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Research Article

The Beginning of Pharmacovigilance in Bosnia and Herzegovina

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ABSTRACT

Aims: The aims of this article are to present the impact of the pharmacovigilance performance improvement in Bosnia and Herzegovina on the reporting results gathered at the national pharmacovigilance database.

Subjects and methods: Bosnia and Herzegovina is a country in Europe with a complicated political structure, the highest rate of unemployment and a low Gross Domestic Product. Although the Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina was established in 2009, with the Main Office for Pharmacovigilance as the national pharmacovigilance center, there were no activities and work in the field of pharmacovigilance. In 2017 several changes were made in the work of the Main Office such as: employment of an external expert for the work of pharmacovigilance, holding lectures and workshops, collecting and analyzing adverse drug reactions, signing various co-operations with professional chambers and health institutions forwarding reports to the World Health Organization and writing annual reports.

Results: These changes showed an increase in the collected adverse drug reactions by 130% and 28% on an annual level for 2017 and 2018, respectively. Bosnia and Herzegovina became a full member of the Uppsala Monitoring Center, a global office for drug monitoring by the World Health Organization.

Conclusion: Bosnia and Herzegovina can be used as an example for developing a sustainable pharmacovigilance system in countries with low economical standards.

Key words: Bosnia and Herzegovina; Adverse drug reaction; Pharmacovigilance, Agency for Medicinal Products and Medical Devices

INTRODUCTION

Pharmacovigilance (PV) comes from the Greek word *pharmakos* (drug) and the Latin word *vigilare* (to keep watch) and it is a fundamental component of all activities from drug regulations, clinical practice and public health system. It is defined by the World Health Organization (WHO) as the *science and activities relating to the detection, assessment, understanding and prevention of the adverse effects of drugs or any other possible drug-related problems* [1]. The main focus of PV are the Adverse Drug Reactions (ADRs) which are defined by the European Union (EU) Directive as *any response to a drug which is noxious and unintended, including lack of efficacy (the condition that this definition only applies with the doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological disorder function was excluded with the latest amendment of the applicable legislation)* [2]. The WHO recommends that every country has a developed PV system and has several requirements for a classification of a good PV system, that include a national PV center, a national spontaneous reporting system, a national database, a national ADR advising committee and a clear communication strategy regarding PV crisis [3]. The importance of a developed PV system lies in the assessment of ADRs and signal development, for preventing future clinical problems and healthcare costs. The history of PV begins in the 1960s, when the world entered a crisis caused by the use of the drug thalidomide, also known as the *thalidomide tragedy* [4]. A notable

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Canadian-American pharmacologist, Frances Oldham Kelsey, was one of the few people that warned the world about the serious ADRs caused by thalidomide use. Since the thalidomide tragedy, world governments and public healthcare systems started paying more attention to PV development. Today, most countries have developed internal PV systems and are collaborating with the global governing body regarding PV, the World Health Organization Uppsala Monitoring Centre (WHO-UMC). PV is mostly very well established in developed countries, that have access to more infrastructure and educated staff dedicated to specific problems. But PV systems in low-income and middle-income countries varies a lot, with some countries have a well-developed PV system and other countries not having a PV system at all [3]. So even today, 60 years after the thalidomide tragedy, there are still countries struggling with the implementation of a stable PV system.

Bosnia and Herzegovina (B&H) is a country located in the Southern/South-Eastern part of Europe, in the Balkan region. It covers totally 51 209.2 km^2 bordering Croatia, Serbia and Montenegro, with an estimate of the current population of 3 511 372 (data from 2016) [5]. The country is mostly mountainous, with an exit to the Adriatic Sea at the South. B&H is one of the poorest countries in Europe, with a Human Development Index of 0.769 [6]. The Gross Domestic Product per capita is one of the lowest in Europe and the unemployment rate with 27% (Figure 1) is the lowest in all European countries [7,8].

Legend: BA – Bosnia and Herzegovina, MK – North Macedonia, ME – Montenegro, TR – Turkey, IT – Italy, LT – Lithuania, HR – Croatia, SE – Sweden, FR – France, FI – Finland, BG – Bulgaria, CY – Cyprus, LU Luxembourg, BE – Belgium, IE – Ireland, MD – Moldavia, RO – Romania, NO – Norway, HU – Hungary, MT – Malta, CZ – Czechia, CH – Switzerland, FO – Faroe Islands

The country gained independence in 1992 after the separation of Yugoslavia, that was followed by years of war. The war was ended after the signature of the General Framework Agreement for Peace in B&H in 1995, also known as the *Dayton Agreement*. The Constitution of B&H, which is a part of this agreement, declares B&H as a country divided into two entities: Federation of B&H (FB&H) and the Republic of Srpska (RS), with an independent administrative unit called Brčko District (BD). FB&H is further divided into 10 administrative units called *cantons* with their own governments, infrastructure and public service (Figure 2) [9].

Legend: green – BD, red – RS, blue – FB&H; 1 - Una-Sana Canton, 2 - Posavina Canton, 3 - Tuzla Canton, 4 - Zenica-Doboj Canton, 5 - Bosnian-Podrinje Canton, 6 - Central Bosnia Canton, 7 - Herzegovina-Neretva Canton, 8 - West Herzegovina Canton, 9 - Sarajevo Canton, 10 - Herzeg-Bosnia Canton

In this article the authors would like to present the development and improvement of the PV system in B&H, with low infrastructure, lack of staff and general knowledge regarding ADR reporting.

THE HEALTHCARE SYSTEM IN B&H

It was already mentioned that the political system in B&H is very complicated and the healthcare system is divided in a similar way. According to the Constitution of B&H, the field of healthcare is in the jurisdiction of the entities: FB&H (including all the cantons), RS and DB. There is no ministry regulating health in B&H on the state level, but health issues are covered by the Ministry of Civil Affairs of B&H. Also, there are health ministries at entity levels; Federal Ministry of Health and the Ministry of Health and Social Welfare. In BD there is a Health Department in the Government of DB and every canton in FB&H has its own ministry of health. The distribution of the health insurance bureaus is the same, on entity and canton levels. One of the rare health institutions in B&H that is regulated at the state level is the Agency for Medicinal Products and Medical Devices of B&H (Agency). The Agency was established in 2009 by adoption of the Act on Medicinal Products and Medical Devices. The Agency was established as the national institute for protecting and promoting public health care by ensuring quality, safety and efficacy of medicinal products and medical devices for use in human medicine, and for the purpose of establishing a functional, coordinate and uniform system for regulation of medicinal products and medical devices [10]. The Agency functions on 3 different locations; Banja Luka, Sarajevo and Mostar, were different departments are settled. The departments for medicinal products, medical devices and clinical trials are located in Banja Luka, the Control Laboratory of the Agency is located in Sarajevo and the Main Office of Pharmacovigilance (MOPV) located in Mostar, which acts as the national PV department for B&H. The mission of the MOPV is to collect, record, analyze and evaluate all ADRs from B&H and outside of B&H related to medicinal products, medical devices, vaccines registered in B&H, received from healthcare workers, Marketing Authorization Holders (MAH) and studies [11]. Also, the tasks include collecting and analyzing data from Periodic Safety Update Reports (PSUR), new information regarding safety of medicinal products obtained from the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA), other global similar bodies, distribution of so called *Dear Healthcare Provider* letters (DHCP), writing annual ADR reports, informing the public on safety of

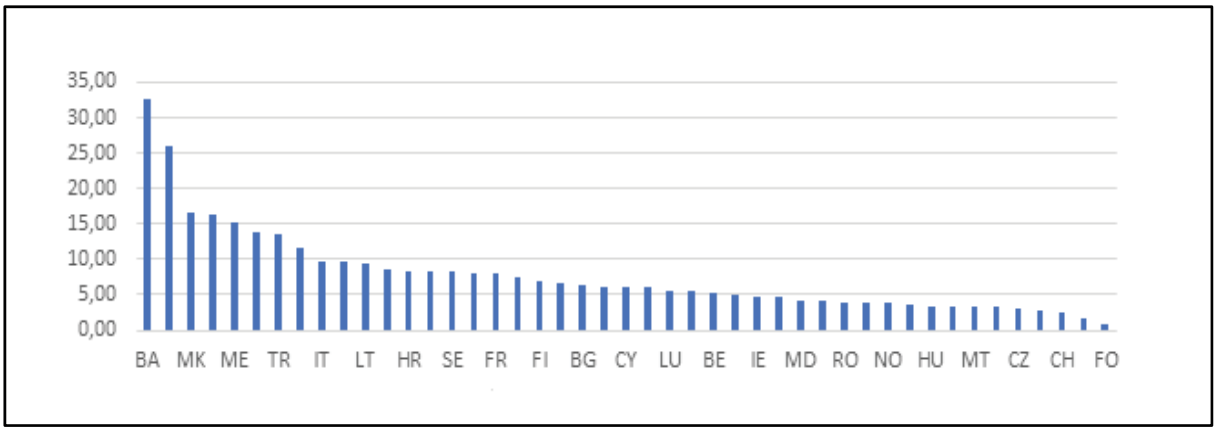

Figure 1: Unemployment rates in Europe.

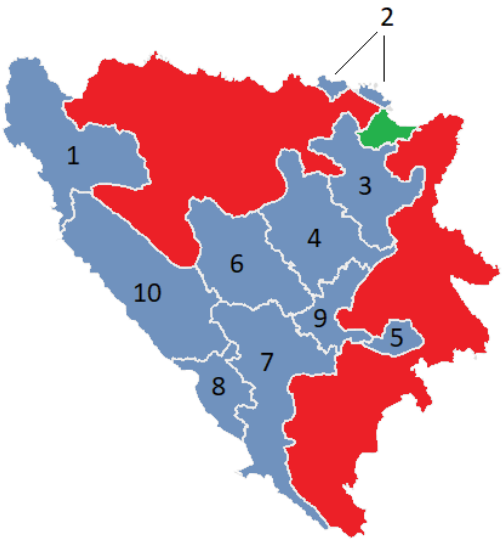

Figure 2: Administrative division of B&H.

medicinal products and medical devices. Since the establishment of the Agency, the MOP has not been functioning in full capacity, doing most of the work in the accordance with the departments in Banja Luka with no staff with higher education.

PV IMPROVEMENT ACTIONS

In 2017 several changes have been made in order to improve the PV processes in B&H. First, an external expert (pharmacist) for the process of PV was hired, as a first person with a higher education in the MOPV. Although the MOPV was established in 2009, there was no process of data collection and analysis. The external expert was included in managing the MOPV work, collection and analysis of data received from 2011 to 2016. Most documents were Individual Case Safety Reports (ICSR) received from healthcare providers (physicians, pharmacists, dentist, medical technicians and others) that are obligated by the Law [10] to report any knowledge of ADRs. The number, characteristics, and sources of reports, suspected drugs, and patient characteristics were analyzed. The results were compared with the publicly available data from Croatia, Serbia, and Montenegro. The number of reported ADRs from B&H was the lowest comparing to other countries [12]. So the main task of the MOPV work was to raise awareness of the necessity to report ADRs to the Agency. That was done in cooperation with several professional chambers in B&H in the field of healthcare: Chamber of Medical Doctors of FB&H, Chamber of Medical Doctors of RS, Pharmaceutical Chamber of FB&H, Pharmaceutical Chamber of RS, Chamber of Doctors of Dental Medicine of FB&H, Chamber of Doctors of Dental Medicine of RS, Chamber of Medical Technicians of FB&H and the Chamber of Medical Technicians of professions of RS. The cooperation included a notice to all of their members that reminded them of their legal obligation and an agreement to include several lectures of Agency officials to their members. Moreover, the Agency made a cooperation with all hospitals and health institutions on tertiary level in B&H. The main part of this cooperation was the appointment of main persons responsible for PV in all hospitals and health institutions on tertiary level. The idea behind this cooperation was to include the main persons responsible for PV as a connection between the Agency and the health institution in a way that the main person responsible for PV would be responsible for the collection and forwarding of all ADRs that occurred at the health institutions to the Agency.

Since Croatia has a good tradition in ADR reporting with 835 reports per million inhabitants [13], several meetings with the Agency for Medicinal Products and Medical Devices of Croatia were held in order to learn from their rich experience in PV. The main aspect of these meetings was the practical knowledge and guidelines to collecting ADRs in PV and vigilance of medical devices.

It has already been mentioned that healthcare is divided in B&H on entity and cantonal levels. The reporting of adverse events caused by vaccines is also monitored by many health institutions; the Agency [11] the Institute for Public Health of FB&H [14] and the Public Health Institute of the Republic of Srpska [15]. So the agenda of the MOPV was to make a cooperation between these three institutions to achieve better communication and forwarding of adverse reactions caused by vaccines. The public health institutes were obliged to report adverse reactions to the Agency on a monthly level.

On the 8th Symposium of Masters of Pharmacy held in Neum, B&H from the 19th to the 21st of May 2017 the Agency and the MOPV was presented with the plans and activities on the field of PV [16]. More than 900 pharmacists and other healthcare professionals were present at the symposium. They were once again reminded of their legal obligation and the importance of a stable and sustainable PV system. Later similar lectures were held in all parts of B&H with pharmacists and physicians as main focus groups [17-23]. All of these lectures and workshops were very well accepted in the healthcare community.

Finally, the last step of this process was to design a functional monitoring system for the control of medical products in B&H. Because of the lack of governmental investments and no budget space for the field of PV in B&H, the MOPV had to design their own monitoring system. The idea is that the system will be used in the future as an *online toot* for ADR reporting for healthcare providers and MAHs. Patients are currently not in a possibility to report ADRs directly to the Agency, but they are obliged to do it via their healthcare provider [11].

The system included all the information regarding the primary source - name, occupation and employment institution details. Patients were identified based on initials, sex and age. The ADR was coded using the Medical Dictionary for Regulatory Activities (MedDRA) in Lowest Level Term (LLT), Prefered Term (PT) and System Organ Class (SOC) categories. Based on the ADR described it was marked as serious if it fulfills one of the following criteria:

- Death
- Life threatening situation
- Hospitalisation or prolonged hospitalization
- Permanent or severe disability
- Congenital anomalies
- Medically significant serious event

The ADR outcome was monitored, as well as re-challenge. The drug/s under suspicion were monitored based on their trade name, international nonproprietary name, pharmaceutical form, dose and MAH. Other drugs that were used were also monitored. The time period of drug consuming was also taken into consideration. Finally, the causality assessment was monitored as certain, probable/likely, possible or not possible. All reports were translated to English and

forwarded to the WHO UMC office via *Vigiflow*, a web-based ICSR management system for national pharmacovigilance centers.

ADR Reporting results

In 2018 for the first time since the foundation of the Agency the Annual report on adverse events caused by medical products and medical devices for 2017 was published [24]. This represents a milestone in the PV system for B&H and the work of the MOPV. The annual report was made in accordance with similar reports in the region [13, 25]. This annual report collected all ADRs from B&H in one place, analyzed the primary source distribution, geographical distribution, ADRs according to MedDRA classification, patients according to sex and age, outcomes, seriousness, causality etc. In 2017 the MOPV received 227 ADR reports that were delivered by healthcare providers (104), MAHs (99) and public health institutes of FB&H and RS (24). These numbers show an increase of reported ADRs by more than 130% on an annual level (Figure 3). These figures show an increase in reported ADRs on an annual level by more than 28%. Comparing the results from the beginning of the PV activities we can see an increase of the reported ADRs by almost 195% (Figure 3). This represented a major breakthrough in the work of the MOPV. In 2018 the same procedure was continued, so the 2nd Annual report on adverse events caused by medical products and medical devices [26]. According to the data in that report, the MOPV received 292 ADR reports that were delivered by healthcare providers (134), MAHs (130) and public health institutes of FB&H and RS (28). For the first time in the history of B&H there was a possibility to see necessary details regarding ADR reporting.

Healthcare providers seem to be the biggest primary source in ADR reporting, with physicians being the group responsible for most reports. Although physicians are responsible for most ADRs in the last year it is possible to see a rise in ADRs received from pharmacists, which can be linked to the above mentioned lectures directed to various pharmaceutical symposia (Table 1).

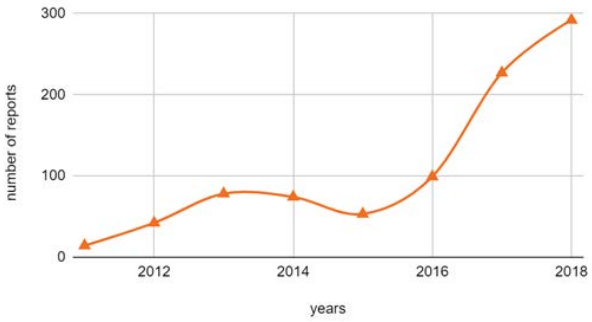

Figure 3: Number of ADR reports in B&H from 2011 to 2018.

Table 1: ADR reports from healthcare providers and MAHs from 2016 to 2018 (%)

Primary source	Year		
	2016	2017	2018
MAH	27	44	45
Public health institutes	0	10	9
Healthcare providers	53	46	46
- physician	96	88	77
- pharmacist	3	11	18
- other	1	1	5

For the two observed years it is possible to see that the geographical distribution of reported ADRs is almost the same between the entities of RS and FB&H, with RS being in a slight advantage. There were no ADRs received from BD. The cities with most reported ADRs were Mostar in 2017 and Bijeljina in 2018 (Table 2).

Table 2: Geographical sources of reported ADRs from 2016 to 2018 (%).

Geographical location	Years		
	2016	2017	2018
Entity FB&H	N/A	41	47
Entity RS	N/A	59	53
BD	N/A	0	0
City/municipality with most reported ADRs	N/A	22	24

The sex distribution of patients in the observed years was also almost the same with more female patients, except in 2018. That was in accordance with most other PV researches [27]. The age classification was done using the following criteria: neonate (1 month≤), child (4 years≤), child (11 years≤), adolescent (16 years≤), adults (69 years≤), old (69 years>). The most patients were adults. The average age of patients was 38,7 and 40,0 years for 2017 and 2018, respectively (Table 3).

Table 3: Sex and age of patients in ADR reports from 2016 to 2018.

Characteristics	Years		
	2016	2017	2018
Male	46	44	48
Female	50	56	47
Unknown	4	0	5
Neonate	N/A	0	0
Infant	N/A	6	6
Child	N/A	1	5
Adolescent	N/A	1	1
Adult	N/A	84	75
Old	N/A	8	13
Average age (years)	N/A	38,78	45,0

An increase in the seriousness of reported ADRs is visible from year to year, with life threatening conditions and hospitalization/ prolonged hospitalization being the main causes for seriousness of reaction (Table 4).

Table 4: Seriousness of reported ADRs and their outcomes from 2016 to 2018 (%).

Characteristics	Years		
	2016	2017	2018
Not serious	82	71	61
Serious	18	29	39
- Life threatening	N/A	52	5
- Medically significant	N/A	38	33
- Hospitalization	N/A	10	55
- Death	N/A	0	5
- Disability	N/A	0	2
Fully recovered	N/A	67	66
Recovering	N/A	28	26
Unknown	N/A	5	8

Using the MedDRA system it was visible that in observed years there were most ADRs in the SOC group *Skin and subcutaneous tissue disorders*. That was in accordance with the most observed PT terms for *Urticaria* in both observed years (Table 5).

The drugs that were reported were classified using the Anatomical Therapeutic Chemical (ATC) Classification. Using this classification it was visible that the same five groups of drugs were responsible for the most reported ADRs in both years, with the group *Antineoplastic and immunomodulating agents* causing the most ADRs in 2017 and 2018. Drugs were also monitored by the International Nonproprietary Name (INN). Iopromide caused the most ADRs in 2017 and adalimumab the most in 2018 (Table 6).

Causality assessment of the drug under suspicion and the observed ADR was done using the Naranjo algorithm [28]. This was one of the most important parts of the PV system implementation in B&H. By taking control over this part of the PV process, the Agency became an independent body in B&H for ADR assessment. Without the causality assessment that is done by the MOPV, the PV in B&H is completely in the hand of the pharmaceutical industry and MAHs, which represents a conflict of interests. Most ADRs in B&H are assessed as possible in both observed years (Table 7).

In 2019 based on the achieved results, the Agency started the project of involving B&H as a full member of the WHO UMC global office. In accordance with the WHO UMC staff necessary documents and procedures for full membership. B&H and Albania were the only countries in Europe that were not full members of WHO UMC. In 2019 B&H became a full member of the WHO UMC global office. This represents the biggest success in the PV system improvement in B&H.

CONCLUSION

Although B&H is one of the poorest countries in Europe with the highest unemployment rate and a very low Gross Domestic Product, it was possible to design and implement a sustainable PV system. Several changes that have been made in the work of the MOPV showed an increase of ADR reports by 130% and 28% on an annual level for 2017 and 2018, respectively. In the two published annual reports for the first time in the history of B&H it is possible to see the ADR distribution by primary source, geographical location, sex and age of patients, ADRs by MedDRA

Table 5: Five most reported ADRs by SOC and PT classification for 2017 and 2018.

2017				2018			
SOC name	**% in total number of ADRs**	**PT**	**% in total number of ADRs**	**SOC name**	**% in total number of ADRs**	**PT**	**% in total number of ADRs**
Skin and subcutaneous disorders	29	Urticaria	19	Skin and subcutaneous disorders	18	Urticaria	12
Gastrointestinal disorders	16	Nausea	7	Gastrointestinal disorders	14	Anaphylactic reaction	11
General disorders and administrative site conditions	16	Anaphylactic reaction	7	Immune system disorders	11	Nausea	5
Immune system disorders	10	Low blood pressure	7	General disorders and administrative site conditions	10	Abdominal pain	4
Nervous system disorders	8	Lymphadenitis	4	Nervous system disorders	8	Colitis *Clostridium difficile*	3

Table 6: ATC classification of drugs that caused the most ADRs in 2017 and 2018, and INNs that caused the most ADRs in 2017 and 2018.

2017		2018		2017		2018	
Anatomical group of ATC	**% in total number of ADRs**	**Anatomical group of ATC**	**% in total number of ADRs**	**INN**	**% in total number of ADRs**	**INN**	**% in total number of ADRs**
L	22	L	36	iopromide	15	adalimumab	10
V	21	J	19	oxaliplatin	8	iopromide	8
J	18	V	13	vemurafenib	8	rituximab	4
C	12	N	12				
N	9	C	6				

Table 7: Causality assessments for reported ADRs in 2017 and 2018 (%).

Causality assessment	Years	
	2017	**2018**
Certain	3	8
Probable	38	58
Possible	19	21
Not possible	5	4
Cannot be assessed	35	9

classification, seriousness, drugs involved, causality assessments and etc. In 2019 B&H became a full member of the WHO UMC which represents the biggest success of the PV improvement in B&H. B&H can be used an example for other countries where it is necessary to develop a sustainable PV system using very low or no resources.

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