awarded Continuous Professional Development Credit (CPD) Points for Participating in Patient Safety

The Pharmacy Council has from January 2018 begun the award of CPD Points to Pharmacists who participate in the Patients Engagement in Medicines Safety Programme by submitting safety reports of health products to the Food and Drugs Authority (FDA).

The Patients Engagement in Medicines Safety Programme was launched by the FDA in June 2016 with the objective to enable patients to report safety issues of their medicines and other health products through Community Pharmacies designated as Patient Safety Centres (PSC) to the FDA. The objective of this programme is to improve adverse reaction reporting rate and increase the chances of signal generation.

A Patient Safety Centre is a Community Pharmacy where the Pharmacist has received the basic training on patient safety provided by the FDA and designated as a point of call where patients could receive minimum information on medicine safety. The Patient Safety Centre will also serve as a centre where patients will receive the BlueForm® for completion of side effects experienced. The PSC then forwards the collated completed forms to the FDA.

Pharmacists who submit safety issues of medicines and other health products will take an online test to be eligible for 2 CPD Credit Points.

The FDA will submit the names and details of deserving pharmacist to the Pharmacy Council for the credits to be assigned.

Four (4) steps to earn the CPD point are as below:

Performance of the Patient Safety Centres

Since the launch of the programme in June 2016, the FDA has received a total of 167 (one hundred and sixty-seven) safety reports from these Centres. Awards have been given to deserving pharmacists at different times in 2016 and 2017.

The Overall Winner from Fabby Chemist Ltd. Pharm Felicia Adu receiving her plaque from Mrs. Nora Teilarbie, Head of the FDA Office in Ashanti Region

The top 14 (fourteen) reporting Community Pharmacies out of the 42 (forty-two) that have submitted reports since the launch of the programme are listed in Table 1 with the corresponding number of reports.

Table 2: Top fourteen reporting Community Pharmacies

FACILITY	NO. OF REPORTS	REGION
Fabby Chemist	15	Greater Accra
Open Arms Pharmacy	15	Northern
Samorak Pharmacy	15	Upper East
Royal Avenue	12	Ashanti
Joegani Pharmacy	10	Brong Ahafo
Obarsi Pharmacy	7	Northern
Bluecross Pharmacy	6	Central
Centinary Pharmacy	6	Northern
B.C. Bencyn Pharmacy	5	Upper East
Barliza Pharmacy	5	Brong Ahafo
Chalmalt Pharmacy	5	Northern
Klad Pharmacy	5	Greater Accra
Kings and Royals Pharmacy	5	Greater Accra
Northern Gate Pharmacy	5	Volta

The contribution of pharmacists to patient safety cannot be overemphasized and one of the several ways to contribute to this is to follow up on patients and report any safety issues they may have with their medicines and also reports on suspected counterfeit and substandard health products.

Some of the award winners at the 2017 AGM in Kumasi

Passionate for Patient Safety

Pharm. Seth Twum has worked with the Ghana Health Service for over 15 years and a member of the West Africa Post graduate College of Pharmacists. At the moment he works at the Eastern Regional Hospital, Koforidua, where he has been the Institutional Contact Person (ICP) for Pharmacovigilance since 2016.

Pharm. Twum loves Pharmacovigilance and believes that Pharmacovigilance is the responsibility for every healthcare worker. To him **accurately completing the Adverse Reaction Reporting Form** is a must for health workers. This will help combat counterfeit and sub-standard medicines, therapeutic failure, ADR associated morbidities and mortalities for the benefit of patients' safety.

As an ICP, Pharm. Twum has assisted the FDA Regional Office beyond the confines of his institution and served as a facilitator during the training of healthcare workers on the use of Pharmacovigilance Assessment Tool (PAT) in all the health facilities in Eastern region.

Pharm. Twum believes that the complete integration of pharmacovigilance into the daily routine activities of healthcare professionals will mark a great milestone in medicine safety monitoring in Ghana and the PAT tool is a great initiative to help this happen.

His advice to healthcare professionals is to always look at the bigger picture of the impact of identifying and reporting a medicine safety issue to the Food and Drugs Authority and be motivated to report religiously.

NEWS

Continuous Professional Development Training Workshop for Medical Doctors

A group photograph of participants at the training workshop in Accra

The Food and Drugs Authority (FDA) with support from the UK Department for International Development (DFID) has started a nationwide training workshop for Medical Doctors on the topic Pharmacovigilance in Promoting Patient Safety. The training workshop has been accredited by the Medical and Dental Council (MDC) as a Continuous Professional Development (CDP) programme with three (3) credit points.

The overarching goal of the programme for medical doctors is to improve adverse drug reaction reporting rate in order to enhance signal generation to achieve optimal benefit-risk balance for health products marketed in Ghana.

The three modules contained in the training course are as below:

MODULE I: Pharmacovigilance and Patient Safety in Ghana

This module discusses the background and objectives of pharmacovigilance and also highlighted on status of pharmacovigilance in Ghana and activities by the FDA to promote patient safety. The module also discussed Spontaneous reporting as a pharmacovigilance method, its strengths and weaknesses will also be discussed.

MODULE II: Adverse Drug Reaction Reporting and Principles of Causality

This module seeks to equip practitioners with transferable skills useful in clinical practice in the prevention, diagnosis, management and reporting adverse drug reactions. It also introduces practitioners to the principles of causality assessment.

MODULE III: Online Reporting of Adverse Reactions and a Tour through the SafetyWatch System (SWS)

This introduces participants to the FDA's real-time online reporting system, the SafetyWatch System (SWS). The SWS is an E2B compliant system which allows patients, healthcare professionals and clinical trial staff to submit adverse reaction reports to the FDA online. Participants will have a hands-on session on the use of the SWS.

Dr. Kenneth Tachi, a Consultant Gastroenterologist from the Korle-Bu Teaching Hospital and a member of the Faculty at one of the training sessions.

NEWS

The FDA Launched an Online Reporting System for Reporting Safety Issues

The FDA in 2017 launched an online reporting system for healthcare professionals and patients to report safety issues of health products using the links **http://adr.fdaghana.gov.gh/** and **http://adr.fdaghana.gov.gh/patient.php** respectively.

Clinical trial investigators can also log onto the system at **http://adr.fdaghana.gov.gh/clinical/** and report adverse events to the FDA.

The system, known as the SafetyWatch System (SWS) is an online ICH E2B compliant Individual Case Safety Reports (ICSRs) data management system for both pre- and post-approval safety data.

Prior to the launch of the system, a total of 955 healthcare professionals nationwide were trained by the FDA on how to use the system.

The online system will complement the paper-based reporting and have the added advantage of reports being received in real-time by the FDA in order to take regulatory action when needed in good time to ensure patient safety.

Group photographs of participants at the SWS Training Programme in Tamale

Pharmacovigilance Training for Senior Lecturers

The FDA's plan to provide adequate training for students in healthcare professional institutions was given an added boost when training was provided for lectures in September 2017 at the Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi to effectively teach the course. The training programme consists of the four modules listed below and was designed to give a complete overview of key principles in pharmacovigilance.

a. Definitions and importance of pharmacovigilance
b. The Pharmacovigilance System in Ghana
c. Prevention, Diagnosis, Management and Reporting of Adverse Events
d. Principles of Causality Assessment of Adverse Events and Signal Detection

The FDA believes that Ghana is on the right path to improve patient safety and looks forward to replicating this training in all institutions involved in training healthcare professionals.

Section of Senior Lecturers at the Training Programme

Ghana Joins Vaccine Safety Net (VSN)

The Vaccine Safety Net (VSN) is a global network of websites, evaluated by the World Health Organization (WHO), which provides reliable information on vaccine safety.

The VSN is a WHO initiative aiming to help internet users find reliable information on vaccine safety. The goal of the VSN is to ensure that reliable, understandable, evidence-based information on the safety of vaccines is available on the web and readily found by all and also to collaborate at an international level to increase awareness about vaccines, reduce vaccine hesitancy and strengthen confidence in vaccines.

Ghana was evaluated and admitted to join the VSN in December 2017. Ghana is the second country in Africa to join this network aside South Africa.

The FDA's website can be accessed through the VSN at **http://www.vaccinesafetynet.org/vsn/network/ghana-vaccine-safety-information**

The Menace of Tramadol and Codeine Abuse in Ghana

Drug abuse is a global phenomenon affecting almost every country though the extent and characteristics vary.

The most commonly abused prescription drugs are benzodiazepines and Opioids (codeine, tramadol and pethidine).

The abuse of tramadol and codeine containing cough syrups has become a menace among commercial drivers,' market women and the youth.

Codeine-containing cough syrups and tramadol are classified as Prescription Only Medicines (POMs) and as controlled drugs.

The approved dosage strengths of tramadol registered for use in Ghana by the FDA are 50mg and 100mg in tablets and capsules and 50mg/ml-2ml as an injectable; however, higher strengths of 120mg, 200mg and 225mg of tramadol were discovered during swoops organised nationwide by the FDA, the Ghana Police Service and the Pharmacy Council.

Some of the reasons for the abuse of codeine-containing cough syrups and tramadol are feeling of euphoria it provides, sexual enhancement, prevention of easy fatigue and pain relief.

What should healthcare professionals do to reduce the incidence of abuse?

- Healthcare professionals should strictly dispense codeine-containing cough syrups and tramadol as Prescription Only Medicines.
- Report suspected unregistered products to the FDA.
- Educate patients on the dangers of abuse of codeine-containing cough syrups and tramadol.

What is the FDA doing?

The FDA has step-up the underlisted regulatory measures to address the problem:

- Technical Advisory Committee on Safety of Medicines has recommended that the product labels are changed to include the Potential for addiction and Do Not Use unless prescribed by your doctor.
- Collaboration with the Pharmacy Council to undertake, restrictions on the display codeine-containing cough syrups on shelves in Pharmacies and dispensing of tramadol as a controlled POM in the Community Pharmacies. These products are to be kept under lock and key, dispensed only on valid prescription and records of prescriptions kept.
- Public workshops with experts including healthcare practitioners.
- Training for the Ghana Police Service and other law enforcement agencies such as Bureau of National Investigations (BNI), National Security and Customs Division of the Ghana Revenue Authority.
- Education on the abuse of tramadol and codeine-containing cough syrups and their adverse consequences to targets groups (students, parents, teachers and the youth)
- Strengthened the follow-up inspections to monitor the distribution records of importers and manufacturers of tramadol and codeine-containing cough syrups.
- Raids on illicit tramadol products on the Ghanaian market.

The FDA believes that the following proposals developed should also be implemented:

- A National Prevention Strategic Plan using documentaries, jingles and community durbars.
- Research into the prevalence of tramadol abuse in the country.

VACCINE SAFETY

Underreporting of Adverse Events Following Immunization (AEFI) is a major challenge of the vaccine pharmacovigilance. The World Health Organization recommends at least 10 AEFI reports per 100,000 surviving infants but over the years the reporting rate in Ghana has been less than the WHO's recommendation except in 2017 where the rate was 23 AEFI reports per 100,000 surviving infants .

Figure 7 shows the regional distribution of the 248 (two hundred and forty-eight) AEFI reports received in 2017 *(bar graph)* from the ten regions of Ghana plotted against the WHO target of 10 AEFI reports per 100,000 surviving infants. *(line graph)*

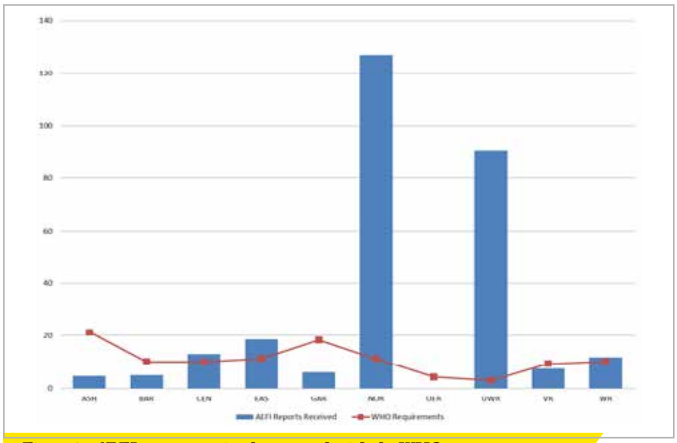

Figure 7: AEFI reports received compared with the WHO target

Five regions, Northern, Upper West, Central, Eastern and Western regions met the WHO minimum target for AEFI reporting rate.

The high number of AEFI reports received from the Northern and Upper West regions was due to the vaccination campaign in these regions as a result of the meningitis outbreak in 2016. It is however, surprising a similar trend was not observed in the Upper East region.

The Food and Drugs Authority is working with the Ghana Health Service (the Expanded Programme on Immunization) to improve AEFI reporting rate to be able to detect any new safety issues which may be inherent with new vaccines to be introduced in Ghana and other African countries.

Out of the 248 AEFI reports received, 12 (twelve) were classified as serious and the results of the Causality Assessment by the Technical Advisory Committee on Safety of Vaccines and Biological Products (TAC-VBP) using the process outlined in the WHO User Manual on Revised Classification of AEFI[1] is shown in Table 2.

Table 2: **Outcome of the Causality Assessment**

CATEGORY OF CLASSIFICATION	NUMBER OF REPORTS
Unclassifiable	3
Vaccine Product related	5
Immunization error	2
Inconsistent Causal Association to Immunization (Coincidental)	2

Malaria Vaccine Implementation Programme (MVIP)

The World Health Organization announced in April 2017 that three countries in Africa; Ghana, Kenya and Malawi will introduce the world's first malaria vaccine through a pilot programme. The pilots are being funded by: GAVI, the Vaccine Alliance, the Global Fund to Fight Aids, Tuberculosis and Malaria, UNITAID, the WHO and GSK.

The vaccine known as Mosquirix™ (RTS,S malaria vaccine) is manufactured by GlaxoSmithKline (GSK) who led the development for over 30 years.

Phase 3 clinical trials to assess the efficacy and safety of the RTS,S malaria vaccine was conducted between 2009 and 2014 through a partnership which involved GSK, PATH Malaria Vaccine Initiative with support from the Bill & Melinda Gates Foundation and a network of African research centres at 11 sites in 7 countries including Ghana. Kintampo Health Research Centre and the School of Medical Sciences, Kwame Nkrumah University of Science and Technology, participated in the clinical trials to determine the safety, immunogenicity and efficacy of Mosquirix™. The trials in Ghana recruited a total of 3,439 infants and children within the ages of 6-12 weeks and 5-17 months.

Mosquirix™ is the first malaria vaccine to obtain a positive scientific opinion from a stringent medicines regulatory authority, The European Medicines Agency in July 2015.

In January 2016, the WHO recommended pilot implementation of the Mosquirix™ in 3–5 distinct settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings in sub-Saharan Africa.

The pilot implementation programme to be coordinated by WHO will evaluate the feasibility of delivering the required 4 doses of the vaccine in children; the vaccine's potential role in reducing childhood deaths and the safety of the vaccine in the context of routine use.

The pilot implementation programme is expected to begin in 3rd quarter of 2018 through to 2022 in three regions of Ghana, namely Brong Ahafo, Central and Volta regions. Four districts in the Upper East region will also be included. These regions were selected based on the malaria burden (parasite prevalence of >20%). Information garnered from the pilots will help inform later decisions about potential wider use of the vaccine.

The existing vaccine pharmacovigilance system will be strengthened to detect adverse event following immunization which may arise during the MVIP.

[1] *World Health Organization. Causality Assessment of an Adverse Event Following Immunization (AEFI). User Manual for the Revised WHO classification. Available at http://www.who.int/vaccine_safety/publications/aevi_manual.pdf. Accessed Feb 6, 2018*

SAFETY INFORMATION PUBLISHED IN 2017

Below is the summary of Safety Communication sent to healthcare professionals in 2017, detailed information on this can be accessed on the FDA's website at **https://fdaghana.gov.gh/index.php/dear-healthcare-professional-letters/**

1 Angiotensin Converting Enzyme Inhibitor-Associated Angiodema: Higher Risk in Patients of African Descent

This reminded healthcare professionals that angioedema is a known side effect of Angiotensin Converting Enzyme (ACE) inhibitors and studies have reported up to three-fold higher risk in patients of African descent compared to white patients.[2]

This side effect is also listed in the product package insert. The FDA received 151 suspected adverse reaction reports of ACE inhibitor-associated angioedema out of the total of 4,618 adverse reaction reports received from 2005 to 2016 in which most of the patients fully recovered.

Angioedema is swelling (oedema) caused by a build-up of fluid in deeper layers of the skin. It tends to affect areas with loose tissue, especially the face and throat, as well as the limbs and genitals. Angioedema may be mild, but if it progresses rapidly, or if it affects the throat, it can cause asphyxiation which requires emergency medical care.

ACE inhibitors registered by the FDA are indicated for the control of high blood pressure, congestive heart failure, prevention of stroke and diabetes-related kidney damage.

2 Update on Safety of Pioglitazone

The objective of this Dear Healthcare Professional Letter was to update healthcare professionals on the outcome of the review of the benefit-risk profile of pioglitazone by the Technical Advisory Committee on Safety of Medicines (TAC-SM) taking into consideration the findings of the association of pioglitazone with small increased risk of bone fracture in women and bladder cancer.

The FDA's Technical Advisory Committee on Safety of Medicines concluded that the benefit-risk profile of pioglitazone remains favourable but recommended actions to guide healthcare professionals on the use of pioglitazone to minimize the risk of fracture in women and bladder cancer in patients who are prescribed Pioglitazone.

Pioglitazone is an oral anti-diabetic drug registered by the FDA as an adjunct to decrease blood glucose levels not controlled by diet and exercise alone in patients with type 2 diabetes mellitus. Pioglitazone is also indicated in combination with a sulfonylurea or metformin when diet and exercise plus the single agent do not result in adequate glycemic control.

[2] *Buckhart DG, Brown NJ, Griffin MR, et al. Angiotensin converting enzyme-associated angioedema: higher risk in blacks than whites. Pharmacoepidemiol Drug Saf 1996; 5: 149–54*

3 Safety of Injectable Gadolinium-Based Contrast Agents (GBCAs) Used In Magnetic Resonance Imaging (MRI) Scans

The review by the Technical Advisory Committee on Safety of Medicines (TAC-SM) is based on recent publications in the medical literature which reported that repeated use of GBCAs for MRI could lead to deposition in the brain and other tissues of patients long after the last administration. Similar reviews were also undertaken by other regulatory agencies like the European Medicines Agency, US Food and Drugs Administration and Health Canada.

The FDA advised Radiologists and other healthcare professionals to:

- Limit the use of GBCAs to situations where the contrast agent is considered necessary.
- Use the lowest effective dose of GBCAs, and
- Assess the benefits and any potential risks to individual patients before administering repeated doses of GBCAs.

The FDA also informed Radiologists that available scientific evidence suggests that gadolinium accumulation in the brain is higher with the use of linear agents than with the use of macrocyclic agents, but it has occurred with both types.

Gadolinium is a chemical element and a component of dyes used to enhance contrast and improve radiology images. Gadolinium-based contrast agents (GBCAs) are administered by injection and used for Magnetic Resonance Imaging (MRI) scans when needed.

4 Rare But Serious Allergic Reactions with the Skin Antiseptic Chlorhexidine Gluconate

This alert was sent to healthcare professionals and consumers following US Food and Drugs Administration Communication of 2nd February 2018.

This alert informed healthcare professionals and consumers about rare but serious allergic reactions associated with use of skin antiseptic products containing chlorhexidine gluconate. These reactions which could occur within minutes of exposure to the products include difficulty in breathing, swelling of the face, hives, severe rash or shock.

Chlorhexidine gluconate may be found in both over-the-counter and prescription products. Prescription medicines containing chlorhexidine gluconate include mouthwashes and oral chips used for gum disease while over-the-counter products include topical
solutions, washes, sponges and swabs.

DRUGS OF CURRENT INTEREST

Below are safety related regulatory decisions taken by the United States Food and Drugs Administration and the European Medicines Agency which have been adopted by the Food and Drugs Authority's Technical Advisory Committee on Safety of Medicines for immediate implementation.

1. Potential for increased long-term risks with antibiotic clarithromycin in patients with heart disease

There is a potential for increased long-term risks with antibiotic clarithromycin in patients with heart disease. It is therefore advised that caution is exercised before prescribing clarithromycin to patients with heart disease because of the potential increased risk of heart problems or death that can occur years later.

This recommendation is based on the review of the results of a 10-year follow-up study[1] of patients with coronary heart disease from a large clinical trial[2] that first observed this safety issue.

Clarithromycin is a semi-synthetic macrolide antimicrobial for oral use and registered by the Food and Drugs Authority (FDA) for the following indications when caused by susceptible bacteria; Bacterial pharyngitis, Mild to moderate community acquired pneumonia, Acute bacterial sinusitis (adequately diagnosed), Acute exacerbation of chronic bronchitis, Skin infections and soft tissue infections of mild to moderate severity, and in appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing agent for the eradication of ***Helicobacter pylori*** in patients with Helicobacter pylori associated ulcers.

Health care professionals should be aware of these significant risks and weigh the benefits and risks of clarithromycin before prescribing it to any patient, particularly in patients with heart disease and even for short periods, and consider using other available antibiotics. They are also to advise patients with heart disease of the signs and symptoms of cardiovascular problems, regardless of the medical condition for which they are being treated with clarithromycin.

[1] *Winkel P, Hilden J, Fischer Hansen J, et al, Clarithromycin for stable coronary heart disease increases all-cause and cardiovascular mortality and cerebrovascular morbidity over 10 years in the CLARICOR randomised, blinded clinical trial. International Journal of Cardiology 2015; 182:459–465.*

[2] *Jespersen CM, Als-Nielsen B, Damgaard M, et al. Randomised placebo controlled multicenter trial to assess short term clarithromycin for patients with stable coronary heart disease: CLARICOR trial. BMJ 2006;332:22–7.*

2. Suspension of marketing authorization for hydroxyethyl-starch solutions for infusion

The Food and Drugs Authority has suspended the marketing authorizations for hydroxyethyl starch (HES) solutions for infusion.

This is because of the risk of kidney injury and death in certain patient populations, including critically ill patients or patients with sepsis. Experience in clinical practice suggests that it is difficult to clearly distinguish patients who can be administered HES solutions for infusion from those who should not. In addition, some patients may become critically ill or septic while receiving the product.

Alternative therapeutic options are available for routine clinical practice (including albumin, gelatins and dextrans) and should be selected according to relevant clinical guidelines.

HES solutions for infusion are used for the management of hypovolaemia (low blood volume) caused by acute blood loss, where treatment with alternative infusion solutions known as 'crystalloids' alone is not considered to be sufficient. They are given by infusion (drip) into a vein and are used as blood volume expanders to prevent shock following acute bleeding. They belong to the class of medicines known as colloids. Besides blood products, there are two types of medicines used for plasma volume replacement: crystalloids and colloids. Colloids contain large molecules such as starch, whereas crystalloids, such as saline or Ringer's solutions, are pure electrolyte solutions.

HES solutions for infusion registered by the FDA are Hestar Injectable and Voluven Injectable Solution.

3. Label changes for prescription opioid cough and cold medicines

The FDA has also adopted the safety labeling change for prescription cough medicines containing codeine to limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18.

The FDA will also request the addition of safety information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing to the labels of these products.

Codeine containing cough syrups are indicated for the relief of cough in adults.

Health care professionals should reassure parents that cough due to a cold or upper respiratory infection is self-limited and generally does not need to be treated. For those children in whom cough treatment is necessary, alternative medicines are available.

Codeine containing cough syrups registered by the FDA at the moment are Diphex with Codeine Cough Syrup, Benylin with Codeine Cough Syrup and Actifed Dry Cough and Cold Syrup.

NOTICE OF MARKET AUTHORIZATION WITHDRAWAL

The marketing authorization of the underlisted medicines have been withdrawn by the Marketing Authorization Holders (MAHs). The decision to discontinue marketing these medicines was based on commercial reasons and not safety or efficacy.

NO.	MAH	NAME OF DRUG	ACTIVE INGREDIENT	INDICATION
1	Pfizer	Cyklokapron Injection	Tranexamic acid	Indicated in patients with hemophilia for short-term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction
2	Pfizer	Fragmin 12500IU/0.5ml Injection	Dalteparin Sodium	i. Prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction. ii. Prophylaxis of deep vein Thrombosis. iii. Extended treatment of Symptomatic Venous Thromboembolism in patients with Cancer.
3	Pfizer	Fragmin 15000IU/6ml Injection	Dalteparin Sodium	
4	Novartis	Lescol 20mg & 40mg Capsules, Lescol 80mg XL Modified release tablet.	Fluvastatin 20mg,40mg Capsules and 60mg XL modified release tablet	Hypercholesterolemia (Hetrozygous Familial and Nonfamilial), Mixed Dyslipidemia, Secondary Prevention of Cardiovascular Disease.
5	Sanofi Pasteur	Meningo A+C Injection	Polysaccharide Meningococcal Vaccine	Hypercholesterolemia (Hetrozygous Familial and Nonfamilial), Mixed Dyslipidemia, Secondary Prevention of Cardiovascular Disease.
6	Novartis	Leponex 25mg Tablets	Clozapine	Schizophrenia

What to Report?

You don't need to be certain, just be suspicious!

The FDA encourages the reporting of all suspected adverse reactions to medicines, including vaccines, over-the-counter medicines and herbal, traditional or alternative remedies. We particularly request reports of:

- All suspected ADRs whether known or not which causes concern in the caregiver/the patient.
- Lack of efficacy/therapeutic failure
- Suspected pharmaceutical defect
- Counterfeit Pharmaceuticals
- Blood and Blood Products

Reports may be submitted using the FDA **"blue form"** available at all hospitals and some pharmacies and also available at the FDA website at **http://www.fdaghana.gov.gh.**

Contact the National Pharmacovigilance Centre: Tel: 024 431 0297
Email: drug.safety@fdaghana.gov.gh

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