

PROSPECTS

IN PHARMACEUTICAL SCIENCES

Prospects in Pharmaceutical Sciences, 20(4), 1-8
<https://prospects.wum.edu.pl/>

Original Article

ANALYSIS OF THE ACTIVITY OF THE POLISH OFFICE FOR REGISTRATION OF MEDICINAL PRODUCTS, MEDICAL DEVICES AND BIOCIDAL PRODUCTS IN THE FIELD OF CLINICAL TRIALS, REGISTRATION OF MEDICINAL PRODUCTS AND MONITORING OF ADVERSE DRUG REACTIONS IN 2017-2021

Lukasz Dobrek¹

¹ Department of Clinical Pharmacology, Wrocław Medical University, 50-556 Wrocław, Poland.

* Correspondence, e-mail: lukasz.dobrek@umw.edu.pl

Received: 15.10.2022 / Accepted: 28.11.2022 / Published: 30.12.2022

ABSTRACT

The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (ORMP) is the state registration authority that grants in the national procedure the marketing authorization for medicinal products on the pharmaceutical market in Poland. ORMP is also involved in approving and controlling clinical trials and in the monitoring of safety of pharmacotherapy (pharmacovigilance) by collecting and analysing reports of adverse drug reactions (ADR). The aim of the study was to review the activity of ORMP in the field of 3 basic competences of this authority: clinical trials, registration of medicinal products and pharmacovigilance in the last 5 years. The evaluation was carried out by the method of document analysis on the basis of data contained in annual bulletins of medicinal products for the years 2017-2021 published by ORMP. In 2017-2021, an increasing trend of clinical trials submitted to ORMP was observed, and they were mainly in phase II and III. Most of the medicinal products introduced to the Polish pharmaceutical market in 2017-2021 were drugs prescribed by a doctor, registered in a decentralized procedure, used in diseases of the nervous and cardiovascular systems and in the treatment of cancer. A relatively low activity of ORMP in monitoring the safety of pharmacotherapy was demonstrated, which was a consequence of low activity of medical staff in the spontaneous ADR reporting. The conducted analysis confirmed the key role of ORMP in surveillance of clinical trials and introducing new medicinal products to the pharmaceutical market in Poland but also indicated the need for increased activity in the area of pharmacovigilance.

KEYWORDS: drugs, medicinal products, registration, clinical trials, adverse drug reactions

Article is published under the CC BY license.

1. Introduction

All medicinal products (colloquially and collectively named “drugs”) currently available on the pharmaceutical market may be commonly used only after obtaining a marketing authorization issued by relevant institutions. In Poland, the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (ORMP) is the national registration authority, which is an equivalent of similar authorities in other countries, e.g. The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte; BfArM) in Germany, State Institute for Drug Control (Státní ústav pro kontrolu léčiv; SUKL) in the Czech Republic or Swedish Medical Products Agency (Läkemedelsverket; LV) in Sweden. In the European Union countries, it is also possible to market a medicinal product in EU countries on the basis of a decision of the European Commission, after a positive assessment issued by the European Medicines Agency (EMA). Regardless of the registration path, in each case the registration of a medicinal product is preceded by a careful analysis of efficacy and safety (determination of a positive benefit-risk

ratio) of the tested drug, which is demonstrated in the course of preclinical trials and phase I-III clinical trials [1,2]. The moment of drug registration and its introduction to the pharmaceutical market after the successful completion of Phase III does not terminate the drug research, but initiates the fourth, still ongoing, phase of clinical trials, focusing on continuous monitoring of the safety of drugs on the market (“pharmacovigilance”) [3,4]. Each stage of drug research is defined in detail by relevant legal regulations. In Polish legislation, ORMP is the institution involved in all stages of the “drug life cycle”, starting from the clinical trials.

Thus, access to pharmacotherapy is strictly regulated by legal requirements. Apart from non-pharmacological techniques, pharmacotherapy is one of the therapeutic options, used especially in the conservative treatment of many diseases. Drugs used in the treatment of a given disease entity, should demonstrate a therapeutic effect in the lowest possible doses, amounts and time of administration, and the person implementing the treatment is obliged to develop a therapeutic plan that

includes a short- and long-term assessment of the effectiveness and safety of the pharmacological intervention used [5]. One of the key issues ensuring health safety is access to health services and new, up-to-date medical technologies, including novel drugs. In accordance with the drug policy, which is an integral part of the 2018-2022 state's health policy, patients should be provided with wide access to effective and safe drugs, in order to meet their health needs. One of the strategic goals of the health policy is to constantly improve the health of the population by optimizing public expenditure ensuring the widest possible access to effective, safe and cost-effective therapies [6]. In this context, the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products plays an important role. The principles of organization and competences of ORMP are set out in the Act of 18 March 2011 on the Office for Registration of Medicinal Products, Medical Devices and Medical Products [7]. Pursuant to Art. 2 and Art. 4 of the aforementioned legal act, the President of ORMP is a state administration agency that conducts proceedings and performs activities in the field of marketing authorization of medicinal products and veterinary medicinal products, as well as making biocidal products available on the market, issuing permits for conducting clinical trials and supervising ongoing clinical trials and pharmacovigilance. In particular, with regard to the registration of medicinal products, ORMP maintains the Register of Medicinal Products Authorized for Marketing in Poland, and in relation to clinical trials, ORMP is responsible for maintains the Central Register of Clinical Trials and their Inspection. The President of ORMP is also responsible for pharmacovigilance, inter alia, by collecting and analysing spontaneous notifications of adverse drug reactions (ADR), reported by healthcare professionals or by patients themselves or their statutory representatives / actual guardians, and evaluating the periodic reports on the safety of medicinal products (e.g. periodic safety update report; PSUR and development safety update report; DSUR) submitted by the marketing authorisation holders (MAH). This competence of ORMP is also consistent with the provisions of Chapter 2 of the Pharmaceutical Law Act, which also clarifies, inter alia, that the President of ORMP collects and analyses documents on the safety of medicinal products, maintains a database of notifications occurring in Poland and transfers ADR reports to the European EudraVigilance database and the global Vigibase database of the World Health Organization, issues safety alerts for medicinal products, intended and addressed directly to healthcare professionals or the general public, and accepts changes introduced into the summary of product characteristics (SmPC) due to the emergence of new information, especially regarding the safety of drugs used in the real clinical practice [8]. To sum up, according to the Polish legislation, ORMP is the institution responsible for the entire "life cycle" of a drug, from approving and inspecting clinical trials prior to possible registration, through issuing a marketing authorization, to continuous monitoring of the safety of all medicinal products currently on the pharmaceutical market.

The aim of the study was to review the activity of ORMP in the field of 3 basic competences of this authority: clinical trials, registration of medicinal products and pharmacotherapy safety monitoring in the last 5 years (2017-2021).

2. Materials and Methods

The data review was carried out in September 2022 using the method of document analysis based on data contained in annual bulletins of medicinal products for 2017-2021 published by ORMP, summarizing the activities of that institution in a given year. The annual bulletins are publicly available and published on the ORMP website in the form of pdf files [9-13]. Each bulletin contains abbreviated information in the form of tables, charts and short comments on the number of ORMP decisions on marketing authorization for medicinal products, registration of clinical trials and clinical trial inspections and the number of received adverse drug reactions notifications.

3. Results

Clinical trials:

In the area of clinical trial regulation, in 2018-2021, ORMP received 2,323 applications to enter a clinical trial of a medicinal product to the Central Register of Clinical Trials. During this period, the President of ORMP registered a total of 2,138 studies in the Central Register of Clinical Trials. On a yearly basis, ORMP received an average of 581 ± 78 applications regarding the initiation of a clinical trial and 5340 ± 1320 entries were made in the central register. More than half (53.4%) of the clinical trials in progress in Poland were during phase III, while 32% were in phase II. Each year, the largest number of applications for clinical trials concerned the field of oncology. For 2017, the bulletin does not provide information on the number of applications received by the ORMP, but mentions the total number of 453 clinical trials registered for that year, mostly phase III (60%) and phase II (29%).

The number of clinical trials entered into the Central Register of Clinical Trials in 2018-2021 is presented in Figure 1.

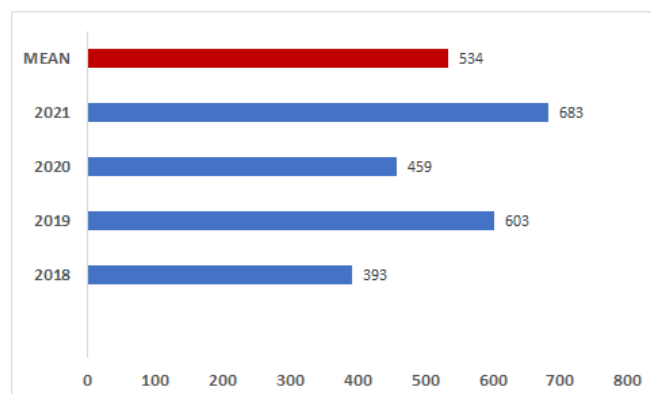


Figure 1. Number of clinical trials entered into the Central Register of Clinical Trials in 2018-2021.

In the period 2017-2021, ORMP conducted a total of 254 inspections of clinical trials, including 170 initiated by ORMP and 84 commissioned by EMA. On average, during the year, ORMP controlled on its own initiative 34 ± 11 ongoing clinical trials and 17 ± 10 trials commissioned by the EMA. The number of clinical trial inspections in individual years is presented in Figure 2.

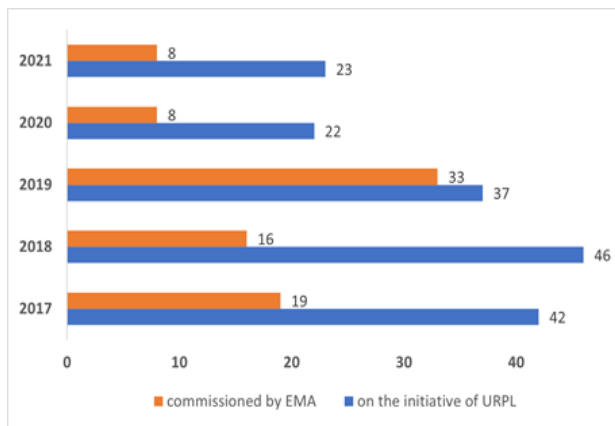


Figure 2. Number of inspections of clinical trials conducted by The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in 2017-2021.

Registration of medicinal products:

In 2017-2021, the President of ORMP issued a total of 3,166 decisions on marketing authorizations for medicinal products, including 585 in the national procedure (NAT), 399 in the mutual recognition procedure (MRP) and 2,182 in the decentralized procedure (DCP). In each of the analysed years, decisions issued under the DCP procedure were definitely predominant. The quantitative analysis of the decisions on marketing authorizations for medicinal products in 2017-2021 is presented in Figure 3.

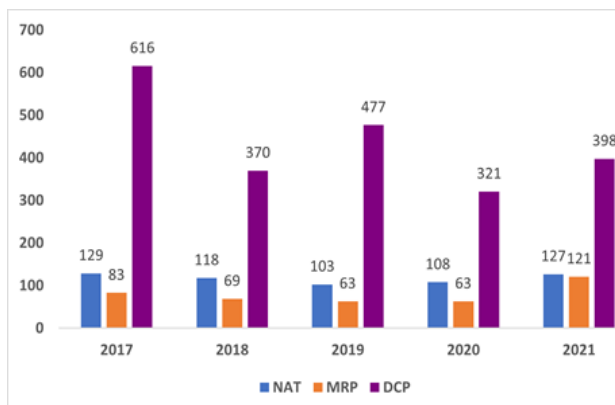


Figure 3. Number of decisions on marketing authorizations for medicinal products in 2017-2021, divided into type of registration procedure (NAT - national (Polish) procedure; MRP - mutual recognition procedure; DCP - decentralized procedure).

Taking into account the legal status of registered medicinal products, it should be noted that considering the years 2017-2021, in terms of the legal status and category of availability of a drug to the patient, the vast majority of medicinal products were registered with the “Rp” category, i.e., dispensed to the patient on a doctor’s prescription (2,058 issued marketing authorizations). Medicinal preparations dispensed with a doctor’s prescription for registered use - “Rpz” category (521 permits) and drugs dispensed without a doctor’s prescription - “OTC” (447 permits), were registered in a smaller number. In the analysed period, the preparations only used in inpatient treatment - “Lz” (88 permits) and preparations prescribed by a doctor containing narcotic drugs or psychotropic substances, specified in separate regulations - “Rpw” (52 permits) were registered in the lowest number. On average, annually ORMP issued 411 ± 99

marketing authorizations for “Rp”, 104 ± 26 “Rpz”, 89 ± 14 “OTC”, 18 ± 7 “Lz” and 10 ± 8 “Rpw” products. The number of registered medicinal products, taking into account the legal status and availability categories, in each year of the analysis, is presented in Figure 4 below.

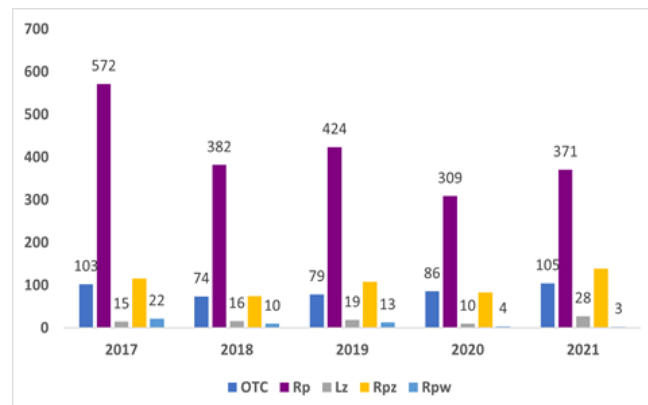


Figure 4. Number of decisions on marketing authorizations for medicinal products in 2017-2021, taking into account the legal status and availability category (OTC - non-prescription medicinal products; Rp - prescription medicinal products; Lz - medicinal products used only in inpatient medicine; Rpz - prescription medicinal products for registered use; Rpw - prescription medicinal products containing narcotic drugs or psychotropic substances).

The total assessment of the quantity of registered medicinal products, taking into account therapeutic areas of use (according to the codes of Anatomical Therapeutic Chemical (ATC) classification) showed that the highest number of registered medicinal products were products used in the treatment of diseases of the nervous (code N; 560) and cardiovascular system (code C; 471), and drugs used in neoplastic diseases therapy (code L; 431). In turn, drugs from the group of antiparasitic, insecticides and repellents (code P; 8), drugs categorized as “various” (code V; 36) and drugs used in dermatology (code D; 48), were the least authorized. In addition, during the analysed period, ORMP issued 27 marketing authorizations for “other” herbal preparations without ATC assigned categories. The detailed analysis of the decision to authorize the marketing of medicinal products in 2017-2021, taking into account the ATC classification, is presented in Table 1.

Reporting and analysis of adverse drug reactions:

In the analysed period of 2017-2021, a total 138,499 notifications of ADR were noted from Poland. A total number of 75,007 notifications of ADR were submitted directly to ORMP, including: 21,216 reports from medical professionals, 19,204 ones from patients or their carers, and 34,587 notifications from the State Sanitary Inspection regarding adverse post-vaccination reactions. On the other hand, 63,492 notifications of ADR were collected by marketing authorization holders and submitted directly to the EudraVigilance database.

The increase in the number of ADR notifications in 2021 compared to previous years of the analysis is noteworthy. Among the 39,994 notifications received by ORMP in 2021, 30,093 (75%) concerned ADR that occurred after the administration of Covid-19 vaccines. Among notifications regarding vaccinations received by ORMP, 12,954 were directly from medical professionals and from

Table 1. Number of decisions on marketing authorization for medicinal products in 2017-2021, including the assignment to the ATC anatomical-therapeutic-chemical classification codes.

	A	B	C	D	G	H	J	L	M	N	P	R	S	V	OTHER	TOTAL
2017	54	24	171	13	72	11	122	68	38	170	0	48	19	11	7	828
2018	27	35	96	3	37	6	50	66	38	141	2	32	13	3	8	557
2019	62	19	78	6	63	10	58	86	48	154	0	37	7	6	9	643
2020	49	28	51	7	42	43	65	69	54	33	2	31	8	9	1	492
2021	85	33	75	19	58	31	33	142	24	62	4	54	17	7	2	646
TOTAL	277	139	471	48	272	101	328	431	202	560	8	202	64	36	27	
MEAN	55.4	27.8	94.2	9.6	54.4	20.2	65.6	86.2	40.4	112	1.6	40.4	12.8	7.2	5.4	
SD	21.0	6.6	45.8	6.4	14.6	16.0	33.7	32.2	11.4	60.6	1.7	10.2	5.3	3.0	3.7	

A - alimentary tract and metabolism; B - blood and blood forming organs; C - cardiovascular system; D - dermatologicals; G - genitourinary system and sex hormones; H - systemic hormones excluding insulins and sex hormones; J - anti-infectives for systemic use; L - antineoplastic and immunomodulating agents; M - musculoskeletal system; N - nervous system; P - antiparasitic agents, insecticides and repellents; R - respiratory system; S - sensory organs; V - various agents

patients, and 17,139 were received from sanitary-epidemiological stations.

A detailed summary of the number of ADR notifications in Poland in each year of the analysis, taking into account the sources of the reports, is presented in Figure 5.

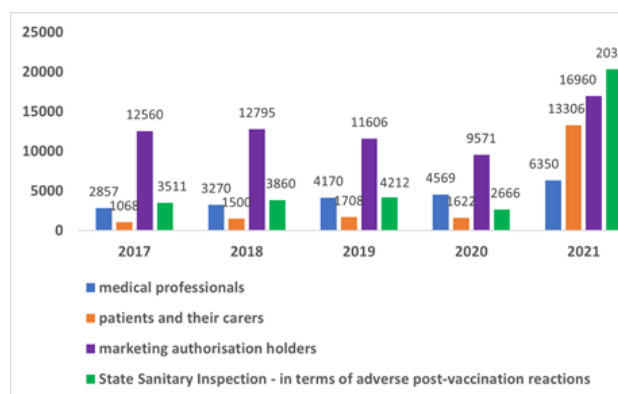


Figure 5. Number of adverse drug reaction reports from Poland in 2017-2021, including the sources of the reports.

4. Discussion

The analysis of data on the activities of ORMP in the field of accounting and supervision of clinical trials showed that in the last 3 years, an increase in entries of clinical trials in the Central Register of Clinical Trials was observed, which is in line with the global trend. According to WHO data from February 2022 [14], in the global perspective, a significant increase in the number of clinical trials is noted. While in 2000, only 2,786 trials were recorded, in 2020, as many as 59,964 were carried out, and the cumulative number of all clinical trials in 1999-2020 was 671,228. In Poland, 14,731 clinical trials were conducted during this period, which accounted for 2.19% of all clinical trials carried out globally and placed Poland on 18th position in the world ranking of countries participating in clinical trials. Most studies were conducted in the USA (23.48%), China (11.97%) and Japan (8.60%). The top five countries with the highest activity in the implementation of clinical trials is completed by Germany (7.25%) and the United Kingdom (6.55%).

A geographical macroanalysis assessing the number of registered clinical trials in 1998-2013 showed a dynamic increase in registered clinical trials in Asian countries (with an increase of 474% in Japan, 407% in China and 367% in India in 2007-2012, compared to previous years) and high activity in organizing clinical trials in Europe and the USA. The areas with the lowest number of registered clinical trials

were Africa, South America and Oceania [15]. According to WHO data [14], phase II and III trials assessing efficacy and safety of drugs used in neoplastic diseases (18.55% of all studies), neuropsychiatric (13.86%), cardiovascular (10.36%), infectious (6.05%) and neuromuscular (5.85%) were predominant [14]. This kind of therapeutic structure of clinical trials is consistent with general epidemiological observations revealing that the main causes of mortality are cancer and cardiovascular diseases [16]. The WHO data is consistent with those published by ORMP - in Poland in the years 201-2022 phase II and III clinical trials were also carried out, mainly in the field of oncology. Similar conclusions also resulted from the analysis by Bartoszkiewicz et al. [17] devoted to the implementation of clinical trials in the countries of Central and Eastern Europe. In two consecutive five-year periods: 01.2000-12.2004 and 01.2005-12.2009, clinical trials were rarely carried out in Central European countries. In this periods, 10 and 48 trials were registered in Poland, respectively, and at the same time, in the Czech Republic - 7 and 30, and in Hungary - 9 and 19, respectively. The increase in clinical trials was noted in another 5-year period (01.2010-12.2014) - the number of initiated clinical trials in the abovementioned countries was 284, 197 and 185, respectively. A significant increase in clinical trials carried out in the Central European countries was demonstrated in January 2015 to December 2019. In this period, 1,498 trials were implemented in Poland, 954 in the Czech Republic and 792 in Hungary. On average, in the years 2000-2019, 460 clinical trials were carried out in Poland over a 5-year period [17]. These statistics correlate with ORMP data for the next 5-year period (2017-2021), indicating that, on average, 518 clinical trials were registered. The analysis by Gresham et al. [18] also concerned clinical trials carried out in the period 2000-2019, registered on the clinicaltrials.gov database. It showed that in these years, 245,999 interventional studies were commenced and 135,144 (54.9%) were completed. Most studies were single-centre (61.3%), randomized (65.6%), open-label (55.7%), and phases I-II (35.5%), or did not have the US Food and Drug Administration-defined phase (38.4%). The median of the study completion time varied by primary sponsor, and it was 3.4 years for national institutes of health (NIH) and US government sponsored studies, 1.2 years for pharmaceutical industry sponsored studies, and 2.1 years for studies sponsored by other sources [18].

In terms of registration of human medicinal products, in 2017-2021, ORMP issued the most decisions on marketing authorizations in decentralized and mutual recognition

procedures, which indicates the close collaboration of ORMP with registration agencies from other European countries. In general, there are various legal regulations regarding the registration of medicinal products. The pharmaceutical market is strictly regulated in the US, EU, Japan, Canada, Australia, New Zealand and South African countries. In the US, the role of the registration agency is played by the Food and Drug Administration (FDA), in Europe - decisions are made by the European Commission after prior assessment of the entire registration dossier by the European Medicines Agency (EMA), in Canada - the Health Product and Food Branch (HPFB), in Australia - Therapeutic Goods Administration (TGA), and in Japan - Pharmaceuticals and Medical Devices Agency (PMDA). Semi-regulations of the pharmaceutical market apply in Asia (Sri-Lanka, India, Bangladesh, China, Pakistan, Bhutan, Nepal), 10 countries (Philippines, Vietnam, Singapore, Malaysia, Thailand, Indonesia, Laos, Cambodia, Brunei Darussalam, and Myanmar) united in the ASEAN organization, African international locations (Algeria, Zambia, Ethiopia, Ghana, Kenya, Malawi, Mozambique, Namibia, Nigeria, Sierra Leone, Tanzania, Zimbabwe and so forth), Middle East nations (Gulf Co-operation Council countries i.e., Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE), Latin America (Mexico, Brazil, Panama, Peru, Guatemala, Argentina, Chile, Dominican Republic) and CIS countries (Commonwealth of Independent States): Russia, Ukraine, Post-Soviet States (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kirghizstan, Moldova, Tajikistan, Turkmenistan, and Uzbekistan etc.) [19,20]. In Poland, it is possible to introduce a medicinal product to the pharmaceutical market in one of four registration procedures: national, central, decentralized and mutual recognition. In the national procedure, ORMP is the "host of the procedure" and the only authority that authorizes the medicinal product to be marketed exclusively in the territory of Poland. On the contrary, the central registration procedure (CP) carried out after the EMA assessment allows the MAH to introduce the medicinal product to all markets in the European Union, Norway, Iceland and Liechtenstein. It should be noted that CP is an obligatory registration path for medicinal products containing new active substances used in the treatment of neoplastic, neurodegenerative, autoimmune, viral (including AIDS) diseases and diabetes. Moreover, the CP procedure is the only way for the introduction of new drugs used in the treatment of rare (orphan) diseases, medicinal products manufactured through biotechnological processes and advanced therapy medicinal products. On the other hand, both DCP and MRP are procedures implemented in the case of medicinal products introduced in parallel to the pharmaceutical markets of at least two countries. The MRP procedure is implemented for a medicinal product previously authorized in one of the EU member states (in the so-called reference member state; RMS) and registered in another EU country (concerned member state; CMS). The evaluation of a given medicinal product in the CMS is based on an evaluation report previously prepared by RMS. On the other hand, DCP is used when the proposed medicinal product has not yet been authorized in any of the EU member states and it is marketed in at least two European pharmaceutical markets at the same time. In this case, the MAH identifies the RMS that prepares the assessment report. The CMS issues its decision on the basis of an assessment report prepared by RMS [21-23]. The analysis of the structure of the decisions to authorize medicinal products issued by ORMP in 2017-2021

showed that most of them were issued under the DCP procedure, which indicates the close cooperation of the ORMP with other registration agencies and confirms the fact that ORMP can function as either an RMS or CMS.

On the other hand, the analysis of drugs registered in Poland in terms of the ATC classification showed that the largest number of products introduced to the pharmaceutical market in 2017-2022 represented three therapeutic areas: neurology and psychiatry (code N), cardiovascular system (code C) and oncology (code L), which is also an indirect consequence of the fact that most clinical trials are carried out precisely in these areas, as mentioned above. Moreover, in leading therapeutic areas, a large amount of generic drugs ("generics") is also registered. The share of generics in the Polish pharmaceutical market reaches 66% and it is the highest share in the European market [24]. Among new medicinal substances that received positive recommendations from the EMA during CP, there were also drugs representing ATC codes N and L. According to data published in the annual Human Medicines Highlights bulletins [25-29], during the years analysed in this paper, EMA issued a total of 431 recommendations regarding the issuing of a marketing authorization by the European Commission, and 200 of these decisions concerned new medicinal substances. Among the new medicinal substances registered in the CP procedure with the participation of EMA, anti-cancer drugs (50 decisions), anti-infectives (22), and drugs used in neurology and psychiatry (20) were the most numerous.

An important role of ORMP is also the participation in pharmacovigilance by collecting and analysing reports on ADR. Pursuant to Art. 2 points 3a of the Pharmaceutical Law [8], an adverse drug reaction is any unfavourable and unintended effect of a medicinal product. This provision indirectly indicates the need to demonstrate a cause-and-effect relationship between the drug's action and the occurrence of an adverse effect, in contrast to the "adverse event; AE". The adverse event term is also present in the Pharmaceutical Law Act. It is defined in Art. 2 points 16 as any medical event causing negative consequences in a patient or clinical trial subject who was administered a medicinal product or an investigational medicinal product or an investigational veterinary medicinal product, even if they were not causally related to the use of this product [8]. On the other hand, the definition of adverse drug reaction provided in 2002 by WHO in the report "Safety of Medicines. A guide to detecting and reporting adverse drug reactions" [30] indicates that ADR is "a response to a medicine that is noxious and unintended, and which occurs at doses normally used in man". Thus, the Polish definition of ADR provided for in the Pharmaceutical Law Act is consistent with the one provided by WHO, although it does not limit its occurrence only to the situation of using the usual doses of drugs. On a margin, it is also worth mentioning the broadly understood definition according to Aronson, according to which ADR is an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict a hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product [31]. Moreover, the ADR term is usually expanded and in the current literature, ADR is also understood as reactions

occurring as a result of error, misuse or abuse, and to suspected reactions to medicines that are unlicensed or being used off-label in addition to the authorized use of a medicinal product in normal doses [32]. Monitoring and reporting of ADR is crucial in ensuring the safety of pharmacotherapy and it is the essence of the still ongoing phase IV clinical trials for all drugs currently available on the pharmaceutical market [33].

Taking into account the participation of ORMP in ADR monitoring, the analysis demonstrated a marked increase in the number of reports in 2021. This year, ORMP received a significantly greater number of ADR reports from healthcare professionals, patients, and The State Sanitary Inspection (SSI). Taking into account the significant increase in ADR notifications by SSI, it should be considered that in 2021 the ADR reports in the form of adverse post-vaccination reactions definitely dominated. It is also worth noting that in each of the analysed years (except 2021), the most ADR were reported by the MAH, while the share of healthcare professionals as well as patients or their carers in spontaneous ADR reporting was relatively low. This is in contradiction with the legal requirements for ADR reporting by healthcare professionals. Legal regulations regarding ADR reporting in Poland by healthcare professionals are based on the provisions of the Act of 6 September 2001 pharmaceutical law [8], as well as on other legal acts, such as the Act of 10 December 2020 on the profession of pharmacist [34], Act of 8 September 2006 on State Emergency Medical Services [35], Act of 5 December 1996 on the professions of doctor and dentist [36] and the Act of 15 July 2011 on the professions of a nurse and midwife [37]. The aforementioned acts impose a legal obligation to notify ADR on medical professionals: doctors, pharmacists, nurses and midwives, and paramedics, and also allow patients or their legal and actual guardians to report ADR. Moreover, anyone can submit a notification of ADR to the ORMP, e.g. laboratory diagnosticians or other unregulated medical professions, such as pharmaceutical technicians and other intermediate medical staff, although these persons are not legally obliged to notify ADR. Unfortunately, as shown by the data presented above, spontaneous reporting of ADR by medical professionals in Poland remains at a relatively low level. The number of ADR submitted to ORMP is disproportionately much lower than the expectations based on the data of the Polish Central Statistical Office (CSO) regarding the estimation of medical staff resources. According to the CSO data, compiled on the basis of registers of relevant professional chambers, in 2020 the right to practice the profession was held by 153,500 doctors, 43,300 dentists, 303,200 nurses, 39,800 midwives and 36,500 pharmacists [38]. Thus, in 2020, a total of 576,300 medical professionals worked in Poland who were required to report ADR occurring during their clinical practice. In 2020, ORMP received only 4,569 ADR notifications from healthcare professionals, which seems to be a very low result considering the total number of active doctors, nurses, midwives and pharmacists mentioned above. The problem of low ADR reporting in Poland was also noticed by the Polish Supreme Audit Office (PSAO), which estimated that, taking into account Polish demographic data, the number of registered medicinal products on the market and the number of medical professionals, annual ADR reporting is expected at the level of 45,000 [39]. These expectations differ significantly from official statistics - in 2020 ORMP received 18,428 reports in total, which was almost three times less

than expected. According to the PSAO findings, the number of ADR reports per 100,000 inhabitants in 2017-2019 in Poland was 5.5, compared to the value of this parameter of 9.0 for France, 8.0 for Sweden and 7.0 for Germany. A consequence of the relatively low ADR reporting in Poland is also a small share of Polish reports submitting to the global ADR database (VigiBase) affiliated to the World Health Organization Collaborating Centre for International Drug Monitoring (UMC WHO). In 2020, the VigiBase database contained a total of 46,405 reports submitted from Poland, while the total number of ADR reports from Poland in 2015-2019 was 98,067. At the same time, the global number of reports coming to VigiBase in 2019 was about 20 million. The share of individual countries in building the database is varied, and USA, Australia, Canada, Germany, France, Great Britain, Sweden, the Netherlands are countries most involved in global ADR reporting [39].

5. Conclusions

1. The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products is a government administration supporting the President of ORMP, which acts as the state administration agency responsible for the admission of medicinal products to the market, registration and supervision over the market of medical devices, and authorization of biocidal products. In addition to registration issues, ORMP participates in the approving and supervision of clinical trials taking place in Poland and collects reports of adverse drug reactions, forwarding them to central databases. Therefore, ORMP is also a key institution in the field of pharmacovigilance.

2. The analysis of the data published by ORMP in 2017-2021 demonstrated a growing trend in clinical trials submitted to the Central Register of Clinical Trials in Poland.

3. The analysis of the data published by ORMP in 2017-2021 also revealed that most medicinal products were marketed in a decentralized procedure in the form of drugs prescribed by a doctor especially in the treatment of nervous and cardiovascular system diseases and cancer.

4. There was a significant increase in adverse drug reactions reporting to ORMP in 2021, especially including vaccine adverse reactions. In a broader perspective, however, compared to analogous data from other countries, the relatively low activity of ADR reporting in Poland should be emphasized. Consequently, there was a small share of ORMP in global ADR reporting into the WHO database.

Author Contributions: Lukasz Dobrek is the sole author of the paper.

Funding: This research received no external funding.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Robuck, P.R.; Wurzelmann, J.I. Understanding the drug development process. *Inflamm Bowel Dis.* **2005**, *11*, Suppl 1, S13-6. doi:10.1097/01.mib.0000184851.46440.a3.
2. Deore, A.; Dhumane, J.; Wagh, R.; Sonawane, R. The stages of drug discovery and development process. *AJPRD* **2019**, *7*, 62-67. doi:10.22270/ajprd.v7i6.616.
3. Dhingra, G.; Tanwar, S.; Sharma, D.; Parihar, S. A review of pharmacovigilance. *JPADR* **2022**, *3*, 7-11.
4. Campbell, J.E.; Gossell-Williams, M.; Lee, M.G. A review of pharmacovigilance. *West Indian Med J.* **2014**, *63*, 771-4. doi: 10.7727/wimj.2013.251.
5. Schiff, G.D.; Galanter, W.L.; Duhig, J.; Lodolce, A.E.; Koronkowski, M.J.; Lambert, B.L. Principles of conservative prescribing. *Arch Intern Med.* **2011**, *171*, 1433-1440. doi:10.1001/archinternmed.2011.256.
6. Ministerstwo Zdrowia. Polityka Lekowa Państwa 2018-2022. [Ministry of Health. State Drug Policy 2018-2022]. Available online: <https://www.gov.pl/web/zdrowie/rada-ministrow-przyjela-dokument-polityka-lekowa-panstwa-20182022> (Accessed 08.09.2022).
7. Ustawa z dnia 18 marca 2011r. o Urzędzie Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Leczniczych. [Act of 18 March 2011 on the Office for Registration of Medicinal Products, Medical Devices and Medical Products]. Available online: <https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20110820451/U/D20110451Lj.pdf> (Accessed 08.09.2022).
8. Ustawa z dnia 6 września 2001r. Prawo farmaceutyczne. [Act of 6 September 2001 on the Pharmaceutical Law]. Available online: <https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20011261381/U/D20011381Lj.pdf> (Accessed 08.09.2022).
9. Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych. 2017. Biuletyn produktów leczniczych ludzkich. [The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. 2017. Human Medicinal Products Bulletin]. Available online: <https://urpl.gov.pl/sites/default/files/zalaczniki/Biuletyn%20URPL%202017.pdf> (Accessed 09.09.2022).
10. Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych. 2018. Biuletyn produktów leczniczych ludzkich. [The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. 2018. Human Medicinal Products Bulletin]. Available online: https://urpl.gov.pl/sites/default/files/Biuletyn%20URPL%202018_leki.pdf (Accessed 09.09.2022).
11. Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych. 2019. Biuletyn produktów leczniczych ludzkich. [The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. 2019. Human Medicinal Products Bulletin]. Available online: https://www.urpl.gov.pl/sites/default/files/zalaczniki/Biuletyn%20URPL%202019_PL.PDF (Accessed 09.09.2022).
12. Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych. 2020. Biuletyn produktów leczniczych ludzkich. [The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. 2020. Human Medicinal Products Bulletin]. Available online: <https://urpl.gov.pl/sites/default/files/Biuletyn%20URPL%202020%20PL-1.pdf> (Accessed 09.09.2022).
13. Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych. 2021. Biuletyn produktów leczniczych ludzkich. [The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. 2021. Human Medicinal Products Bulletin]. Available online: https://urpl.gov.pl/sites/default/files/pictures/BIULETYN_2021_LUDZKIE_1.pdf (Accessed 09.09.2022).
14. World Health Organization. Number of clinical trial registrations by location, disease, phase of development, age and sex of trial participants (1999-2021). Available online: <https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-trial-registrations-by-year-location-disease-and-phase-of-development> (Accessed 14.09.2022).
15. Viergever, R.F.; Li, K. Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013. *BMJ Open.* **2015**, *5*, e008932. doi: 10.1136/bmjopen-2015-008932.
16. World Health Organization. Global Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2019. Available online: <https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghle-leading-causes-of-death> (Accessed 14.09.2022).
17. Bartoszkiewicz, M.; Kufel-Grabowska, J.; Litwiniuk, M. Number of clinical trials of new therapeutic agents in the European Union countries of Central and Eastern Europe, 2000-2019. *Pol Ann Med.* **2022**, *29*, 26-30. doi:10.29089/2020.20.00146.
18. Gresham, G.; Meinert, J.L.; Gresham, A.G.; Meinert, C.L. Assessment of trends in the design, accrual, and completion of trials registered in ClinicalTrials.gov by sponsor type, 2000-2019. *JAMA Netw Open.* **2020**, *3*, e2014682. doi:10.1001/jamanetworkopen.2020.14682.
19. Sowjanya Reddy Singam, S.L.; Yetukuri, K.; Nadendla, R.R. Drug registration requirements for pharmaceuticals in emerging markets. *Int J Drug Reg Affairs* **2020**, *8*, 73-82.
20. Handoo, S.; Arora, V.; Khera, D.; Nandi, P.K.; Sahu, S.K. A comprehensive study on regulatory requirements for development and filing of generic drugs globally. *Int J Pharm Investig.* **2012**, *2*, 99-105. doi: 10.4103/2230-973X.104392.
21. Singh, P.M.; Pahwa, S.; Chaudhary, S.; Sethi, V.A. New drug approval procedure in different countries: a review. *Int J ChemTech Res.* **2017**, *10*, 1-21.

22. Jawahar, N.; Lakshmi, T. Regulatory requirements for the drug approval process in US, Europe and India. *J. Pharm. Sci. & Res.* **2017**, *9*, 1943-1952.
23. Sawant, A.M.; Mali, D.P.; Bhagwat, D.A. Regulatory requirements and drug approval process in India, Europe and US. *Pharmaceut Reg Affairs* **2018**, *7*, 210. doi: 10.4172/2167-7689.1000210.
24. Polska Agencja Informacji i Inwestycji Zagranicznych S.A. Sektor farmaceutyczny i biotechnologiczny w Polsce. [Polish Information and Foreign Investment Agency S.A. Pharmaceutical and biotechnology sector in Poland] Available online: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwjw2LjlmKb6AhXyilsKHSt6ApgQFnoECAMQAw&url=https%3A%2F%2Fwww.paih.gov.pl%2Ffiles%2F%3Fid_plik%3D19607&usq=AOvVaw0s99qnth6_9NJ-UMmYi2c (Accessed 16.09.2022).
25. European Medicines Agency. Human medicines highlights 2017. Available online: https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2017_en.pdf (Accessed 16.09.2022).
26. European Medicines Agency. Human medicines highlights 2018. Available online: https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2018_en.pdf (Accessed 16.09.2022).
27. European Medicines Agency. Human medicines highlights 2019. Available online: https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2019_en.pdf (Accessed 16.09.2022).
28. European Medicines Agency. Human medicines highlights 2020. Available online: https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2020_en.pdf (Accessed 16.09.2022).
29. European Medicines Agency. Human medicines highlights 2021. Available online: https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2021_en.pdf (Accessed 16.09.2022).
30. WHO. Safety of Medicines. A guide to detecting and reporting adverse drug reactions. 2002. Available online: http://apps.who.int/iris/bitstream/handle/10665/67378/WHO_EDM_QSM_2002.2.pdf;jsessionid=3813F236B4D0C206EAA5C1F536B5EFD5?sequence=1 (Accessed 16.09.2022).
31. Aronson, J.K.; Ferner, R.E. Clarification of terminology in drug safety. *Drug Saf.* **2005**, *28*, 851-70. doi: 10.2165/00002018-200528100-00003.
32. Coleman, J.J.; Pontefract, S.K. Adverse drug reactions. *Clin Med (Lond)*. **2016**, *16*, 481-485. doi: 10.7861/clinmedicine.16-5-481.
33. Suvarna, V. Phase IV of drug development. *Perspect Clin Res.* **2010**, *1*, 57-60.
34. Ustawa z dnia 20 grudnia 2020r. o zawodzie farmaceuty. [Act of 10 December 2020 on the profession of pharmacist]. Available online: <https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU2021000097/U/D20210097Lj.pdf> (Accessed 19.09.2022).
35. Ustawa z dnia 8 września 2006r. o Państwowym Ratownictwie Medycznym. [Act of 8 September 2006 on State Emergency Medical Services]. Available online: <https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20061911410/U/D20061410Lj.pdf> (Accessed 19.09.2022).
36. Ustawa z dnia 5 grudnia 1996r. o zawodach lekarza i lekarza dentystry. [Act of 5 December 1996 on the professions of doctor and dentist. Available online: <https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU19970280152/U/D19970152Lj.pdf> (Accessed 19.09.2022).
37. Ustawa z dnia 15 lipca 2011r. o zawodach pielęgniarki i położnej. [Act of 15 July 2011 on the professions of a nurse and midwife]. Available online: <https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20111741039/U/D20111039Lj.pdf> (Accessed 19.09.2022).
38. Główny Urząd Statystyczny. Zdrowie i ochrona zdrowia w 2020 r. [The Central Statistical Office. Health and health protection in 2020]. Available online: <https://stat.gov.pl/obszary-tematyczne/zdrowie/zdrowie-i-ochrona-zdrowia-w-2020-roku,1,11.html> (Accessed 19.09.2020).
39. Najwyższa Izba Kontroli. Monitorowanie działań niepożądanych leków. Informacja o wynikach kontroli. 2020. [The Supreme Audit Office. Monitoring of the adverse drug reactions. Information on the results of the control. 2020.]. Available online: <https://www.nik.gov.pl/plik/id,23133,vp,25839.pdf> (Accessed 19.09.2020).