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Warranty Issues of PDE-5 Inhibitors as Off-Label Use Action Mechanism based on Pharmacoeconomics for Patient Safety in Taxation System

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ABSTRACT

Every government system follows the principle of ultimate powers in divided authorities responsible to promote public welfare and safety through constitutional practice of economic freedom. Pharmacoeconomics deals with cost-effective analysis in alignment with administrative functions of the government in relation to ethical behavior of private companies to comply with the rules and regulations expressed by the legislation and its comparative parliamentary legal system for guidance and control of appropriate ethical conduct as advocated by warranty issues of intellectual property. The intended design of PDE-5 inhibitors for marketing their products for public use as medication is indicated in their patent registration as strict compliance of advocating patient safety. Hence, ethical issues on product warranty of declared intended use, health risks for economic benefit, sexuality, and gender as socio-legal utilization of resources, empirical healthcare practice based on registered declared intellectual property of product design, and economic interventions in advocacy of constitutional monetary freedom are aimed to be discussed and resolved in this paper. Public funds are used by the government to advocate cost-effective analysis in pharmacoeconomics. Therefore, direct taxation of product services and practice of health promotion must be properly addressed and coordination in aligning the institutional goals with employment law for proper compliance of handling patented products. Furthermore, indirect taxation based on public funds must resolve issues concerning taxes collected from private companies handling patented drug products with clear specification of intended design for patient efficacy and safety. It is recommended to provide ways of promoting pharmacoeconomics without the conflict of suffering the declared intellectual property design for handling and misleading the acquired taxes for public funds, which in turn will also be compensated for unregistered intellectual property design based on patent law.

Keywords: pharmacoeconomics, off-label use, taxation, intellectual property, patient safety

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INTRODUCTION

From the period of 1901 to 2000, pharmaceutical transactions, also termed as pharmacoeconomics, has engineered various constitutional freedom of monetary success for public welfare and safety as it gained a lot of importance together with the legislative body to provide cost-effective medications. The population growth alarmed the community, as well as the drug manufacturing companies, to develop and innovate economical medicines aiming to control the problems associated with human diseases aside targeting the constitutional rights of its citizens. Hence, the increasing complexity of effective and cheap medicines in various conditions influenced the government system to create ways towards its constitutional purpose for public utilization [1].

The relevant global practice of politicians and healthcare professionals towards patient safety is constitutionally promoted to follow the utilitarianism doctrine of evidence-based medicine advocating its clinical practice guidelines. However, presumptions from its therapeutic levels of hierarchy using various allied health interventions did not meet some of its encountered challenges. Pharmaceutical marketing requirements for wide trade use have strict registration compliance, hence, the stage for randomized clinical trials (RCTs) is obligated to document the registration criteria for drug efficacy proving patient safety of manufactured medicines promoting product quality with legal guarantee following the authorized socio-legal protocols validated by daily monitoring [2].

There are two (2) research methods to evaluate the impact of pharmacoeconomics. First is the quantitative usage of scientific areas using visualization maps on the grounds of bibliometric evaluation, known as the scientometric examination. Second is the provision of the quantitative publication summaries, termed as bibliometric examination. In healthcare industry and its innovations, scientometric examination has been widely used to practice its relevant disciplines.

The constitutional purpose of drug therapy lies on the branch of pharmacoeconomics dealing with cost-effect analysis of health economics. Its relevant purpose promotes the practice of pharmacoepidemiology resulting to waste reduction of various resources. Today, pharmacoeconomics has more than 40 health policy publications across several countries for inclusion of its analytic methods, yield indicators, and economical processes [3].

In the United States, dysfunction of male erection, termed as impotence which disturbs 30 million people, tends to weaken the erectile maintenance to attain adequate satisfaction of sexual intercourse. Its degree varies from a partial erectile decline to a complete failure.

The common basis of erectile dysfunction (ED) is the inadequacy of blood flow in the arteries. This type of disorder is known as corporal veno-occlusive mechanism which impairs

and interferes the arterial system leading to inability to maintain erection due to failed blood trap and fluid impediment [4].

On the 27th of March 1998, the US Food and Drug Administration approved Sildenafil citrate for marketing the first oral drug known to inhibit phosphodiesterase type 5 intended for ED treatment in more than 120 countries worldwide. Following 7 years of approval, many physicians have prescribed sildenafil for men in treatment of ED [5].

Its 1998 introduction strengthens a novel tool for sex therapy to widen the ED treatment of many people. This drug quickly qualified to be the primary treatment for sexual dysfunction replacing all other means [6].

This paper aims to discuss educational practice gaps in terms of business ethics of code of conduct compliance in alignment of administrative regulations and legislations pre-emptive with their constitution of providing public welfare and safety to its citizens as intellectual property of drug safety starts from drug discovery and clinical trials leading to professional practice of using taxation system to conduct their knowledge management practice.

MATERIALS AND METHOD

The US FDA approved sildenafil for treating pulmonary arterial hypertension (PAH) designed for improvement of ability to exercise and deferment of clinical exacerbation in adults. Its approval is intended for adults, while the off-label use of sildenafil has augmented its design in infants [7].

Economists have debated for several years to restrict manufacturers in the market in an appropriate means that would impose court penalties against any forms of breach or violation. A manufacturer who violated in any means of its quality assurance and control is deemed to perpetrate breach in either implied or express warranty, or to perform fraud. An express warranty is a clear contractual obligation subject to court sanctions for any modes of breach that would encompass its approved complete specification. Manufacturers may adjust the range of warranty for appropriateness of its clinical assessment. Lacking express warranty, courts ensure its compliance for its declared intended design [8].

In the start of 1916, the case of MacPherson v. Buick Motor Co. initiated to permit act of negligence for sustaining lack of privity in a harmless and usual situation including occurrences of a product being negligently produced forming a risky result. Currently, privity is no longer required in claiming damages from personal harm in a negligent performance of a producer [9].

The Food, Drug, and Cosmetic Act (FDCA) of US federal states provides legal authority to FDA in resolving several public health issues. The crucial problem is the clear evidence that off-label prescriptions can convey substantial dangers due to inadequacy of clear

documentation leading to risks for patients. Hence, allowing to advertise this type of off-label performance could result drug producers to infringe the market with subjective details of insufficient support resulting to diversion of prescription practices. In the acknowledgement of some unallowed off-label communication, the FDA has listed secured protection for producers: answering unnecessary issues from doctors, disseminating peer-reviewed journals, documenting its purposes, and promoting legal medication practice through continuing professional education. In the past 30 years, however, a hundred billion dollars in criminal and civil sanctions have been compensated by approximately all major drug firms for supporting off-label engagement beyond restricted jurisdictions resulting to questionable outcomes for patients in each scenario.

In 2016, the 21st Century Cures Act permits producers to render healthcare details for economic purposes concerning usage of off-label medicines to formulary committees that aid insurers in deciding for its coverage of drugs. Such entities have more access than sole doctors to assess critically raised issues despite of its substantial refinement range across the US trade. During March 2017 in Arizona, the Free Speech in Medicine Act passed a clear permission for producers to connect with several doctors regarding off-label practice. FDCA rendered this legislation to have a poor probability to sustain continuing legal risks concerning some unapproved practices. Hence, the Goldwater Institute may advocate its aim in support of restricting the capability of FDA to permit off-label practice due to mentioned legal harms.

In 2017, the US House of Representatives introduced two bills for the expansion of allowing the scope of off-label practice. The Medical Product Communications Act aims to make a novel secured protection of technical substitutes with physicians in connection to off-label practices in a condition that the advertisement is not deemed to promote naturally its information, the report is asserted with validated scientific facts and producers render suitable purposes from its mathematical algorithms of computer-aided designs following equational principles or rules governing various components of pharmaceutical engineering concepts. This bill strengthens the evidence that the producers' marketing representatives should communicate more usual with doctors in prescribing patented drugs for the reason of compliance with their aims of advertisement, not by its natural or official composition but with the permitted scope of off-label promotion, and through compliance, the legislation would permit clinical report distribution although the FDA's substantial proof of its performance standard would be inadequate due to incomplete specification from subjective and unreliable studies. The observed attempt in the 21st Century Cures Act for widening the scope of coverage insurance in relation to communications permits the producers, under the Pharmaceutical Information Exchange Act, to report clinical and pre-clinical data concerning

unapproved designs to formulary committees about its scientific review could be an adequate anticipation to assist future approvals of FDA regarding some of its unapproved usage. Both bills are necessary for the producers to cover disclaimers regarding the scope of FDA for its unapproved designs of data, and there are also currently accessible disclaimers in the condition of advertisement claims without the approval of FDA concerning nutritional supplements in lack of its working demonstration.

Since one court appeal has a slight chance of success, supporters have moved to federal and state legislatures to clarify current rules of FDA in connection with off-label practice, since these regulations are crucial for the FDA's ability to comply with its mission of performing its defined public health in terms of communicating with the advantages of drug usage lessening the harms against those with insufficient facts to warrant such design. These differences are important for sole prescribers in lack of expert time to conduct the same risky evaluation of clinical information done by high rated and skilled FDA scientists for their patients in possible exposure of insufficient facts and potential risks for expensive off-label medicine practice [10].

The United States Patent Act (35 U.S.C. §112) has codified its disclosure specification. In reference to Section 112, a proper specification demands 3 doctrinal elements: the ID card of the invention, the instructional manual, and the best mode of design or invention [11]. Similar goals are being raised involving the U.S. Food and Drug Administration (FDA), World Health Organization (WHO), and other proficient authorities in motivation to conduct clinical research for protection of children using off-label practice, unsuitable formulations, and poor quality of drugs. Hence, these measures cannot be easily avoided and would certainly have an impact on the biotechnology firms prioritizing research and development under international context of clinical trials.

Since 1979, the US legislation demanded pediatric information for the label of drug medicines and the Final Pediatric Rule on data observations for children is ordered in 1998. In 2002, the Best Pharmaceuticals for Children Act (BPCA) was made to stimulate 6 months of market restriction on given products being assessed through a written communication from a request of pediatric evaluation and the Pediatric Research Equity Acts (PREA) subsequently corroborated it. In Europe, the ICH Guidance 11 introduced Pediatric Regulation for facilitating evaluations of children population. It also mandates drug firms to perform clinical pediatric assessments based on an agreement in Pediatric Investigational Plan (PIP) in exchange of patent security for 6 months. This regulation is guided by documentation of several pediatric studies involving ethical behavior, project on risk management, choice formulation for children population, the drug development function of pharmacokinetics, and the product assessment in the population of neonates. It has been

observed that there is a clinical research harmony of rules across the jurisdictions of United States, Japan, and Europe, but provisions or regulations for children are not yet perfectly coordinated or even established across all mentioned global territories [12].

RESULTS AND DISCUSSION

Pharmacoeconomics is defined by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) as an area of discipline that examines the monetary behavior of drug services, products, and promotions for private and public utilization focusing on expenditures and results of clinical usage. In 1986, it was published in literature as Townsend's article emphasizing the importance of engineering its research agendas towards novel approach, and in 1992, a particular pharmaeconomics journal was introduced for healthcare legal system and its society.

Moreover, the increasing total health expenses gained attention to healthcare individuals to focus on cost-effective examination. Hence, the quality of healthcare goods and services must be in harmony with the constitutional rights of their citizens in advocacy of personal economic freedom promoting administrative health policies in mitigation of public welfare and safety. Thus, both disciplines must be constitutionally aligned in promoting efficiency as their principle must follow the pre-emptive doctrine of the U.S. Constitution comparable to other foreign trade laws related to its international rules and policies in commercial transactions.

There are restrictions that must be maintained in healthcare expenditures from various sources of equipment and materials allocating its infinite utilization. Thus, the obligatory provision of healthcare professionals is challenged to render optimized patient safety using cost-effective medicines to harmonize the registered norm of standard despite limited health-oriented resources. Hence, there is an increasing demand to advocate economic efficiency considering the importance of money for healthcare programs and interventions. Therefore, pharmacoeconomics serves as a crucial monetary principle in providing efficient and affordable treatment designed to resolve organizational goals in advocacy of administrative functions of the government.

As the complexity of business environment continues to grow and develop in expense of increasing demand of healthcare costs, private insurance companies are looking for economical evidence that is constitutional to corroborate decisions made in the contract purchase and inclusion of new medicines in the formularies. Hence, it is an obligation for drug manufacturers to weigh the medicinal value using cost-effective analysis. Meanwhile, government insurance companies, using public funds, serve as the third contracting parties paying the medical bills of their clients as patients with doctor's prescription indicating the

drugs necessary for their recovery. Thus, pharmacoeconomics is the identified measurement for qualitative and quantitative analyses in comparison with the outcomes of drug services and products from clinical trials of drug development to marketing its approved production advocating economic clause for constitutional compliance as doctrine of pre-emption [13].

Furthermore, in focus of political expression, participation on both Atlantic sides in the declaration of the Human Genome first draft fulfillment exhibits many opinions concerning the usage and information abuse that had been generated or could be made during the genome completion. With this common type of substantial innovations from engineering concepts, a lot of issues can be quickly resolved by through computational data systems aided with computer concepts. As a result, the outcome is merely a genomic sequence in representation of commands through quantitative and regulated details. Thus, the issues raised through the interest in computational biology, bioinformatics and systems biology are translated into a more beneficial information involving a more complicated task of data interpretation. Several wealthy nations have divided their budgets allocating some portions of it to novel insights of pharmacogenomics since massive developments in genomic designs must be pushed through along with its trade value in the market [14].

The biotechnology field that follows the combined concepts of bioinformatics and genomics through the pharmaceutical product development of pharmacogenomics is crucial for the study of genomic function. The computer-aided design (CAD) has shifted scientific developments from laboratory practices into digitization of data. Large collections of databases are evident to be advantageous in organizing genetic variations and ascertaining environmental determinants leading to identify which variants greatly contribute to sickness resulting to properly addressing of ethical and legal problems [15]. Hence, personalized medicine has a lifetime goal of treating various people in a population in a safe, effective, and economical means[16]. Furthermore, systems medicine is a term pertaining to research methodologies designed for improving interpretation of biotechnology principles through the application of genome architecture, artificial intelligence and pharmacogenomics. Hence, pharmacogenomics is used for tailoring medicines in order to design a concept of "one size does not fit all [17]."

Patent licenses are agreements in which a licensed firm usually shares or transfers the rights for use and later enhance a technology with another license firm in exchange of money. In this condition, the license holder commonly enjoys some versatility degree due to possibility of shelving the basic patent and expecting novel data without spending additional expenses. Shelving happens in the event that the license holder concludes to delay or stop the firm's investment in the marketing and development of licensed innovation. This may occur if the produced technology has lesser value or its market potential is highly unreliable [18].

The disclosure required in patent law is assigned to discuss information pertaining to a patented invention to permit proper invention usage and comprehension. There is an inherent incompatibility in patent law observed between genome technology and disclosure specification that impedes its full completion of desired goals. Its sources lie in the network of needed disclosure in which its presented result has a concealed presumption in patent law concerning the crucial concept of the intended components of the invention. In acknowledgement of this technological presumption, the issue is on its broader concept without restricting its generic sense [11].

Penile erection can be initiated to begin via the three (3) major stimulatory pathways, in which two (2) of its sexual excitement trigger cyclic guanosine monophosphate (cyclic-3', 5' GMP) formation and are known to be the primary and secondary cGMP pathways, while the third arousing stimulation influences cyclic adenosine monophosphate (cAMP) formation.

The parasympathetic nervous system triggers the acetylcholine (Ach) release innervating nonadrenergic–noncholinergic (NANC) sensational impulses in the primary cGMP pathway manifesting visual or tactile arousal stimulation. NANC nerve cells and vascular endothelial cells discharge nitric oxide (NO) leading to guanylate cyclase enzymatic activation which is responsible for conversion catalysis of guanosine 5'-triphosphate (GTP) to primary and secondary cGMP stimulatory pathways. Specific protein kinases are activated by cGMP triggering the opening of potassium channels known as phosphorylation and closing of calcium channels termed as hyperpolarization. Hence, there is an apparent drop in intracellular levels of calcium simultaneously with relation of smooth muscles resulting to penile erection as its arteries dilate and veins are compressed for more blood stream supply to corpus cavernosa.

Moreover, the cAMP formation is catalyzed by the adenylate cyclase enzyme for manifestation of third arousal pathway resulting to cavernosal relaxation of smooth muscle and penile erection. Thus, the adenylate cyclase is triggered based on the following routes: (1) autonomic nerves synthesizing vasoactive intestinal peptide, (2) smooth muscles distributing prostaglandins (PGE1 and PGE2) via relaxation effect and adrenergic tone reduction as noradrenaline release is inhibited and through cAMP-dependent protein kinase and hyperpolarization, and (3) circulating or neural catecholamines (epinephrine and norepinephrine). In erectile dysfunction (ED), the isoenzymes of PDE5 are apparent for cGMP degradation that impedes penile erection due to insufficiency to accumulate adequate supply of intracellular sensational components [19].

There are three (3) cardinal symptoms as specified by the European Male Aging Study frequently to be associated with low testosterone levels, namely, erectile dysfunction, sexual arousal reduction and penile erection loss.

Testosterone performs a crucial role of process coordination and facilitation restricted within smooth muscles and vascular endothelium cells. Hence, two (2) independent pathways are triggered by testosterone for arterial functions [20].

From the record of United States, it is widely known that the FDA had no official approval of off-label" uses although physicians can legally write it in their prescriptions, and drug firms could not dynamically advertise their products for such purposes claimed to be used as an "off-label [10]."

It is crucial to extrapolate its design since there are only a few PAH therapies being targeted and strictly applied and observed in children. Hence, the US FDA exhibits an "off-label" use as an indication of its non-approval for pediatric treatment [21].

CONCLUSIONS

Pharmacogenomics deals with issues on personalized medicine based from its patented design in support of clinical data sufficiency involving equation developments on kinetic control, computer-aided design (CAD), and body enzymes. As of the moment, the off-label use for pediatric treatment lacks not only with sufficiency of scientific documents for approval of its regulatory use but also with uncoordinated legal principles to official establish its safe usage for neonates across continents of Japan, Europe, and United States. Hence, medical peer-reviewed articles may be continuously done in order to address issues on pediatric safety of neonates for proper calling of all concerned authorities to legally establish an appropriate means of resolving these type of issues involving incongruity of passed legislations and administrative functions for official enforcement of its policies concerning safety and protection of neonates under an approved drug patent with a raised issue of an option for an alternative treatment, instead of an off-label use.

Pharmacoeconomics plays as the constitutional foundation of advocating public welfare and safety through cost-effective analysis of commercial transactions in promotion of monetary freedom. The practice of law is quite broad in nature since it would deal with various multi-disciplinary fields pertaining not only to several legal theories but also with various principles already established and being developed in domains of medicine and engineering. The application of legal scholarship is restricted to some law practices such as in court system and law firms since the compliance and adherence of its trained legal principles were all integrated from an academic institution that must be strictly followed to execute all that had been developed resulting to a strong tied up connection and excellent compliance of honed

cognitive domains. However, political science is another field being covered by law practice to formulate various legislations for maintenance of both private and public interests aimed to regulate gaps found in the community practice, and for establishment of proper regulations. Some legal medicine peer-reviewed articles are academic publications aimed to document public safety and some of its scholarly works are deemed to be secondary authority explaining the constitution, statutes, administrative regulations, and other primary authorities. Unfortunately, some academic publications, although officially declared, document regulatory practices that are still deemed to be unconstitutional due to non-approval of an administrative office. Drug patenting is a legal research process to officially declare a trademark (technical substitutes) from its complete specification gaining protection of intellectual property for legally marketing its product through its intended treatment although its mechanism of action is quite diverse that it may also be useful to some other therapeutic effects. If academic and practical principles must be strictly followed, hence, some off-label medicines must undergo the similar clinical trial process before it can be offered to public for proper compliance of safety due to well-established scientific facts and secured observation and protection that standard care of duty is properly followed beyond negligence. Gaining of intellectual property means is the most suitable method to address specific gaps of legal safety in which the academic advocacy of legal research process is properly complied. Therefore, direct and indirect taxation concerning the patented products handled by authorized professionals obligatory to comply with ethical issues of intellectual property in terms of handling services and health promotion practice must be properly coordinated and addressed for alignment of institutional goals of relevant and involved organizations advocating to enforce administrative functions as interpreted by the legislation and comparative parliamentary system for compliance of strict monetary goals of pharmacoeconomics based from clinical practice guidelines for perusal of legal authorities. It is suggested to render ways of strongly complying with taxation law relevant to handling of patented products for services and provided health programs as harmonized with registration criteria for patent approval of the intended drug design as a form of clear specification of its registered intellectual property for monetary profit on patent law.

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