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Off-Label Medicines Shepardizing Intellectual
Property Law towards Pharmacoeconomics: A
Discussion of Pfizer's Norvasc Patent Case**

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Abstract

Purpose: Pharmacoeconomics is a pharmacy discipline designed to tackle issues on clinical, ethical, and safety factors leading to advocacy of healthcare corporate governance in fulfillment of the pillars of sustainable development. Thus, it is necessary to discuss illegal diversions of Intellectual Property of drug patents as these legal problems serve as impediments to Pharmacoeconomics. This paper aims to elucidate the advantages of Off-label medicines in favor of clinical, ethical, and safety aspects of Pharmacoeconomics towards patient safety and treatment for welfare.

Methodologies: Quantitative measurement is crucial for validation of drug quality products. It is used for comparison of both legal and illegal diversions of healthcare corporate governance. Patent Law and its policy options are tools to measure the violations of the perpetrator under Intellectual Property Law. Meanwhile, the British National Formulary follows the Human Medicines of 2012 and communicate with FDA for the implementation of off-label medicines as policy for clinical practice under legal removal of patent protection for medical research and practice. This study follows a diagnostic design as a research method based on ethical, regulatory, and legal presentations to characterize problems involved in drug management system towards efficiency of evidence-based medicine practice utilizing theories, models, and frameworks towards financial intelligence.

Findings: The elucidation of Kano Model Framework exhibits the aberration and compliance of

patent drugs towards compliance of healthcare corporate governance. Based on exhibition of intellectual property law, it can be extended to fulfill the goals of sustainable development of monetary success and hence, the human society can be reflected as their success to their financial intelligence as their inventorship is declared as non-obviousness to public welfare and safety. Moreover, the moral standard of ethical decision-making illustrated the importance of opting to off-label medicines emphasizing cost-efficiency goals of Pharmacoeconomics in drug therapy. Hence, the Shariah Jurisprudence Method for Pharmacoeconomics is the modelling of Clinical Pharmacy Practice towards Healthcare Corporate Governance in fulfillment of business ethics as public welfare and safety of human society.

Recommendation: Kano Model Framework is an integrated tool of measuring the success of healthcare corporate governance. With the elucidation aids of modelling the importance of Pharmacoeconomics, it is recommended to develop ways of making artificial intelligence as a sole success, profit, benefit, and contribution to clinical pharmacy practice, starting from its drug development up to its intended purpose of human drug treatment in healthcare setting, in relation to its accompanied FDA regulating bodies, as British National Formulary team compliance of maintaining the crucial functions of observing and monitoring document for patient safety.

Keywords: *Pharmacoeconomics, Patent Drug, Off-label Medicines, Clinical Pharmacy, Healthcare Corporate Governance*

1.0 INTRODUCTION

Artificial Intelligence (AI) is becoming prominent as a transformative power across several industries, changing completely the practice of pharmacy towards clinical setting encompassing patient counseling, medication management, and medication safety. In this emerging analysis of integration, AI embraces great potential to make better patient outcomes, improve efficiency, and propel innovation. Since AI holds the ability to assess enormous amounts of data, detect patterns, and create intelligent authorless predictions, AI has the capacity to deal with the most crucial challenges in healthcare and reshape to Pharmacoconomics. By adopting patient-specific data, such as genetic profiles, medical history, and drug interactions, AI machine learning can create recommended pharmacogenomics as personalized medicines. AI technologies can significantly contribute to clinical pharmacy settings, leveraging advanced machine learning powered systems and scientific procedures by providing enormous amounts of patient information and giving tailored medication regimens.¹

Off-label practice is a clinical concept created towards advantages on patient's safety and liability perspectives. It was first acknowledged in the European Directive 2010/84/EU, which deals with the marketing authorization holders' (MAHs) responsibility to continuously observe, check, and report the drug product and render all the available information, including inter-related aspects outside the scope of marketing authorization. The European Committee (EC) or other governmental agencies have attempted to render a comprehensive off-label use summary from a legal and regulatory practice. In clinical setting, the most crucial aspect concerning the off-label practice is the fulfillment of the unmet healthcare needs by traditional therapeutic methods, augmenting the access to special categories of medication for patient safety. The EC report had revealed agreement on off-label practice discussing the literature on its widespread usage in rare diseases, oncology, pediatrics, and psychiatry. It is complex to establish a general off-label prescribing pattern since it encompasses several methods, and it is divided into various categories, such as, dosage regimen modification, different indication, pharmaceutical form, administration route, different age group, and different patient categories.²

For more than 4 decades, therapeutic orphans were established to emphasize the fact that children were not usually included in clinical trials for new drug development. There were cases, such as, thalidomide tragedy resulting to congenital malformations, kernicterus development with the use of sulfonamides in neonates, chloramphenicol drug problem leading to gray baby syndrome, and, recently, cisapride gastroesophageal reflux treatment with occurrence of cardiac arrhythmia that brought attention to modify the standards needed to control the experimentation and trade of new drugs for advocacy of safety, quality, and effectiveness. According to research regulations for novel drugs, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have supported developmental studies in population of individuals with less than 18 years of age to promote the improvement in drug safety via the establishment of sufficient formulations and pharmacokinetic assays.³ The administration of off-label medicines is not similar with unlicensed drug use. The safety usage of these medicines is validated by FDA regulating body, hence, their efficiency has been confirmed only with approval from physicians.

¹Muhammad Ahmer Raza and Shireen Aziz, 'Transformative potential of Artificial Intelligence in pharmacy practice' (2023) 31 *Saudi Pharmaceutical Journal* 1.

²Carmen-Maria Ruzs, Bianca Eugenia Osz, George Jitka, Amalia Miklos, Madalina-Georgina Batrinu, and Silvia Imre, 'Off-Label Medication: From a Simple Concept to Complex Practical Aspects, (2021) 18 *International Journal of Environmental Research and Public Health* 1-4.

³L. Dos Santos and I. Heineck, 'Drug utilization study in pediatric prescriptions of a university hospital in southern brazil: off-label, unlicensed and high-alert medications' (2012) 36(4) *Farmacia Hospitalaria* 181.

Thus, physicians may opt to prescribe off-label drugs if they find it useful and suitable for their patients.⁴ Until 2003, only 20-30% of drugs were approved for pediatric use in the United States, and only 35% of all marketed drugs are approximated to be licensed for children usage. The high prevalence of prescriptions with unlicensed for pediatric use (11%) and approved off-label drugs (30-50%) in hospitalized children has been discussed in many studies and is recognized to be a common practice in hospitals. For summary, 16-62% of drugs are approximated to be off-label or unlicensed in pediatric units. Similarly, the off-label and/or unlicensed drug medications to children outside the hospital institution is high, with an estimation of 11-37% prevalence rate.⁵

It is recognized that medication administration has a goal of achieving beneficial effect to clients, otherwise, pharmacological explosion may take place resulting to fatality and permanent abnormalities. When a drug is opened to the market, all the knowledge is referred on their pre-marketing studies known as evidence-based medicine with corresponding hierarchy. Thus, it is strongly discouraged to use off-label medicines with known severe adverse effects.⁶ This paper aims to characterize the measurement of financial intelligence using off-label medicines in clinical pharmacy practice of drug management system for modeling of assessments and evaluations towards the success of Pharmacoeconomics under the clinical, ethical, and safety determinants for compliance of healthcare corporate governance under diagnostic design of research method.

2.0 METHODOLOGY

Quantitative Legal Research

Ten tablets of Amlodipine besylate were purchased. Total weight was quantified, and the average weight was calculated. It was grinded and powdered using mortar and pestle. The contents were transferred into a vortex tube and extracted by adding sufficient volume of chloroform. Extraction was done by shaking the tube using a vortex mixer for 5 minutes. The content was filtered and evaporated to dryness. Dry residue was dissolved with 10 ml glacial acetic acid and diluted with distilled water and made up to mark using a 50 ml volumetric flask. Assay of commercial product was done and analyzed using UV-visible spectroscopy set at 500 nm.⁷

Patent Law and Policy Options

The 1970 Patents Act was revised in 2005 requiring that inventions must be “new” inventive step that cannot be predicted involving industrial utilization. Hence, it should demonstrate technical advancements in comparison with current knowledge that would highly result to economic significance. Moreover, the invention must exhibit a feature known as non-obviousness creating commonness to all people to be skilled in the art.

According to section 3(d) of the Act, the following are not considered invention:

(d) The known substance discovery is not a mere new form, thus, not original, resulting to non-improvement in enhancing the known substance efficacy, including already known property substance,

⁴ Seyyed-Reza Sadat-Ebrahimi, Neda Parnianfard, Nafiseh Vahed, Hossein Babaei, Morteza Ghojzadeh, Sydney Tang, and Amir Azarpazhooh, ‘An evidence-based systematic review of the off-label uses of lisinopril, (2018) 84 *British Journal of Clinical Pharmacology* 2503.

⁵ L. Dos Santos and I. Heineck, ‘Drug utilization study in pediatric prescriptions of a university hospital in southern brazil: off-label, unlicensed and high-alert medications’ (2012) 36(4) *Farmacia Hospitalaria* 181.

⁶ Marisa Lima Carvalho, ‘Challenges on off label medicine use’ (2016) 34(1) *Revista Paulista de Pediatria* 1.

⁷ Zharama M. Llarena, ‘Legal Issues of Cardiovasc as Quality Drug Patented Product Based on Pharmaceutical Formulations Using Spectrophotometric Validation for Healthcare Corporate Governance’ (2023) 5(2) *American Journal of Law* 15.

not to be of new use, and already existing process, apparatus or machine, unless the product cannot be anticipated resulting to a “new” creation with application of at least one reactant as “new” for the non-foreseeable process.

Table 1: UK Intellectual Property Options under Action Principles

Computer-Generated Works	
Option 0	Make no legal modification on Artificial Intelligence
Option 1	Protection is removed for computer-assisted works
Option 2	The current protection is replaced with a new right of reduced scope or duration

Based on the study of Kretschmer, Meletti, and Porongaba, pertaining to s 9(3) of the 1988 Copyright, Designs, and Patents Act (CDPA), UK has no corresponding laws comparable to majority of other jurisdictions, hence, this UK law is deemed as unique due to its complexity. As a result, after Brexit, issues concerning this legal provision may seek other particulars of copyright law for effective operation of its corresponding law. Thus, there is an imposed question being developed for legal complexity as to what originality standard must be applied to these issues. Hence, computer-generated outputs must be regarded as authorless works aligned with the criteria for originality involved in literary, dramatic, musical, or artistic (LDMA) creations as matters to be answered restrictedly in UK law.

The standards needed as evidence are high in specifications during this era of rapid industrial change and technological advancements. Thus, the burden of proof points to fundamentally advocate new rights required and the estimated production prices, the people who will avail their invention as consumption. Hence, Option 1 has an invention provision that requires copyright creation to maintain a standard without devotion to a particular creation or work. Otherwise, UK government shall remove their computer-generated AI protection based on s 9(3) for the emergence of substantial evidence in their AI businesses. Furthermore, the UK IPO policy provides Option 2 concerning additional IP rights regarding cumulation issues on reduced duration and scope in processing time that would basically categorize into two types, resulting to expensive prices and loss of invention as reviewed by Gower (2006) and Hargreaves (2011).

Table 2: UK Intellectual Property Options in Research and Databases

Text and Data Mining (TDM)	
Option 0	Make no legal change on TDM
Option 1	Licensing environment is improved for TDM design, intent, and purpose
Option 2	The existing TDM exception to encompass commercial research and databases is extended
Option 3	TDM exception for any use is adopted with a rights holder to participate
Option 4	TDM exception for any use is applied which does not authorize rights holder to participate

In UK law of Intellectual Property, extraction of evident materials from already existing copyright-protected creation is not accepted for acquisition of TDM as IP in this pertinent act (Option 2). Hence, in this IP acquisition, industrial firms should present more robust evidence in empirical research, not just only for the requirement of authorless computer-generated works, but also to exhibit more related research on database, otherwise repealed. Moreover, the offered Option 1 should render a lawful access to public interests for legitimacy of its creative environment to be socially immersed as an invention as non-obviousness.

Table 3: UK Intellectual Property Options in Patent Inventorship

Patent Inventorship	
Option 0	Make no legal change in Patent Inventorship
Option 1	Inventorship is expanded for the inclusion of human responsibility to an AI system which invents patentability
Option 2	Patent applications are allowed to recognize AI as inventor
Option 3	AI-devised inventions are protected through a new type of secured patentability

In patent inventorship, Option 0 is very substantial in advocating Intellectual Property without any raised issues in their creation. Hence, Artificial Intelligence, as copyright-generated works, has maintained its high quality of research originating from authorless invention in lack of any dedicated working output of human assistance. Moreover, any needed requirements which deemed by the government to be vital in advocating substantive law, may reform the policy in alignment with the international level in accordance with their own interpretation of constitutional law. Furthermore, the European Patent Office (EPO) clearly stated that only a human being can be an inventor and computer-generated works cannot transfer any rights to a person (Thaler v Comptroller General of Patents).⁸

British National Formulary

Human Medicines Regulations 2012 (Statutory Information)

The British National Formulary (BNF) routinely processes relevant information from various Government bodies including Statutory Instruments and regulations affecting the Prescriptions, specifically, only Medicines Order. Official compendia such as the British Pharmacopoeia and its addenda are processed routinely to assure that the BNF complies with the relevant sections of the Human Medicines Regulations 2012. The BNF maintains close communication with the Home Office, concerning controlled drug regulations, and the Medicines and Healthcare products Regulatory Agency, including the British Pharmacopoeia Commission. Safety warnings issued by the Commission on Human Medicines (CHM) and guidelines on drug are issued by the UK health departments are dealt as a matter of routine. Important professional documents issued by the Royal Pharmaceutical Society are stated in the BNF as policy guidelines from bodies such as the Royal College of General Practitioners.⁹

⁸ Zharama M. Llarena, ‘Shepard’s Validation of Antitrust Relief Framework on Patent Infringement of Novartis’ Cancer Drug Using Genomic Architectures of Legal Literature Based on UK Intellectual Property Law’ (2023) 5(2) *American Journal of Law* 4-7.

⁹ BMJ Group and the Royal Pharmaceutical Society, *British National Formulary* 78, (September 2019 – March 2020), ‘Statutory information’ [ix].

Medical and Pharmaceutical Literature

Clinical writers monitor core pharmaceutical and medical journals. Research papers and reviews associated to drug treatment are carefully processed. When there is discrepancy between the advice in the BNF and the paper is documented, the new information is evaluated for reliability, and importance to UK clinical practice. If it is found to be essential, new text is drafted and discussed with the Joint Formulary Committee with expert advisers. The BNF performs a close working communication with several national information providers.¹⁰

Discussion

According to Llarena, Amlodipine besylate is comparable to the reference standard in performing the designed therapeutic effect based on the intended mechanism of action specified on its product label for performing treatment actions as part of contract law in commercial transactions. Based on reference standard, Figure 1 shows the bioavailability performance of the drug relative to its effective therapeutic action based on package insert for detailed specifications as part of its obligation of consumer awareness for market availability to the public advocating patient safety.¹¹

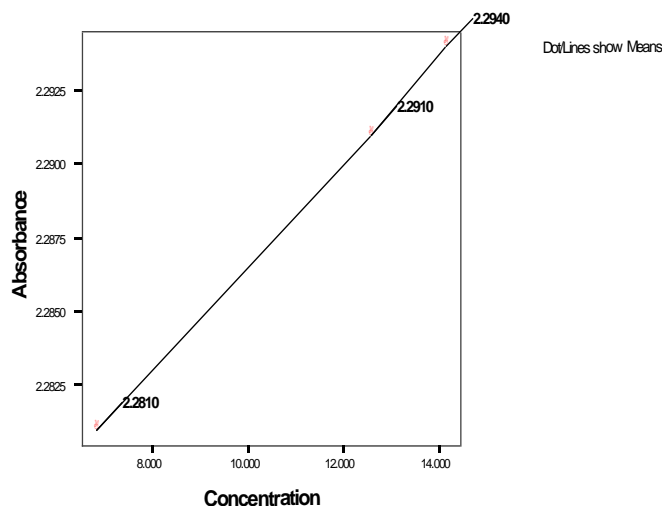


Figure 1: UV-Vis Analysis of Amlodipine Besylate at 500nm

The Pfizer's Norvasc Patent Case

The US Court of Appeals for the Federal Circuit has reversed the judicial opinion of Pfizer's patent infringement lawsuit against Dr Reddy's Laboratories' generic version of Amlodipine besylate with salt modification based on the decision of New Jersey District Court, with split decision (2/3) from Federal Circuit judges, as Dr Reddy's modified its salt as novel approach to make the expiring patent of Norvasc a generic drug application.

Pfizer's Amlodipine besylate (US Patent 4,572,909) expired its original patent in 2003, although extension was permitted until 2007 to compensate the lengthy US FDA review process. The legal issue being raised in the court was whether the patent extension was restricted to Pfizer's Norvasc as product marketability,

¹⁰BMJ Group and the Royal Pharmaceutical Society, *British National Formulary* 78, (September 2019 – March 2020), 'Literature' [viii].

¹¹Zharama M. Llarena, 'Legal Issues of Cardiovasc as Quality Drug Patented Product Based on Pharmaceutical Formulations Using Spectrophotometric Validation for Healthcare Corporate Governance' (2023) 5(2) *American Journal of Law* 20-21.

or the chemical alterations of their patented product, Norvasc, under the International Non-Proprietary Name, Amlodipine besylate, can claim Intellectual Property violations as Dr Reddy's Laboratories argues that their drug product, Amlodipine maleate, was allowed for market operations as novel approach to generic drug. Similarly, Pfizer's Norvasc is secured with original patent protection encompassing their commercial agreements from chemical structure to other modification of its sister compounds or relative salts in performing same actions under their marketability rights.¹²

The US Court of Appeals for the Federal Circuit went for a two-year legal battle as Dr Reddy's Laboratories' drug product, Amvaz, the generic version of Amlodipine maleate after chemical alteration based on the expiring patent of Norvasc designed for commercial agreements, dissents that the patent extension of Norvasc is limited to FDA review process to Amlodipine besylate alone and that other salt modifications shall not be included and covered by their extended patent protection.

The US Court of Appeals overturned the lower court's ruling based on the split decision of the Federal Circuit judges affirming that Norvasc had extended their patent protection to cover Amvaz' marketability rights from Dr Reddy's. The judicial decision represents close to a \$200 million loss opportunity for Dr Reddy's market of commercial agreements. Pfizer's Norvasc led the global drug sales for the treatment of hypertension and angina with more than \$2 billion in 2003. Several news reports pointed out that Dr Reddy's Laboratories spent more than \$10 million of legal costs in defense of their drug product, AmVaz.¹³

Shepardizing Pharmacoeconomics

The Kano Model Framework is adopted to illustrate the UK Intellectual Property in various policy options, integrating computer-generated works, text and data mining, and patent inventorship, towards pharmacoeconomics. Figure 2 categorized UK Intellectual Property requirements into five types of options for exhibition of Drug Patent Law:¹⁴

1. Must be quality attributes: Removal of patent application (Option 1)
2. One-dimensional quality attributes: Patent extension with protection (Option 2)
3. Attractive quality attributes: The participation of banking institution and its allies for climate change protection (Option 3)
4. Indifferent quality attributes: The non-participation of the human society in fulfilling the goals of business ethics (Option 4)
5. Reverse quality attributes: Changes in Artificial Intelligence (Option 0)

In comparison with the Pfizer's patent lawsuit of Norvasc against Dr Reddy's Laboratories, the Patent Law in drugs is illustrated in Option 2 of Kano Model Framework (see Figure 2). Dr Reddy's Laboratories altered the salt of Norvasc to Amlododipine maleate, making their application to a novel approach of generic medicine to be filed under extended patent claims of Norvasc. The must-be quality attributes of Option 1 was violated by Dr Reddy's Laboratories, hence, the US Court of Appeals favored the patent

¹²PatentWatch, 'Court reversal in favour of Pfizer', (April 2004) News and Analysis 3.

¹³Business Standard, 'US Court smashes Dr Reddy's \$200m amlodipine dream' (Media Release, 6 February 2013).

¹⁴Zharama M. Llarena, 'Shepard's Validation of Antitrust Relief Framework on Patent Infringement of Novartis' Cancer Drug Using Genomic Architectures of Legal Literature Based on UK Intellectual Property Law' (2023) 5(2) *American Journal of Law* 61.

lawsuit of Pfizer, hence, Dr Reddy's Laboratories lose their claim of AmVaz' commercial drug performance through salt modification of Norvasc.¹⁵

According to the study of Llarena in Figure 1, Kano Model Assessment is the illustration of Healthcare Corporate Governance. The obligations and duties of banking institutions and its allies are extended to promote sustainable development of business ethics in advocacy to fight climate change (see Option 3). The human society must enjoy their constitutional rights of public welfare and safety as intellectual property designs are invented for their consumption and utilization under the Trade Law of making their high quality products to be in appropriate shape as immersion to public daily usage of patent inventorship as non-obviousness (see Option 4).¹⁶

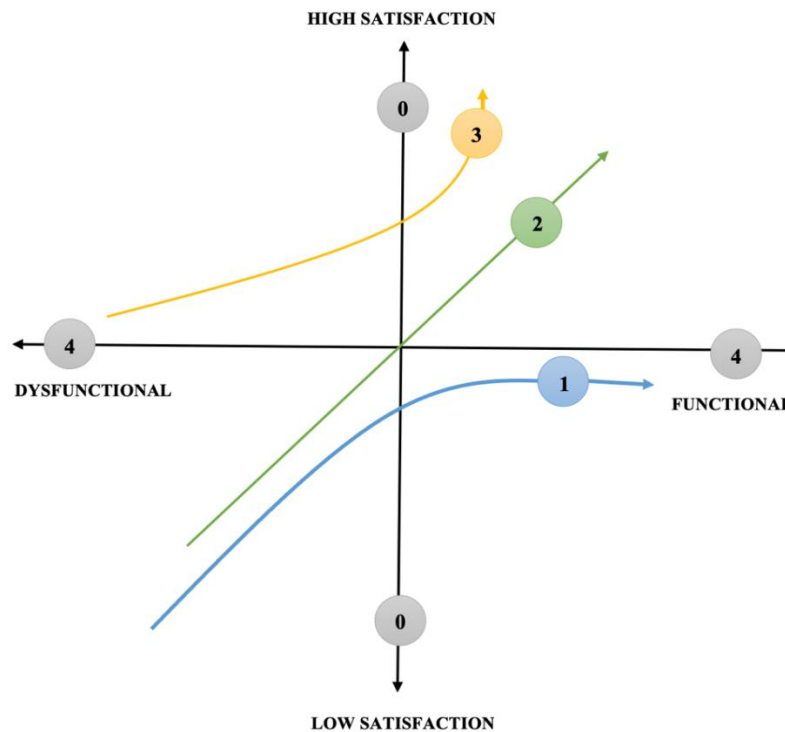


Figure 2: UK Intellectual Property Law using Kano Model Framework

The Off-label medicines are being permitted by Food and Drug Administration (FDA) to allow the removal of patent products under medical research and practice as British National Formulary routinely processes the documentation of any unwanted effects of off-label drugs, while keeping noted through record-keeping any found relevant medical and pharmaceutical publication, and hence, maintaining the integrity of clinical practice of pharmacy.

The Off-label medicines are expected to promote pharmacoeconomics in Clinical Practice towards ethical decision-making in advocacy of public welfare and safety (see Figure 3). Public safety is granted if off-label medicines are excuted under Statutory information of Human Medicines Regulations of 2012 and

¹⁵Zharama M. Llarena, 'Legal Issues of Cardiovasc as Quality Drug Patented Product Based on Pharmaceutical Formulations Using Spectrophotometric Validation for Healthcare Corporate Governance' (2023) 5(2) *American Journal of Law* 10-31.

¹⁶Zharama M. Llarena, 'The Kano Model Assessment Framework for Soil Environmental Quality under Good Governance Doctrine of Bank Independence and Accountability for Code of Conduct towards Corporate Ethics' (2023) 8(2) *Journal of Strategic Management* 56-63.

implemented under FDA as their regulatory body in policies exercising the removal of certain patent drug products under medical research and practice. Kano Model Framework is a reflexive judgement for conscious rationalization of the environment as part of business ethics of corporate governance. Hence, if the Intellectual Property shown in Figure 2 is extended to promote and exercise sustainable development and fight climate change, method validation of drug analysis is the basis of active judgement to detect traces of environmental pollutants as problems in pharmacoeconomics. Therefore, off-label medicines are the legal version of exercising medical research and practice under removal of patent protection, hence, this type of healthcare corporate governance promotes pharmacoeconomics in their practice as advocates of public welfare and safety, emphasizing cost-efficiency in off-label medicines.¹⁷

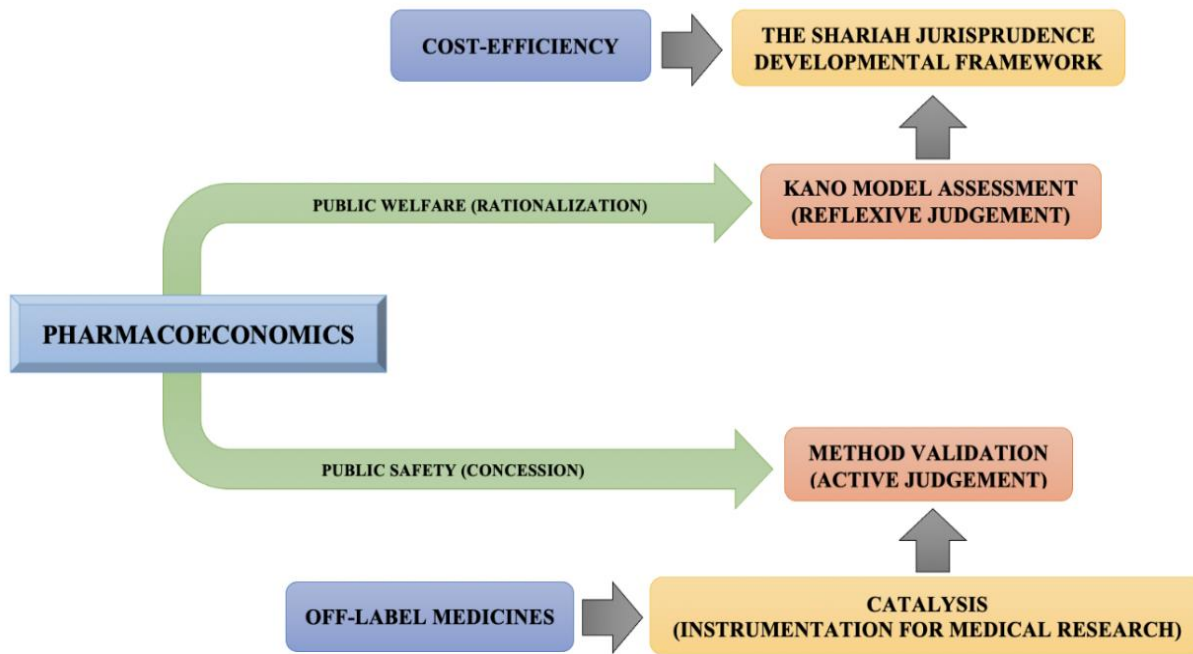


Figure 3: The Moral Norm: Pharmacoeconomics for Ethical Decision-Making

The legal system of pharmacoeconomics, shown in Figure 4, must exhibit the difference between illegal diversion of pharmacoeconomics and promote the constitutional rights of the human society of patient safety and their respective welfare. The Clinical Conceptual Framework, based on Shariah Jurisprudence Method, is the compliance aspect of pharmacoeconomics designed to exercise the duties and obligations of clinical pharmacy practice of drug treatment as recovery or remediation from unexpected harms and damages caused by other individuals or by nature itself.¹⁸

¹⁷Zharama M. Llarena, 'Engineering Game Theory of Green Hydrogen towards Energy Transition using Shariah Jurisprudence Developmental Framework based on Ethical Decision-making from Philosophy of Technology' (2023) 7(1) *European Journal of Technology* 49.

¹⁸Zharama M. Llarena, 'Engineering Game Theory of Green Hydrogen towards Energy Transition using Shariah Jurisprudence Developmental Framework based on Ethical Decision-making from Philosophy of Technology' (2023) 7(1) *European Journal of Technology* 50.

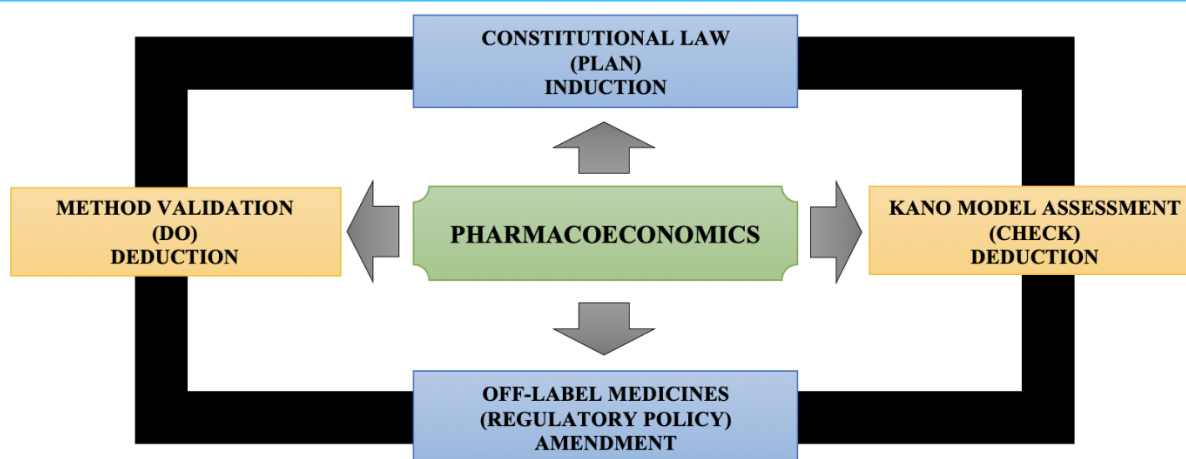


Figure 4: The Legal System: Clinical Conceptual Framework

3.0 CONCLUSION AND RECOMMENDATIONS

Off-label medicines are emphasized as an option for patent removal as cost-efficiency promotion of Pharmacoeconomics advocating patient safety under medical research and practice. Pharmacoeconomics is the advocacy of healthcare corporate governance to fulfill the pillars of sustainable development for patient safety. Kano Model Framework is an integrated tool of emphasizing Pharmacoeconomics in clinical pharmacy. The Patent case of Pfizer's Norvasc is limited to illegal diversions of clinical pharmacy. Hence, upon compliance, all options of off-label medicines in clinical practice can be extended towards the fulfillment of business ethics, reflecting the constitutional rights of the human society in fighting climate change, hence, "shepardizing" Pharmacoeconomics.

This study recommends that Artificial Intelligence used in drug development may be extended to clinical pharmacy practice, while FDA regulating bodies implement the British National Formulary, as the patent removal of off-label medicines is restricted to medical research and practice, hence, computer-generated works must exhibit its patent protection up to clinical pharmacy setting, since the patent inventorship of drugs must also be reflected as patent drugs of authorless inventions based on Intellectual Property Law and its policy options.

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