İlaç Firmalarının Çıkar Çatışması ve Tıbbi Gelişim Alanına Getirdiği Etik Sorunlar

The Conflict of Interest of Pharmaceutical Companies and The Ethical Issues Brings to The Field of Medical Development

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Özet

Bilim ve tıp alanındaki gelişmeler sağlık hizmetleri endüstrisinin hızla gelişmesine de izin veren ilaç çalışmalarını güçlendirmiştir. Böylece ilaç firmaları, sağlık sektöründe önemli bir rol oynar hale gelmiştir. İlaç firmalarının temeli, 19. yüzyılın sonlarında İsviçre'deki kimya endüstrilerine dayanmaktadır. 1928-1950 yılları arasında ilaç firmaları laboratuarlarda ilaç geliştirmeye başlayan ilaç firmaları ciddi başarılar elde etmiştir ve geçtiğimiz yüzyılda birçok tıbbi ilerlemeyi sağlamıştır. Bunun sonucu olarak büyük ilaç endüstrisi hızla gelişmiş ve ilaç araştırma-geliştirme endüstrisi daha güvenilir hale gelmiştir. Bunun ile beraber İlaç endüstrisi, yeni ilaçlar geliştirmek için klinik ve ilaç araştırmalarına çok ciddi para ayırmaktadır. Ancak, etkisiz ilaçların üretilmesi veya bazı ilaçların piyasadan çekilmesi olasılığı, ilaç şirketlerinin para kazanma hedefini tehdit etmektedir. Bu sorun, İlaç endüstrisi, ticari uygulamalarda iş etiği açısından bazı kavramsal zorluklar içermektedir. Bunlardan ilki, "etik ve kâr güdüsü" ile "özel fayda ve kamu yararı" ikilemleridir. Kar amacı ve özel fayda, iş etiğine uygun değildir. Pek çok firmanın etik sorumluluk taşımadığı ve çoğu firmanın çevre ve tüketici sağlığı ve güvenliği pahasına faydalarını acımasızca artırmaya çalıştığı fikirleri son 10-15 yıldır yaygınlaşmıştır. İlaç şirketlerinin uygulamalarını yürütürken "insan değerini" göz önünde bulundurmaları gerekmektedir. Karar vericiler, insanları sadece bir araç olarak değil, aynı zamanda amaç olarak da görmelidir. Böylelikle ilaç firması yöneticileri, verdikleri kararlarla tanımadıkları insanların var olan değerlerini koruyacakları gibi, kendi değerlerini de koruyacaklardır.

Abstract

Advances in science and medicine have strengthened pharmaceutical work, which has allowed the healthcare industry to develop rapidly. Thus, pharmaceutical companies have become to play an important role in the health sector. Pharmaceutical companies have their roots in the chemical industries in Switzerland in the late 19th century. Pharmaceutical companies, which started developing drugs in the pharmaceutical companies laboratories between 1928-1950, achieved serious success and made many medical advances in the past century. As a result, the large pharmaceutical industry has developed rapidly and the pharmaceutical research and development industry has become more reliable. However, the pharmaceutical industry devotes a lot of money to clinical and pharmaceutical research to develop new drugs. However, the possibility of producing ineffective drugs or withdrawing some drugs from the market threatens the pharmaceutical companies' earning goal. The pharmaceutical industry poses some conceptual challenges in terms of business ethics in commercial applications. The first of these is the dilemmas of "ethics and profit motive" and "private benefit and public interest". Profit and private benefit are not in line with business ethics. The ideas that many firms do not bear ethical responsibility and that most firms are relentlessly trying to increase their benefits at the expense of the environment and consumer health and safety have spread over the past 10-15 years. Pharmaceutical companies need to take "human value" into consideration while conducting their applications. Decision makers should see people not only as a tool but also as an end. In this way, pharmaceutical company managers will protect the existing values of people they do not know with the decisions they make, as well as protect their own values

Introduction

The advancements in science and medicine and the increasing knowledge about existing disease-causing bacteria and related subjects, rather than common observation, have led to a new scientific medicine which has allowed the health care industry to flourish rapidly (1).

Pharmaceutical companies play a major role in health care idustry. The cornerstone of pharmaceutical companies roots back to the chemical industries in Switzerland in the late 19th century. After recognizing that the dyestuffs have an antiseptic properties (1,2). that slow or stop the productivity of microorganisms on the external surfaces of the body in order to prevent infections (2,3) Between 1928 and 1950, pharmaceutical companies (PC) started to develop drugs in laboratories and it was until the discovery of penicillin in the 1960s when pharamaceutical companies took the lead and achieved phenomenal success. The terms big pharma referring big pharmaceutical companies and biopharma emerged (1,2). As a result of these findings big pharma industry expanded rapidly and the drug research and development industry became more trustworthy.

In their fisrt experiments, most pharmaceutical companies aimed to develop plant-based drugs to treat different symptoms. The idea of drug industry speard into many different countries not so long after the huge success of big pharma. For example, in 1952, the drug production of pharmaceutical companies started in Turkey. The Turkish ministry of economics has shown in 2018 that Turkey has about 39 pharmaceutical local construction and 14 multinational firms mainly centered in Marmara region (4).

The pharmaceutical industry spends a lot of money on the clinical research to develop new drugs. Drug research has lead to many medical advancements in the past century. However, the possibility of producing uneffective drugs or withdrawing some drugs from the market threats the money making goal of the PC. This isssue creates a gap between the two main goals of PCs: producing a real therapeutic benefit drug to improve public health and enriching their profits (5). Thus, it is very important to consider the relationship between the pharmaceutical industries and other participants on the arena of health system including universities, hospitals, health practitioners, and scientific publishers.

Developing and testing a new medicine is an expensive process. It was found that the cost of developing new drugs worldwide in 2015 was approximately $89 billion. In 2019, Eli Lilly spent around $900 billion on the research and development of new medications. Bigpharma makes huge investments in drug development and they expect big earnings in return. Studies have shown that PCs are experiencing substantial growth in profit. A study made by US accountability office on November 2017 showed that between 2006 to 2015 approximately 67% of all drug companies in the US have grown on their yearly revenue. And among the largest 25 firms the profit margins reached 15 - 20% per year (5,6). Another study presented that Turkey is categorized as the 29th largest pharmaceutical sales in the world and its income is expected to grow from 7.6 billion dollar in 2015 to 9.8 billion dollar by the 2020 (7) The profit and increased sales of pharmaceutical companies might not seem a bad thing at a glance. This big expansion in the revenue of drug companies has lead to increase the numbers of new medications a few of which presents a real therapeutic benefit (4). The great gain of pharmaceutical companies from releasing new drugs and their huge investments in medical research caused a shift of focus of PCs. Thus, creating drugs with real benefits and few or less lethal side effects is no longer, if it ever was, the main goal of bigpharma, they also aim to make enough money to pay off the

researchers and labs in addition to insuring their profit. Thus, proving the inefficiency of a drug, withdrawing it from the market or even patent expiration of a moneymaking drug represent some serious issues for bigpharma. In order to protect their gain, pharmaceutical companies put so much effort in creating and marketing their drugs. Creating and marketing drugs is totally reasonable keeping in mind that these companies need their profit to go on and make new drugs. However, the main concern about pharmaceutical companies is the way they market their drugs. It has been a while since people started to notice that some PCs follow strategies, ethical and unethical, to make their medications more accepted and prescribed. (8,9)

The Effects Of Gift On Doctor

PCs market their products in many different ways. One of the common methods that are widely used is the media. Different advertisements on television, radio and social media promote the companies products. Too many people know about marketing through the media; however, a few are aware of other approaches of drug promotions. Companies advertise their medicine by influencing the field of healthcare. Doctors are the mediators between drug companies and their students and patients. Thus, provoking health practitioners to prescribe a drug is a primary method that PCs follow to boost their sales. Gifts, honorarium, and traveling are used by PCs to establish a connection with health practitioners and convince them to prescribe the companies' products . (8,9,10)

The studys published showed that every year the pharmaceutical industry spend about $12 billion on health practitioners to promote their products (9). In 2012, $24 billion were spent on marketing first-rate branded drugs to health-care providers while patient targetting advertisements only costed $3 billion (11).

In other words, the expenditure of pharmaceutical companies on marketing increased eight folds between advertising to consumers versus promoting to health practitioners.

A 2017 survey about the prescribing practices of health practitioners in DC found that those who received benefits from pharmaceutical companies tended to prescribe the company's more expensive drugs than those who did not receive any benefit. Another analysis has shown that doctors who received benefits as simple as meals prescribed the companies drug twice to three times more than those who did not receive any benefit. The same study has shown that more prescribtions were associated with more benefits received (12). Means that patients who do not have a health care provider might not be able to afford their treatments or couldn't adhere to it although there might be a cheaper and equally useful alternative that is not prescribed for them (10). Basically, these studies/surveys suggest that by making a long-term relationship between the PC and specialists, the physicians consciously or unconsciously recommend the company's drug even if it has an alternative lower price drug.

Off-Label

Furthermore, PCs embolden doctors to use "off -label" drug prescriptions. Off labeling simply means regarding the medication to treat a disorder other than its original approved usage by US Federal and Drug Administration (FDA) (13). Thus, the practitioner can use the drug openly without the need to reassure the regulatory authorities, as the drug is reported to be safe from the FDA.

For instance NeurontinTM (gabapentin) was accepted by FDA in 1994 as an epilepsy drug. In 1996, David Franklin, an employee of Parke-Davis, claimed that there was a suspected illegal conspiracy to market Neurontin for off-label use. But the court investigation revealed that the firm had offered researchers a lot of money for giving their names to poorly constructed research to show that the medication can be used to treat other diseases (bipolar disorder, post-traumatic stress disorder, insomnia, restless legs, hot flushes, migraines, tension headaches, etc.) (14).

Another off-label drug use incidence is Quetiapine (Seroquel) that was licensed by the FDA in 1997 and commonly used as an antipsychotic drug in the US with an annual sale of about $6.8 billion. By 2010 the Quetiapine pharmaceutical corporation has obtained a legislation from the government to use this drug as an off-label prescription after paying $520 million. Meaning that the drug will be used to treat non-psychiatrist conditions such as Dementia, Alzheimer's disease, obsessive-compulsive disorder, etc. (14). Off-labelling can be beneficial in introducing existing drug into a new context where they can be useful, extending the patent of a drug with cheaper cost than developing a new formula. The success of the claimed to be safe drug in treating other ailments is not garanteed and it opens up a debate about the ethicality of off-labelling. Many ethicists claim that off-labelling can be associated with misleading representations and interpretations of information in low quality studies and ghostwriting in lectures Medical journal editors would also have no way of knowing whether an article from a seemingly independent author is truly objective or is company-sponsored and ghostwritten (15).

Omperazolein 2001 was about to close its license so that the producing company, Astra, realized that it would lose its benefit from the drug. Therefore Astra wanted to find another way to protect their profit from omperazole. Simpley, Astra researchers produced a, so called, new drug with a very simillar formula, repackged it, and called it nexiom (12). This inexpensive method garanteed the company a few more years of profit before needing a new patent.

Hiding Undesirable Side Effects

In order to market their product, bigpharma aims to convince people about the positive effects of a drug. Companies hide the undesired side effects of their drugs and inflate the positive results of drug-testing trails (16). By hiding the negative side effects of a drug pharmaceutical companies can prevent withdrawing their drug from the market, maximizing their profit. Hiding the side effects include manipulating the data of the studies conducted by the companies' researchers or even redesigning a whole trail in order to conclude positive desired results. An example of that is the Merck's Vioxx (rofecoxib) which was approved by the FDA as a safe pain reliever in 1999, but in 2004 it was withdrawn from the market because it tripled the risk heart attacks (17). Later documents revealed that Merck's researchers knew about this dangerous side effect but the decided to hide it because Vioxx was the company's moneymaker and they manipulated the results by a pattern of ghostwriting (18).

Another approach that pharmaceutical companies follow to keep their drugs on the market by exaggerating the positive outcomes of a drug. This method seems slightly less biased than the previous one since independent researchers can criticise the effectiveness or uneffectiveness of a drug. However, companies can still sponsore researchers in order to make their data more appealing to the public and to the health practitioners. A 2005 survey showed that 76% of the positive studies about prescription drugs were conducted by researchers who had direct financial ties with the company compared to 49% of the negative studies researchers. Another

survey found that 15% of positive results researchers admitted that they felt pressured by the company to redesign the results. These surveys indicate that pharmaceutical companies can and do affect the researchers in simillar ways to how they infleuce health practitioners.

Studies financed by the drug company are much more likely to generate positive results than studies of the same drug carried out by experts not linked to the sponsor. Pharmaceutical companies provide vast bulk of funds to research their products. Overestimating the benefits of a drug garantees increasing sales since it will affect doctors as well as patients. Patients normally prefer what is presented for them as safer and more effective; hence, positive data about a medcine would drive their attention and they might ask their doctors to prescribe a specific medication that they have seen or read about. A US study shows that around 30% of patinets come to their doctors with a therapeutic plan in mind; they ask their doctor to prescribe a specific medication. 44% of the reported cases, the doctor prescribed the patients their requested medicine (19).

Hiding the side effects and inflating positive results may not only mislead the public; they also can misinform the health care givers who are responsible for providing the best care possible for their patients. Many doctors depend on science in designing their patients' treatments. A survey published in 2014 found that 75% of doctors change their treatment plans monthly or quarterly based on the medical literature they read. If this literature was biased or inaccurate, it can lead to dangerous health impacts.

Ghostwriting

Pharmaceutical companies do not always transparently declare their sponsored studies or the company-directed research to the public. Instead, they use different techniques to hide the real author of a research or to disguise the company-author relationship. Ghostwritting is one of the common methods used to serve the purpose of hiding any potential biased and making the study more trustworthy. Ghostwriting is when a writer writes a significant portion of a paper, or all of it depending on company-owned data, but isn't credited. Instead, an academic or other notable figure's name is recognized as the author. In this way, the company's researchers can coduct a study and credit it to someone else in order to hide the bias. After publishing the article, no one would know that the real author is not recognized in the article.

A statistical study in Australia showed that more than 12% of specialists signified that the first draft documents were published by pharamceutical compaies' workers, but the final studies ended up referring to unknown writers. Another study claimed that in Canada the researchers with industry funded trials were more likely to report instances of ghostwriting than those with non-industry funded trials (20). Some companies provide ghostwritting services; they publish studies agreed on with pharmaceutical companies as their own. These companies facilitate bigpharma-public relationship by generating customized studies, promoting the products of the contract company. In 1994, A New Jersey publishing company, Ecerpta Medica, cooperated with an American pharmaceutical company, Wyeth, to publish studies about the company's nutritional drug, Redux. Ecerpta generated many studies, paying the orginal writer $5000 and the "claimed" writer $1500. The published articles targeted different audience and focused on promoting dietary information to advertise the Redux (21). Ghostwritting mainly allows companies to gain people's trust and cover any possible doubts about the objectiveness of the research.

Genuinely, ghostwritting presents a serious issue in the field of medical research. It supplys the literature with studies that may lack objectiveness and integrity. The orginal authors can make, or cherry pick, the data that they want to supply their study with and their names will not be on the publication, so any potential bias could be hid by putting the name of an independent medical figure. Also, ghost writers are not held responsible for any of the information published since their names will only be on the preliminary draft. Thus, a ghostwriter can be paid for designing a study that is not necessarily 100% accurate, supplying the medical field with biased literature.

The Conflict Of Interest

The conflict Of Interest (COI) can be simply defined as circumastances in which any personal considerations interfere with morals. Basically, it is the risk of acting biased due to personal interests. The COI can appear in individual or instutional aspects. The COI is driven by personal interests, which are divided into two main classes: primary and secondary. Primary interests will always affect the secondary ones (21). Pharmaceutical companies fund huge capital investments to create drugs. They promote by influencing healthcare providers, directly affecting the wellbeing of patients. Thus, their primary interests are usually related to protecting their profit, maintaining their trustworthiness, and the welfare of people. Secondary interests include the honorable gains associated with achievements and becoming leading developers of a drugs (22,23).

The advertising processes of PCs in sales are crafted to impact the public consumers as well as healthcare providers. Influencing the decision-making process of patients and health practetioners which alters the prescribing patterns of certain drugs. For instance, many researches have presented that health professionals are promoting the PC by prescribing its medicine and sometimes physcians prescribe it not for accurate purpose thus the results of given drug going to be pointless and the risk from using it may extends to include both patients as well as the expenses of the health services, which have to cover the cost of these drugs.

While the interests of doctors can overlap with the interests of patients, PCs, and health care provider; hence, the COI emerge. Most doctors believe that the promotions of the PCs that include gifts and payment do not have any effect on their actions. Actually, different studies have shown that the capability of these publicities are more effective than expectations. The effects of advertisments on doctors do not only include altering the prescribing patterns, but they extend to impact the students as they learn about particular medicines (24).

Current Measures to Minimize the Conflict of İnterests

Pharmaceutical companies make tremendous efforts to improve the production of medical drugs and development of research to produce optimum results for public health. Essentially, we cannot disregard the effort these companies have put to advance medicine and improve new treatments. However, the serious COI issues that lead the companies to market their drugs regardless of their benefits to the public health (5). Thus far, pharmaceutical companies and some organizations has set some ethical codes that take into considerations the objectives of PCs as well as the complains about the current COI in pharmaceutical companies. There is a range of

legislations, regulations, and laws created by PCs and governments to make standard industry codes of drug developments, marketing, and distribution (22).

The International Fedration of Pharmaceutical Manufractureres and Association (IFPMA) is a non-profit international orginaization that was first established at 1981. Its code of practice aims to create policies that establish the ethical framework of pharmaceutical industries in each market arround the world. In addition to IFPMA codes along with the legislations of national industry associations around the world, many pharmaceutical companies have approved to manage self-regulation standard of ethics and legal controls (ethics behinde PC the last file). In 2006, the new IFPMA Code Compliance Network (CCN) brought together more than 100 regulatory specialists selected to represent member associations and companies to exchange knowledge and assure the most successful way of managing the Code at national and international levels. In 2012 the IFPMA code of practice reviewed and modified its code once again. New prinicipals were added into the code to make balanced standards between all codes of ethical regulation in phamaceutical industries worldwide (25).

This revisions on the IFPMA Code of Practice has also developed limitations on gifts that are given to health care providers, supporting the objective medical education and the unbiased prescribing patterns. The code provides the companies' employees with necessary information to deal with complaint issues in the light of ethical code and current laws. The modifications of the code extend to include regulations to the marketing practices that also have regulations beyond the IFPMA code of practice. These regulations declare that the promotional activities must adhere to the highest ethical standards. The IFPMA code states that the material provided by PCs must appropriately encourage appropriate use of medicines by presenting information objectively and without exaggeration. In other words, all data provided to healthcare providers should aime to serve them and their patients in the best way; it should be objective, accurate, and easiy to understand. The code also gives healthcare practitioners the right to provide feedback about the therapeutical value and the side effects of the prescirbed drug.

Although, these requirements set some basic frames to regulate and restirct the COI in bigpharma, they vaguely draw the margins of drug marketing and provide no strict regulation of the overall COI in the process of drug development.

Conclusion

All of these COI-prone issues might rise doubts of whether or not the bigpharma should be trusted. The existence of these doubts and uncertinties is a misfortune for the public consumers as they are for pharmaceutical companies. It is unreasonable to deny the role these companies had played in developing new drugs and treatments which, in turn, contributed to increasing the level of health. However, as discussed these companies have serious conflict of interest and money making issues, so their studies' results cannot be taken for granted. The increasing public awarness about the COI in bigpharma should alert the pharmaceutical industry to the importance of forming some ethical principals in order to regulate their COI and regain the public trust. The goal of achieving optimum profit will not be satisfied if the PCs lose their integrity and trustworthiness in the eyes of the people who are the main consumers and profit makers. It is crucial to regulate the interaction of the PC and the practitioner, on one side, and the doctor-patient relationship, on the other side. PCs might need to develop disclosure policies where every in charge person who has financial ties with the company is addressed along with what type of

ties he/she has. Including physicians who should be required to inform their patients about alternative drugs if any available. The PCs must assure that all of its products have reliable quality and it works to improve the public health such this obligation require from the PC to establish a truthful data that make both of patients and health care practitioners clearly understand the use of medicines. The continuity in growing the number of the available drugs also give a necessity from the health proffisionals to be always in contatct with the latest scientific progression of the new drugs. The patients always need to know the information about the medicine given by their doctors, which provokes the practitioners to be always up-to-date with new drug. Accordingly, the PCs are responsible to give the right, precise and truthful informations about its products to the doctors. In order to serve the ultimate goal of medicine by maintain the wellbeing of the patients, doctors should obtain the data from many resources such as clinical trials, published reviews, or from medical and scientific articles etc… There many other measures that pharmaceutical companies can take to regain people's trust so they won't feel cheated or taken advantage of by big pharma.

The pharmaceutical industry contains some conceptual difficulties in terms of business ethics in commercial operations. The first one of these is the dilemmas of "ethics and profit motive" and "private benefit and public beneficence". Profit motive and private benefit do not comply with business ethics. The ideas that many companies do not bear the ethical responsibility and that the most companies ruthlessly try to increase their benefits at the cost of the environment and consumers' health and safety have become widespread in the last 10-15 years (26). However, Kant, who brought the concept of "value" and the "value of the person" to the forefront and placed these in the foundation of ethics (philosophy of ethics), defined "practical imperative" as "Act to treat humanity, whether yourself or another, as an end-in-itself and never as a means" (27). According to Kant, the value of every object that will be owned with our actions is always conditional and they only have a relative value as a means. In other words, "things" have prices, but human, who is above all prices; thus, have no equivalent, is valuable. Things with a price can be replaced with another thing as its equivalent. While things related to the general inclination and needs of people have a market price, the things that make up the only condition for itself to be the end have relative values. In other words, they do not have a price but an internal value so they are valuable by themselves. Therefore, humans must be placed on the basis of actions as the supreme limiting condition for the use of all means and always as an end at the same time (27).

Pharmaceutical companies need to consider "the value of human" while conducting their operations. Decision-makers should see people not only as a means but also as the end. Thus, pharmaceutical company executives will protect the existing value of people they do not know with the decisions they made as well as protecting their own values as humans.

Decisions of the pharmaceutical company executives affect both the business and ill people who contribute to the business indirectly. The rule of "not harming anyone directly", which is the first one of nine behavior rules proposed by Goodpaster under the heading of "moral common sense", is not sufficient for the business ethics that is expected to include pharmaceutical companies. Because the decisions that pharmaceutical companies will make with regard to the determination of pricing policy and the diseases about which they will carry out research and development activities affect millions of people "directly" and "indirectly" (26). Possible ethical actions of company owners are based on a person-"situation" relation instead of a person-person relation: "A person is always in an ethical relation while doing an act, and doing something

about people he/she is face to face or he/she does not see their face, people near and far away - people she/he does not know who they are as a person: the person always does what she/he does as a person with a certain integrity, and always do acts loaded with value problems" (28). What makes drugs valuable is not associated with the strong demand in the market but with their direct relation with the value of humans. It is the special place of the drug within other similar products.

Which practical rules the companies in the pharmaceutical industry, which is directly related to humans and will follow while determining their strategies, policies, programs, and projects, and conducting their operations are explained in the Report of Paul Hunt, the United Nations Special Rapporteur, in detail. The main purpose of the report named the "Human Rights Guidelines for Pharmaceutical Companies in relation to Access to Medicines" (2007) is to provide guidance to pharmaceutical companies in practice. This report is the most comprehensive study ever conducted in this field. In the introduction of the report, Hunt emphasizes that the main responsibility of the implementation of the right to health belongs to governments. However, he also mentions that pharmaceutical companies have quite important positive and negative effects on the actualization of the requirements of the right to health by governments. The assignment of non-governmental actors in the realization of human rights is always considered within the framework of "respecting". However, Hunt's Report did not limit the responsibilities of pharmaceutical companies regarding human rights to respecting but also assigned them to "implement". In this regard, Hunt's Report can be summarized as follows:

The obligation of pharmaceutical companies to "respect" (negative)
The obligation of pharmaceutical companies to "implement" (positive)

Paul Hunt's Report is an important guideline, and the realization of referred initiatives in practice will be possible if supported with international treaties bringing protection and enforcement mechanisms as well.

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