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PHARMACEUTICAL INDUSTRY AND ITS INFLUENCE ON THE STATE OF HEALTHCARE IN POLAND, IN VIEW OF THE LOCAL INNOVATIVE POTENTIAL

PRZEMYSŁ FARMACEUTYCZNY I JEGO WPŁYW NA STAN OPIEKI ZDROWOTNEJ W POLSCE, W ŚWIETLE LOKALNEGO POTENCJAŁU INNOWACYJNEGO

Summary: *Availability of medicinal products is a crucial issue of any healthcare system. Pharmaceutical industry, which is a global conglomerate of profit-driven private enterprises, needs much regulation and control from international and governmental agencies, to be able to fulfill its humanitarian mission efficiently. Serious concerns about local and regional pharmaceutical safety, fuelled by recent drug availability crisis, leads to conclusion that state support for mobilization of the local innovative potential in life sciences is desirable, particularly in a view of urgent need for revival of pharmaceutical active substance manufacturing.*

Keywords: *pharmaceutical industry, active pharmaceutical ingredients, pharmaceutical innovation, innovative drugs, generic drugs, new drug development, markets of pharmaceutical products.*

Streszczenie: *Dostępność produktów leczniczych jest kluczową kwestią każdego systemu opieki zdrowotnej. Przemysł farmaceutyczny, który jest globalnym konglomeratem prywatnych przedsiębiorstw nastawionych na zysk, potrzebuje wielu regulacji i kontroli ze strony agencji międzynarodowych i rządowych, aby móc skutecznie wypełniać swoją misję humanitarną. Poważne obawy dotyczące lokalnego i regionalnego bezpieczeństwa farmaceutycznego, podsycane niedawnym kryzysem dostępności leków, prowadzą do wniosku, że pożądane jest wsparcie państwa dla mobilizacji lokalnego potencjału innowacyjnego w naukach przyrodniczych, szczególnie w obliczu pilnej potrzeby ożywienia produkcji substancji farmaceutycznych.*

Słowa kluczowe: *przemysł farmaceutyczny, aktywne składniki farmaceutyczne, innowacje farmaceutyczne, leki innowacyjne, leki generyczne, opracowywanie nowych leków, rynki produktów farmaceutycznych*

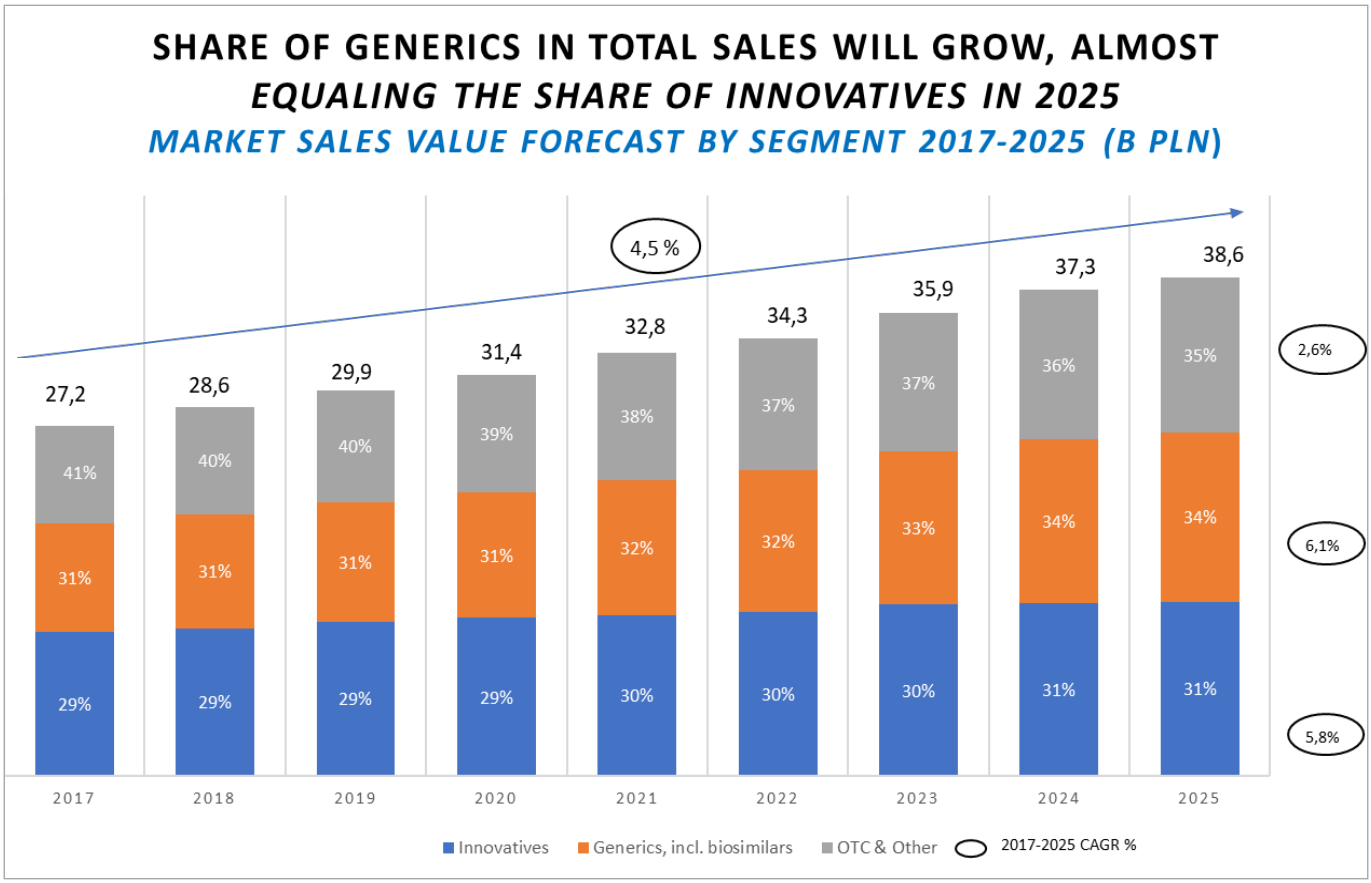
Introduction

Modern pharmaceutical and chemical industries are indisputably strongly interrelated and they both belong to the realm of high-technology, which is characterized, among other features, by the extensive innovativeness implemented by strong and dynamic R&D initiatives, and huge potential for generating very high value added products. This is achieved by advanced technical means among which modern chemical synthesis plays the leading role. On the other hand, these industries are worlds apart in terms how their manufacture their commodity and specialty products, shape their markets and relate to the individual customers. The chemical industry in Poland has been recently expertly characterized in this journal [1]. The authors take this opportunity to juxtapose the leading features of both sectors, in context of more general interest in innovativeness as an answer to challenges facing technical civilization.

Short characteristics of the contemporary pharmaceutical products, markets, and processes

General public perception of pharmaceutical industry is that of drug products' provider, expected to fulfill crucial healthcare needs of individuals, unconditionally. Such wishful thinking often collides with tough reality of highly competitive post-industrial economy, which is far from desired self-sustenance state. Among many systemic problems which recently plague contemporary pharmaceutical industry, these which cause painful drug shortages are much publicized [2-5], therefore make a good start for drafting some characteristic of the sector of such great importance for individual customers, patients populations, and the state organizations which are responsible for their well-being. According to the experts of the World Health Organization (WHO) medicines shortages occur when the supply of medicines identified as essential by the health system is insufficient to meet public and patient needs. This definition describes situation in which patients are unable to receive their prescribed treatment or a direct alternative for a period of time which their health outcome may be impacted. "Direct alternative" is defined by substitution due to medical need to the same chemical molecule produced by a different manufacturer. This applies to innovative drugs, as well as generics. In our country drug safety is traditionally taken for granted, as a consequence of the state declarations assuming responsibility for the public healthcare as a fundamental human right secured by the Constitution. As it is generally agreed that humanitarian missions should be supported by the governments and state organizations, the point should not be missed that pharmaceutical industry (often called "big pharma") is a global business, privately own and driven by profit. The basic conflict between pharmaceutical

Fig. 1 Trends in market value segmentation of pharmaceutical products in Poland; (Quoted by permission from IQVIA Poland)



companies interest, and individual customers (patients) of retail pharmacies rights, has evolved throughout the 20th century into rigorously regulated drug manufacturing ("good practices" like GMP assuring products quality and safety) and initially tightly controlled markets, which now comprise three distinctly different kinds of products: branded drugs and generics (available only upon prescription), and over the counter products (OTC), which contain potent, registered active pharmaceutical ingredients and are formulated as prescription drugs, but are freely available not only in pharmacies but also in places like supermarkets and gas stations.

The key points illustrated by Fig. 1 are the following: 2017 was a turning point in market value shares balance – share of generics started growing while share of innovative drugs started declining. Share of OTC and other products in total sales is also expected to grow faster than the entire market. This trend will inevitably result in co-existence of two kinds of pharmaceutical market customers; these taking only doctor's prescribed medicines are already in minority according to recent polls, which indicate that ca. 90% citizens of this country practice self-medication, at least to some extent. Polish pharmaceutical market (supplied by over hundred local manufacturing enterprises), which ranks 6th in the EU, attained 38 billion zlotys value level in 2017, and is currently split almost evenly between innovative medicines (manufactured by foreign companies, in most cases packaged locally), generic drugs, and the OTC products [6]. As a result of globalization, all three segments of pharmaceutical industry products depend on API substances which are presently produced outside Europe, formally under surveillance of the authorized final product manufactures. Such radical separation of the drug manufacturing process between API production, principally in China, and formulating finished pharmaceutical products in European countries is not without consequences which can jeopardize regional drug safety, as experienced recently in the EU. Recent example from the Polish market, of a drug withdrawal caused by the safety concerns illustrates how serious consequences could result from the total API outsourcing strategy, generally implemented by major drug manufacturing companies. In summer 2018, Polish authorities (GIF) withdrew from the market all pharmaceutical preparations containing valsartan as API of cardiovascular (CV) drugs, following information from European controlling agencies which identified potentially carcinogenic N-nitrozodimethylamine impurity in the active substance. Incidentally, it become evident that API manufacturing of the important drug, taken by millions of blood high pressure patients around the world, is practically monopolized by a single Chinese manufacturer - Zhejiang Huahai Pharmaceutical Co., Ltd.

The new regulations introduced in the UE in 2014, which enforced implementation of "good practices" in pharmaceutical manufacturing has involved many costly changes in API syntheses, particularly their safety, quality control and their environmental sustenance. As a consequence, over 400 pharmaceutical plants in India and China have been closed down, resulting in periodical API shortages in some regions. General trend to move over chemical plants from the European countries to Asia, for economic and environmental reasons proved rather short-sighted, since in case of complicated and multistep pharmaceutical processes the implementation time is considerably longer than in case of commodity chemical production.

Additional complication may result from a shortage of high quality technical staff in new factories, new local regulations concerning environmental safety, and last but not least – political stability. Enforced consolidation of the global API manufacturing business has resulted in drop of its potential for 30%, only in the last couple of years (2015-2017), which is a matter of serious concern for the European Union countries [7]. This situation is easy to explain in the retrospect, when European drug producers being under pressure of finished drug market prices, decided to look for the cheapest possible sources of the API in Asia, where labor force was temporarily available on competitive conditions, but it turned out that in the process both: the drug quality and safety could be seriously compromised. Since ca. 80% of the API formulated in EU is currently supplied by Asian manufacturer, the question of possible trend reversal is becoming serious, since it has been recently clearly demonstrated that not only economic efficiency is at stake when European drug markets are concerned. Italy has already decided to resurrect its API manufacturing potential, and France has proposed that EUC should encourage return of the API production, possibly as an all-union initiative [8].

Current global market value of the API substances is estimated at 182.2 USD bn., and predicted to reach 245.2 billion by 2024, while its largest part is generated by innovative (branded; still under patent protection) drugs. However since few years the trend of the generic drug segment value growth prevails, with a good likelihood to become constant for a while. According to pharmaceutical market analysts and experts, the decline of old blockbusters which come out of patent, will coincide with the global growth of generics and biosimilar products, and the average value of the mass unit of API is consistently diminishing (in the last period from 6695 USD/MT to 5483 USD/MT) [9].

Innovation in pharmaceutical industry beyond new drug discovery

During the last 25 years 943 new chemical entities (NCE) were introduced into medicinal use, to top 9 thousand compounds in current registry of western medicine (out of which a countless number of preparations, single API or composed, are prepared by pharmaceutical enterprises all over the world) [10]. A cost of novel API design, development and registration, counted as an average including many failures of advanced drug candidates during mandatory clinical studies is estimated at 2.6 bn. USD [11-12] but can vary largely. For companies, which introduced 8 – 13 new drugs over 10 year period, the cost of a single launch was estimated at 5.5 billion USD, while Astra-Zeneca reported 11 bn. USD figure [13]. Based on the data from big pharma, it seems evident that achievement of a new drug development and registration in Poland, based on own resources, is out of question, for as simple reason as lack of proper funding. This statement should not however exclude a debate over a potential of local academic and otherwise organized scientific manpower, which should not be underestimated, despite of greatly complicated management tasks involved in such lengthy and cost extensive projects as new drug discovery and development. Against popular opinion that drug discovery and development (DDD) is best institutionalized inside of private business of big pharma, there are numerous examples of breakthrough discoveries essential for pharmaceutical development which were initiated in academia, and later successfully commercialized, in industry. Admittedly, translation between basic science discovery and its technical implementation is much easier achieved in countries with a long tradition of civilization progress than in local environment. Thus, outstanding Polish scientists achievements in life sciences, which reached global markets are few (remarkable examples include Hilary Koprowski (Thomas Jefferson University) work on polio vaccines, Wacław Szybalski (University of Wisconsin-Madison) advancements in biocatalysis and biotechnology, or more recent participation of Ryszard Andruszkiewicz (Northwestern University) in discovery of a new drug – pregabalin), and were commercialized by big pharma. Nevertheless, there are many convincing signs that presently local academic discoveries get enough recognition of their potential to obtain necessary intellectual property protection, which allow for translation toward commercialization. Examples include: genetic oncology diagnostics (J. Lubiński, PAM Szczecin; K. Jażdżewski WUM Warszawa), innovative anticancer APIs (Selvita Kraków; Celon Pharma Łomianki, OncoArendi Warszawa), novel catalysts for olefin metathesis (K. Grela, IChO PAN Warszawa; Apeiron Wrocław), innovative drug encapsulation systems (T. Ciach, PW Warszawa), new advancements in synthesis of MOF materials (J. Lewiński, PW Warszawa), new methods for 5'-RNA end-capping (J. Jemielity, UW Warszawa). A special mention is deserved by innovative IT tool devised for assistance in multistep chemical synthesis planning, called Chematica. This very useful computer program was designed, developed and commercialized by B. Grzybowski (IChO PAN, Warszawa), and is currently globally available through license from Merck.

Recent changes in EU pharmaceutical regulation and IP protection are likely to cause some revival of an interest even of big and innovative companies in generic business. Since effective patent protection time is only approximately half of the 20 years granted by law, supplementary protection certificates were introduced (SPC), which can extend the protection period up to 5 years [13], which was challenged from the beginning as discriminating generic development. After nearly a decade, European Generic Association, (now Medicines for Europe), under active support of the Polish Union of Pharmaceutical Employers and Lewiatan Confederation, an important change of the regulation was attained, which now allows for an API under SPC production in EU countries, for the purpose of its distribution at third party markets were patents are not valid, and also for storage, until SPC expires in the EU [14]. It is hoped that this change will increase chances of EU manufacturing enterprises of effective competition on the ground of API synthesis.

It is expected that Polish population in 2030 will contain ca. 18% fraction of citizens who are 65 and older, with characteristic for that age need for treatment of multiple ailments (diabetes, cardiovascular diseases, cancer, neurodegenerative diseases etc.), which will make a significant impact on the country drug requirements and availabilities. For the rapidly ageing society, the need for easier affordable generic drugs seems a critical issue in a foreseeable future. It should be reminded that generic drugs contain the same API, in the same dose as the reference drug. The two are in principle equally bioavailable, and have identical clinical efficacy, for which appropriate evidence has to be presented in the registration procedure [15]. Since manufacturers of generic drugs undergo substantially abbreviated registration procedure, without long and very expensive clinical trials, their products are considerably cheaper (sometimes up to 20 – 80%) than innovative drugs under patent protection, which can have a powerful impact on the total costs of the state healthcare system.

The generic drug sub-sector, which is a principal platform of Polish pharmaceutical industry, still leaves plenty of room for minor (or incremental) innovation, concerning APIs, finished products, synthetic or biotechnological intermediates, and processes of their manufacturing, sometime even suitable

for IP protection and patenting. Nanotechnology constructs and new tools and methods for analytical chemistry open additional avenues for such innovation. Traditionally well-educated life science specialists, alumni of local universities, constitute a great potential, which has not been sufficiently exploited for benefits of local pharmaceutical industry which needs revival in many aspects of its current activity. The state funding agencies like National Center for Research and Development (NCBiR) should strongly promote all forms of pharmaceutical innovation, in consideration for strategic planning of inevitably large future expenses of the public healthcare. Only systemic support of the translation process, from academic discoveries and innovations to pharmaceutical technologies can improve current, and potentially devastating future situation, in which large funds are spent on import of innovative medicines, for which export of relatively cheap generics could not possibly compensate.

Some good examples of bilateral industry – academia cooperation in the field of pharmaceutical API manufacturing can be drawn from recent technical and market achievements of Polpharma SA, which is known for long term cooperation with chemical team from Gdansk University of Technology (GUT/PG). Approximately two decades ago a formal agreement concerning research cooperation on synthesis of hydroxybisphosphonates, which are applied in treatment of osteoporosis, was signed featuring model sharing of patent ownership and split of production profits, in which GUT/PG participated. As a result of successful research of synthetic team led by Professor J. Rachoń, followed by joint development efforts at Polpharma, the partners have become owners of original and patented technical process for manufacturing of alendronic acid API and its salts. Following this success, Polpharma has started regular alendronate production and launched Ostemax 70 Comfort preparation, based on sodium alendronate as the active substance, which has established its position as manufacturer for the global market. The cooperation is continued, aiming at next generation hydroxybisphosphonates – risendronic, ibandronic and zolendronic acids, for which new processes have been already patented and implemented. Other examples of innovative generic processes of former blockbusters, commercialized recently in Poland include: sildenafil (Polpharma and PRI) and imatinib (non-alkylating, protein kinase inhibiting anticancer drug; PRI). Pharmaceutical Research Institute (Sieć Badawcza Łukasiewicz - Instytut Farmaceutyczny, formerly Instytut Przemysłu Farmaceutycznego) which was founded in the beginning of 1952 has a rich record of R & D achievements and their commercialization, spanning over the entire period of its existence, with a list of over 400 designed and developed processes (API syntheses as well as pharmaceutical formulations). It seems obvious that at present time innovative potential of research enterprises like PRI, has to be validated through active participation in, and contribution to, international scientific environment, not only in form of own patents and publications. PRI has performed well in this respect, participating in international programs like Orbis (Horizon 2020). Even in older EU programs, like FP6 and FP7, PRI took active part in development of very innovative pharmaceutical technologies like Microdosing, (also described as Clinical Phase 0) ; EU Programs: EUMAPP and ERA-NET PRIOMEDCHILD project - Paediatric Accelerator Mass Spectrometry Evaluation Research Study (PAMPER), which allows to study pharmacokinetics and metabolism of drugs and can eliminate much costs and efforts of advanced preclinical and early clinical studies, through application of sophisticated analytical methods based on accelerator mass spectrometry for isotopic label analysis [16]. What is important, the results of these multinational cooperative studies led by British researchers, are now available in public domain, contributing to open science, dedicated to wider and more efficient development of new drugs, globally.

It seems reasonable to postulate, based on the presented above evidence, that strategic program (focused on new original methods for the synthesis of API and generic drugs) directed at pharmaceutical security and basic drugs availability, is urgently needed in Poland for social reasons, among which poor prognosis for future safety of people suffering from so called civilization diseases – metabolic syndrome (diabetes, CVD, obesity, cancer, neurological ailments, etc.) should be considered as the crucial argument.

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