The Legality Aspects of Off Label Prescription in Malaysia: Challenges Related to Off Label Prescription

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Abstract:- ***Off label prescription occurs when a drug is prescribed for an indication, a route of administration, or a patient group that I snot included in the approved product in relation to the Federal Drug Administration (FDA). Off label prescription has been a major challenge for patients as most of time they are not aware of the indication they are prescribed for. For instance, the drug Methotrexate to treat cancer is being prescribed as off label to treat psoriasis. The adverse drug reactions incurring from a cancer drug can cause severe reactions, in which the burden being passed to a patient suffering from auto immune disease and skin disorder such as psoriasis.***

The legality aspects are certainly importance to enhance the role of the doctors which prescribing the off label prescription to the patients. The lack of awareness by the practitioners while practicing off label prescription for the sake of insufficient medication or lack of medication for certain diseases does not give a room to practice off label prescription. The purpose of this paper is to further define and discuss the status of off-label use of medications in children as the medication of children is lacking compared to adults. The legality of off label prescription has not been addressed and mainly left at the discretion of medical practitioners to apply off label prescription. The legality aspect of off label prescription can be addressed with improvise interpretations under Section 14(4) (d) of the Patents Act 1983.

Keywords: Off Label Prescription, Second Medical Use, Patentability, Health, Elderly, Children

I. INTRODUCTION

Off-label prescription is defined as drugs prescribed and used outside their licensed indications with respect to dosage, age, indication or route. In general, off-label prescription rates ranged from 10.5 to 80% and higher rates were found in younger vs older paediatric patients. The reasons for prescribing off-label medicines established were lack of paediatric dosage information, lack of appropriate paediatric formulations, hospital consultation advice, and lack of clinical trials data. (S. Balan, M.A Hassali & V.S.L Mak, 2015).

The researchers aim to address the implications which incur from the use of off-label prescriptions by physicians.

Research methodology which is adopted is a qualitative method which consists of library research and in-depth interviews with physicians, specialists, surgeons, pharmacists, chemists, relevant government authorities from NPCB and MOH, Malaysia. The thematic and coding analysis with carefully selected themes and coding will be generated through the NVivo software.

The significance of the output of the research is to address issue of the discretion and freedom given to medical practitioners prescribing off-label medicines. Off label prescription which been prescribed for children and elderly and life threatening conditions still at alarming rate and must be addressed wisely.

Furthermore, the impact of this research as follows; The most common off-label respiratory drugs prescribed to children at the outpatient setting in a Malaysian hospital are antiasthmatics, followed by cough and cold medications. (Nurul Fadilah M Adliah Mhd Ali and Noraida M. Shah, 2015). The researcher intends to critically analyse the legality and ethical aspect of improper use of the off-label prescriptions by the medical practitioners in Malaysia as medical practitioners are the frontline experts. There is an urgent need for well-designed research to be carried out on commonly prescribed off-label respiratory drugs, to ensure their safety and efficacy in children.

The term “off-label” use refers to the use of a drug that is not included in the package insert (approved labelling) for that drug. The application of drugs in accordance with the marketing authorization issued by the regulatory authority is considered on-label use, while off-label drug use frequently occurs in medical practice. Physicians, however, are free to prescribe drugs for any uses they believe are appropriate. There are a number of ways in which the use of a prescription drug can diverge from the FDA approved uses described on its labelling. For example, physicians may prescribe a drug to treat conditions other than those for which the drug was originally intended. Physicians may also prescribe a drug for patient groups other than those for whom the drug was originally approved, as when children are pre scribed a drug approved for use on adults only. Finally, physicians may vary the dosage or method of administering a drug, as when a drug approved for injection into muscles only is injected into a vein. (Kaspar J. Stoffelmayrt, 1996).

Medical specialists frequently prescribe an off-label drug in paediatrics, neonatology, geriatrics, psychiatry, and oncology. Off-label medication use accounts for an estimated 50% of medication prescribing. According to the Food and Drug Administration (FDA), good medical practice and the best interests of the patient require that

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physicians use legally available drugs, biologics, and devices according to their best knowledge and judgment.1 If physicians use a product for an indication, not in the approved labelling, they have the responsibility to be well informed about the product and to base its use on firm scientific rationale and sound medical evidence. (Xiulu Ruan, and Alan David Kaye, 2016). Physicians sometimes prescribe drugs without adequate knowledge of label requirements, such as approved indications, dosages, routes of administration, or patient age and this is the drawbacks of having off-label prescription. (Final Report, 'Review of Laws, Regulations, and Uses of Off-label Drugs in Indonesia, June 2017, Access and Delivery Partnership, New Health Technologies for TB, Malaria and NTDs).

The purpose of drug licensing is to ensure that medicines are examined for safety, efficacy, and quality. For a drug to be used, it must have a product license. In the UK, a Marketing Authorisation (MA) is issued by the European Medicines Agency (EMA) or the Medicines Health and Regulatory Agency (MHRA). Without a MA, the medicines are not licensed. On the other hand, the use of licensed medicines outside the terms of their MA is referred to as the off-label use of medicines. In Malaysia, under the Control of Drugs and Cosmetics Regulations (CDCR) 1984, R7 (1) (a), no person shall manufacture, sell, supply, import, possess, or administer any product unless the product is a registered product. The Drug Control Authority (DCA) was established under the CDCR 1984, to ensure the safety, quality, and efficacy of pharmaceuticals, health, and personal care products that are marketed in Malaysia. This is achieved through the registration of pharmaceutical products and cosmetics; licensing of premises for the importer, manufacturer, and wholesaler; monitoring the quality of registered products in the market; and monitoring adverse drug reactions.

Pharmaceutical companies then need to register their pharmaceutical products with the DCA, together with the submission of the preclinical and clinical trial results, information on the dose, dosage form, indication, route of administration, and target group for which the drug is intended. Most medicines administered to adults have a product license that outlines the particular indication, dose, and route of administration for a drug. However, most of the drugs used to treat children in hospitals are either not licensed for use in children or are used off-label. Therefore, the risks or benefits of using these drugs in children have not been examined by the licensing authority. The main reason for the common use of unlicensed and off-label drugs in children is that children are excluded from clinical trials during the drug development process. Physicians face a dilemma when prescribing medicines for use in children due to the lack of detailed information available. Consequently, children may receive drugs in unapproved dosages that lack efficacy or have safety issues. The prescription of off-label medicines covers a wide range of scope as follows; a medicine was classified as an off-label prescription for any of the following reasons: (i) contraindicated in children of all age ranges, (ii) off-label use by indication, (iii) off-label use by age, (iv) off-label use by route of administration, (v) lower than the licensed dose, (vi) higher than the licensed dose, (vii) lower than the licensed frequency, and (viii) higher than the licensed frequency. (Nurul Fadilah Mohamad, Adliah Mhd Ali and Noraida Mohamed Shah, 2015). Therefore, challenges still remained unsolved as lack of clinical trials data for children and medical practitioner's role need to be enhanced and monitored carefully when prescribing off label medicines to children.

The main issue related to the implications from off-label prescription is the adverse drug reactions. Adverse drug reactions are on ongoing issue which must be take into account by medical practitioners while prescribing off-label medicines. An Adverse Drug Reaction (ADR) is any unexpected, unintended, undesired, or excessive response to a drug that requires following actions as follows; i) discontinuing the drug (therapeutic or diagnostic), requires changing the drug therapy ii) modifying the dose (except for minor dosage adjustments) iii) necessitates supportive treatment iv) significantly complicates diagnosis v) negatively affects prognosis or vi) results in temporary or permanent harm, disability or death. It is the pharmacist's responsibility to monitor and report any suspected adverse drug reactions (ADR). 'Guidelines for In Patient Pharmacy Practice' ,2010 Pharmaceutical Services Division, Ministry of Health, Malaysia.) A significant example of a drug named Thalidomide was first synthesized in Germany in 1954, by Wilhelm Kunz, as an antihistamine, and in 1956 was introduced as a sedative by the German company Chemie Grunenthal. Thalidomide was available over the counter and physicians prescribed as off-label to pregnant women to combat morning sickness. Serious safety problems with the drug specifically the possibility of peripheral neuritis, a form of neurotoxicity and more than 10,000 babies worldwide were born with serious birth defects due to exposure to thalidomide. The thalidomide disaster generated momentum for drug regulation among the general public, turning the FDA from a modest agency into one of the world's strongest and strictest regulatory, which required that drug manufacturers had to prove not only the safety but also the efficacy of the drug. (Stefan Timmermans and Valerie Leit, 2000). Another notable example is the drug named Yasmin, which is primarily used to prevent pregnancy. This prescription birth control pill works in several ways -- it stops ovulation, alters the cervical mucus, and changes the lining of the uterus. On occasion, a healthcare provider may prescribe the Yasmin drug in an off-label fashion to treat various conditions such as acne and premenstrual dysphoric disorder. Another significant example is a drug named Lorazepam, which is used to treat anxiety disorder and anxiety associated with depressive symptoms. Lorazepam also used as off-label prescription in insomnia, muscle spasm, alcohol withdrawal psychosis, headache, panic disorder, acute mania (adjunctive), acute psychosis (adjunctive), delirium (with haloperidol) and catatonia, which can lead to severe and life-threatening side effects such as respiratory depression, renal dysfunction and blood dyscrasias. (Stephen M. Stahl, 2017).

Importantly, the reasons for and implications of off-label prescribing, including the potential clinical benefits/risks

and medico-legal implications, are often poorly understood by both patients and prescribers. An important unintended consequence of the uncertainties and confusion surrounding the status of off-label prescribing for children and adolescents may be that effective drug treatments are being withheld or underused. The off-label use of medicines for children and adolescents remains a common and important issue for prescribing practice across child and adolescent psychiatry, paediatrics and primary care. Very few psychotropic medications are developed for and tested first in a paediatric population, an example being ADHD medications where adult testing and marketing authorisation came later. Until relatively recently, there were no statutory requirements for drugs to be tested in younger age groups, and although companies were encouraged to undertake studies in children and adolescents, few did. This meant that for most drugs, data relating to safety and effectiveness in adolescents were extremely limited, not only at the point of entry into the market but continuing throughout the life of the drug. (Aditya N Sharma1, Celso Arango, David Coghill, Paul Gringras, David J Nutt, Peter Pratt, Allan H Young and Chris Hollis, 2016).

According to the Food and Drug Administration (FDA), good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labelling, they have the responsibility to be well informed about the product, and to base its use on firm scientific rationale and sound medical evidence. (Xiulu Ruan, and Alan David Kaye, 2016). Thus it is important for medical practitioners to use off-label prescription taking into account the efficacy and safety of the drug. In the view of the research, off label prescription shouldn't be prescribed in a situation the severe adverse drug reactions are suspected by the practitioners even though the drug has high efficacy in treating the off-label indication.

A. Legality Aspect of Off-Label Prescription

The legality aspects of off-label prescriptions can be argued with relations to the Patents Act 1983. The question is whether patentability of second medical uses impliedly encourages prescriptions of off-label medications. This can be impliedly seen in the section 14(4) of the Patents Act 1983 which read as follows; "The provisions of subsection (2) shall not exclude the patentability of any substance or composition, comprised in the prior art, for use in a method referred to in paragraph (d) of subsection (1) of section 13, if its use in any such method is not comprised in the prior art. Section 13 (1) (d) excludes non-patentable invention on "methods for the treatment of human or animal body by surgery or therapy, and diagnostic methods practiced on the human or animal body." Section 14(4) of the Patents Act 1983 is an exception to Section 13(1) (d) of the Patents Act 1983.

B. Challenges to the Recognition of Second Medical Use Patents

The interview results which emphasizes coding derived from analysis of Nvivo software concluded that new molecule is much preferred than existing new uses of known substances. As stated by Respondent 9, who is from a non-governmental organization, Malaysia should adopt a higher standard to restrict evergreening patent. This opinion concurs with that of Respondent 13, Mr. U, whereby MR U mentioned that if an antibiotic has the same class but different properties, it can be patented as changes in the molecule levels or molecule structure which are essential to restrict evergreening patent. New molecules are considered important in the view of this respondent and by having and requiring new molecules from the inventor; it implies that higher patentability standard need to be adopted. A similar opinion is adopted by Respondent 5, Mr.S stating that Rovastatin is a totally different chemical name where Rovastatin patentability looks more deserving and worthy. However, he also emphasized that chemicals which possess novel technology are equally significant with new molecules. Metformin, despite having similar chemicals, possesses novel technology. The comparison of the significance of new chemical molecule name and novel technology is a tricky situation indeed, although Respondent 13, Mr. U strongly emphasized that patent should be given only to new chemical entities. Similarly, he stated that an antibiotic which has the same class but different properties can be patented even if there are changes in the molecule level or molecule structure. In coherence with the view, Mr. U even said that second indication should not be patented. To concur with this point, Respondent 7 from NPCB said that the second medical use should have the same molecule and not new.

However, Respondent 7, NPCB also explained about the exceptions of the patentability of second medical use indication in Malaysia. If there is evidence based on trials, special consideration must be given. The respondent explained and gave illustrations on how Lamivudine created for HIV patients. Through clinical trials, it is well tolerated and managed well with hepatitis C patients. In Malaysia, we follow the European standard and thus, granted patent for the second use of Lamivudine. Second medical use should be carefully considered for patentability and should not be allowed as a general exception according to Respondent 7. Similarly, Respondent 3, MR. C stated such patentability of second medical use is a hindrance and could cause obstacles for generic companies and therefore second medical use should not be allowed.

C. Overview of Second Medical Use

In the case of patented drugs, the ingredients and usage are clear. Above that, most of the drugs have second medical use and incremental innovations after patents are granted.

The possible undesirable effect of the second use of a drug when treating another disease must be given serious consideration in the medical field. Most off-label prescriptions for such second medical use are not backed by evidence that the drugs will work as intended. For instance, many medications approved for the treatment of depression are prescribed by doctors for other problems such as pain, insomnia and migraine. Only a small fraction of such off-

label treatments have been tested for efficacy and side effects, according to researchers as reported in the medical journal. Apart from second medical use, the off label prescription related to first medical use is also widespread especially on off label use of existing drug and new medicines in children. The lack of complete evidence of efficacy and safety making children as 'therapeutic orphans as considered as relatively small sample size of the children who will receive anti-hypertensive medications.

In relation to the second use of the prior drug in most instances the efficacy is not proven. The efficacy of a drug differs from various age groups. For instance, giving adult medication to children or in doses different from those tested in clinical trials and specified by drug makers, is also considered as off-label usage. The common example is off label anti-depression use. The study found about a third of anti-depressants are prescribed for conditions other than depression. According to Jenna Wong, "there is a lot of off-label use going on, but we don't have good ways of tracking, especially when anti-depressants are taken to treat other conditions.

In relation to the laws related to patentability of second medical use, the law and regulations have not addressed specific conditions. The question is whether patentability of second medical use can prevent off-label use not backed by science. It can be argued that patentability of second medical use and incremental innovations are much related to off-label prescription.

The same drugs may be prescribed for diseases based on the second medical use by medical practitioners without same being licensed by the NPCB. The usage of drugs for second medical use can be abused and also usage based on the incremental innovations can be wrongly prescribed. For example, a drug named Methotrexate is licensed to treat cancer, and one of its second medical uses is being used in the treatment of psoriasis. However, second medical use for psoriasis is not patented and licensed. Therefore, patients taking the drug for skin problems could potentially suffer side effects of the primary use. In such situation, NPCB should step in to ensure the second medical use of such drugs are licensed and patented by the inventor. If these drugs are required to be licensed, then the inventor will be compelled to disclose the side effects in the patent claim itself and conduct all clinical trials on patients for the disease to be treated based on the second medical use of the same drug.

Respondent 17, an academician defined second medical use patents as "new therapeutic uses for known active ingredients, possess important component of the potential second medical use patent protection. For example, Aspirin's first medical use is an antipyretic and analgesic while the second medical use is as an anticoagulant and further medical uses are as anti-stroke and anti-ischaemic drug. Respondent 6, Mr. T, defined second medical use as an additional usage of one product.

D. Examples of Second Medical Use

Respondent 20, Mr W, defined second medical use by highlighting a noted example on the use of Aspirin, as follows; "The notable example is Aspirin is used in preventing stroke and to treat irregular heart beat and heart valve in elderly patients. Thus, for such use, the off label use has been practiced. We still cannot obtain a newer medication than Aspirin. Off label use is at the discretion of doctors and doctors must evaluate the risks and the benefits to the patients." Respondent 20, Mr W, also gave other noted example; "An example is the anti-psychotic drugs which is used treating attention deficit syndrome in children which is also used also for certain pain relief. Another example is the diabetic medication, Metformin (XR), which is used in the management of polycystic ovary syndrome (PCOS)."

Respondent 18 also gave an example, that is, "Thalidomide, which in the early 1950s was used to prevent morning sickness in women. Thalidomide was withdrawn due to safety issues as development on drug safety were not well developed in the United States. During pre-clinical trials the drug entered the market and was widely prescribed. With the O & G specialists' approval, the drug was widely prescribed in Europe but the side effects could be having a child without limbs. In early 2000, the drug Thalidomide was claimed for its second further use for leukemia.

Further example of second medical use is, Statin, an anti-cholesterol drug. Merck claimed new use of this drug for osteoporosis to prevent fracture. Another instance of second medical use is the drug called Metformin used in the treatment of diabetes. Since the first use of the drug had been off patent, then inventors enhanced the use of the drug to treat skin cancers.

Respondent 19 also cited an example on second medical use for the drug, Viagra, which was initially designed to treat hypertension, but now can be used to treat erectile dysfunction. Another example is the inhaler used to treat asthma and COPD. Respondent 5, Mr. S, also reiterated on the same examples as given by Respondent 19.

Yet another example of second medical use was illustrated by Respondent 4, Ms. N. She stated that a drug called Alprim was first used for for kidney infections but was also used later for vertigo as an off-label prescription, although clinical studies for vertigo is not yet evidence based.

Another example of significant type of second medical use described by Respondent 10, Mr. Z, too gave an example is, as follows; "A drug named Colchicne, which is a mimotic inhibitor used in the treatment of gout and colchicines, has been investigated as an anti-cancer agent and has proven to be effective in treating cancerous cells."

Respondent 10, Mr. Z also strongly believes that; "Granting of second medical use can help the patients to be treated for another disease, thereby expanding the coverage in the medical field. For instance, alpha blockers are used for the treatment of benign prostatic hyperplasia and at the same time alpha blockers are medicines that are mainly used to treat hypertension and enlargement of the prostate gland.

Another example is the effectiveness of a drug named Tricimcinolene (tramcinolone acetoide) used for middle ear infection (eosinophilic otitis media) which is associated to

treat bronchial asthma. Triamcinolene is also used for allergies, skin conditions, ulcerative colitis, arthritis, lupus, psoriasis or breathing disorders.

Respondent 14, Mr. K as an ear, nose, and throat surgeon gave the following views;

"The anti-cancer drug named "Methotrexate" is used to treat leukaemia, head or neck cancer. In certain severe cases of osteoarthritis or severe pain of arthritis, Methotrexate is used. This anti-cancer drug can have severe side effects, for instance, the reduction in the bone marrow cells. Methotrexate is not the first line of treatment for arthritis but used as the last resort if there is no alternative than methotrexate is used." Other side effects as explained by Mr K, on the drug, Methotrexate includes liver damage, stomach ulcers, mouth ulcers, renal damage, and urinary bladder damage problems, where it can alter cells in your blood and can also lead to menstrual problems or infertility. Respondent 12, Mr. I, gave a similar explanation on Methotrexate, thus, agreeing with Mr K that methotrexate also possesses second medical use to treat rheumatoid arthritis."

Benadryl that is used to treat cough has a second use in assisting to lessen the itchiness of the throat. Respondent 14, further illustrated another example of the anti-physiochatic drug called Chloperazine Maleate, which is also used to prevent severe vomiting or hiccups.

E. The Importance of Recognition of Second Medical Use

The interpretation of second medical use must be carefully considered as recognition of second medical use to be patented as an eligible invention that can prevent the drug compound from being prescribed negligently. According to the Respondent 15, Mr. IS, use of the substance recognized for the first use should be carefully applied for the second medical use. He cited an example as follows; For instance, Bisoprolol is a group called beta blockers. Beta blocker affects the heart and circulation blood flow of arteries and veins. The second use of beta blockers is used to treat hypertension. Bisoprolol may also be used for other purposes not listed in this medication guide. Bisoprolol can also cause termination of pregnancy or used by the doctor for the purpose of abortion. The respondent was reluctant to explain regarding Bisoprolol, as the off label prescription is not clinically a proven use.

The second medical use indications can be beneficial if it brings goodness to the patient. Respondent 16, an academician stated as follows; For instance, erythromycin created by company A slows the growth or kill sensitive bacteria by reducing production of important protein needed by the bacteria to survive. Another example is where company B comes out with use of erythromycin for treating severe constipation in children, as most antibiotic known to have laxative effect. For instance, Panadol being analgesic to treat fever and pain then innovators had Panadol Active 5 or other formulation to extend patent for better process. If company B comes out with new formulation of Panadol to treat cancer, then the reasons for the patent claim must be disclosed.

The second medical use in the medical field should be used with caution. The non-patentability of the second and further uses related to dangerous and poisonous drugs should be patented. For instance, drug used to treat cancer need to be monitored carefully for second and subsequent uses. Respondent 11, Mr. H said the following;

"Second medical use or incremental innovations are beneficial in first line treatment such as cancer as the original patented drug/medications will be the first choice. In contrast, for mild diseases such as cough and cold such incremental innovators should not be utilized."

Importantly respondent 11, Mr H also addressed that second medical use can be recognized for dangerous or poisonous harmful drugs. For instance, patient cannot be treated with a drug for its second medical use if it is life threatening.

Another noted example of a drug for treating diabetic is Metformin. The second usage of the Metformin can also be used to reduce weight or obesity but it should not be encouraged as it is not being proven through evidence based clinical trials as it may be harmful or detrimental to the patients.

Respondent 14, Mr. K was also of the same view with Respondent 11, Mr. H when Respondent 14, Mr. K said the following; "Second medical use can be recognized in special or specific circumstances. For instances, an anti-cancer drug claimed for further uses must be carefully determined by physicians as part of dangerous drugs. Doctors should use it indiscriminately from risking patients. Doctors should monitor blood of the patients and this type of second medical use often creates heavy responsibility towards doctors.

The respondent 11, Mr. H stated second medical uses or further uses should be dealt carefully as dangerous drug like cancer drug can possess severe adverse drug reactions while treating another disease.

Allowing a second medical use of a drug may prolong the lifespan of a product and this could increase revenue. Apart from second medical use, incremental innovations such as choice of an alternative drug are also important. Respondent 6, Mt. T stated as follows;

"For instance, earlier we have drug like aspirin as analgesic, now the newer version is Panadeine, Panadeine is an effective pain reliever for strong pain, which contains the combined strength of paracetamol and codeine phosphate. Panadeine is a good choice for pain reliever for people with sensitive stomachs, stomach ulcers and other stomach disorders. Panadeine is also suitable for people who suffer from asthma and those who are sensitive to NSAIDs such as aspirin and ibuprofen."

Respondent 5, Mr. S formed a positive view on the recognition of second medical use. Respondent 5, Mr S stated as follows; "Reassurance on the chemical name is important." "When you apply for increased bioavailability, the use is still the same. However, if the use is not same then invention can be granted patentability. In other words, second medical use is encouraged for patentability than improving the first medical use."

F. Restrictions on Application of Second Medical Use

The effect of the first medical use must be considered

before recognizing its second medical use. Respondent 2, Mr. B stated as follows; "For instance, Ranitidine intended use is actually the second use. Reducing the acidity is the second use of ranitidine. The first use is the relaxation of the smooth muscle which must be for the purpose of heart, but as through clinical studies it is not effective in heart as more effective as acidity reduction medicine shown in the first use.

Another example of the restriction of second medical use is Pharmotidine for reducing stomach acidity when for the first medical use it also can be used for smooth muscle relaxant. So the side effects of its first medical use should be disclosed.

Many drugs for second medical use are being treated for first medical use. Second medical use (SMU) can be accepted provided the first medical use as no adverse drug reactions and harmful. For instance, one is Ranitidine for long period but where heartbeat is reduced then it should be used for the second medical use as intensity of the first medical use is high.

If the clinical trial shows the drugs is more effective as a second medical use such as reducing acidity, then such second use deserves patentability provided clinical trial results given by the inventor show the worthiness of the invention.

Medicines with multiple uses need to be carefully patented. Similar view adopted by Respondent 8 where second medical use should not be given freely if the side effects are too adverse. Many medicines have stronger use like relieving acidity but it may at the same time damage one's kidney. In such situations the second medical use should be restricted.

G. Off Label Prescription.

The recognition of non-patentability of non-use of drug for further uses is important to prevent improper off-label prescription use without proper efficacy and safety studies. For instance, an example cited by respondent 15, Mr.IS on off-label prescription use of Bisoprolol by some gynaecologist which should be prevented. Bisoprolol is a group called beta blockers which affects the heart and circulation of blood flow of arteries and veins. The second use of beta blockers is used to treat hypertension. However, Bisoprolol may also be used for other purposes not listed in the medication guide. Bisoprolol can also cause termination of pregnancy or used by doctors for purpose of abortion. The off-label prescription use of bisoprolol for termination of pregnancy is not a clinically proven second use.

The second medical use should be encouraged especially in situation where the non-use of substance of a drug prohibited for dangerous use. For instance, the non-use of substance X (bisoprolol) for the purpose of abortion should be prohibited for patentability. The view of respondent 15, Mr.IS is similar with the view of Mr.H and Mr. K regarding the non-use of drugs for first indication for second medical use. Respondent 15 stated since bisoprolol is considered as off-label prescription by some gynaecologist, creating claim for a patent for such non-use for second medical use must not be granted in order to prevent side effects.

A special consideration must be given for diseases related to cancer as off label prescription is often prescribed often due to scarcity of drugs for further indications. The often use of off label prescription is used to treat cancer drug and anti-psychotic drugs must be legally patented.

Respondent 20, Mr W stated "the reason cancer drugs often used in off label prescription by doctors because studies on cancer drugs are limited. The use of a drug to treat a particular form of cancer is repeated in another type of cancer which must be carefully applied by the doctors otherwise it will be detrimental to patients. This concurs with the view by Respondent 11, Mr H on that non-patentability of dangerous drugs especially related to cancer drugs and sleeping tablets which the adverse drug reactions can be fatal in the application to treat for another use. Thus the application of dangerous drugs especially cancer drugs must be carefully considered and off label prescription should not be encouraged. Respondent 20, Mr W while giving examples on anti-psychotic drugs which used for children treating attention deficit syndrome, are also used for unapproved pain relief symptom is another case of off label prescription.

H. Legality of off-label prescription.

Legality of off-label prescription is still yet to be affirmed and uncertain according to respondent 10, Mr Z. Respondent 12, Mr. I is of an opinion that as long as instructions are followed by doctors they will not breach the duty. However, respondent 12, Mr. I view is only based on doctor's responsibility related to dosage regime. Flexibility of doctors to modify dosage instructions as per manufacturer's labelling will not impose doctors for any breach of their duty. For instance, Claritin prescribed 5 to 10mg per day for a period of five to ten days must be monitored by doctors. However, legal obligation of doctors in prescribing the drug for another disease still needs to be carefully considered. As stated by respondent 14, Ms. N, whose is also of the same opinion with respondent 2, Mr. I that off-label prescriptions need to be carefully monitored. Another example of cautious second use is a drug called Alprim, a drug for which the first use is for kidney infections. The off-label prescription of Alprim is used for vertigo and the use is not based on evidence based clinical studies. The off label prescription in the treatment of vertigo can be detrimental to the patient because it lacks efficacy and safety.

I. The Implications of Scarcity of Medicine and Off Label Prescription

Increased scarcity of medication is a worrying trend, which is likely to continue for the coming decades. Drugs with high level of adverse can pose heavy responsibility to the physicians especially when the clinicians and physicians do not have the choice of an alternative drug. For certain diseases where there is no alternative means we need more alternative drug according to the clinical pharmacist, respondent 19. An example illustrated by respondent 19 is anti-TB drug which is a toxic medicine and can lead to liver failure although the efficacy of the drug is high. In term of treating (TB) tuberculosis there is no alternative drug and clinician has no other choice then monitoring the liver of the

patient. "We need more alternative choice of drug with the lesser ADRS and this is a challenge faced by clinician pharmacist.

J. Undesirable effect of the first indication

An existing drug which has a minor property or undesirable side-effect can be used to treat other diseases. The legality of such undesirable side-effect from the first-use to treat another disease is still questionable. For example, compound X sulfonamides an anti-bacterial agent which has side-effect of hypoglycemia or lowered glucose levels in the blood. Can compound x for the treatment of diabetes be patented? The question is the compound X having undesirable side-effect as an anti-bacterial agent with the ability to lower glucose levels could be useful in the treatment of diabetes. According to respondent 17, second-medical uses may be successfully implemented in the United Kingdom and other country. In India, mere application of second use of the drug for treatment of another disease need not be patentable unless additional patent application is worded as drug composition. For example, a change in the sulfonamides drug composition or regime which leads to better or enhanced efficacy, especially in terms of better anti-bacterial action and lowering side-effects can be considered as patentable invention.

However, the second medical use of sulfonamides used on certain class of populations who do not have diabetic can be harmful as the glucose level in the blood could drastically be lowered. In such cases Respondent 17 did not give his opinion on the non-patentability of undesirable side effect of the doctors should use the drug for off label prescriptions.

K. Depriving Benefit to the Patient

For instance, if second medical use can be given patent, if it is proved that it can benefit the patients without any side effects. If unnecessary restrictions are posed for patentability of a drug for second medical use patients of a certain group of people may be deprived from the benefit of its second medical use.

L. Discretion and Intervention by Doctors.

According to respondent 19, Federal Drug Administration (FDA) indication is based on a proper clinical trial but the doctors have the discretion to prescribe the medicine outside the blue book indication. In considering off-label prescription, the drug must have efficacy and safety standards.

According to Respondent 10, Mr Z, if second medical use is recognized it will not affect the doctors' discretion to treat the patient. The respondent Mr. Z of a view doctors must have the discretion and as a noted example by respondent 10 Mr Z is when beta blockers can be used for treating hypertension and heart disease as second medical use. But for the purpose of patentability the dosage regime must be carefully considered as adjustment of dosage regime can be off label. The recognition of second medical use for patentability should be considered as to prevent the abuse of off label prescription.

M. Challenges for patentability of incremental innovations and second medical use Evergreening patents

In relation to the evergreening patents respondent 21, Mr O stated as follows "firstly one must look at the chemical structure." The chemical structure is related to the activity, such as optimal isomer. For instance, if there are two activities the drug will rotate 180% percent and will result in a different form. The big shape capsule and tablet will dissolve easier in water. The heating and stirring process of making the drug is not novel and can be considered as evergreening patent. Respondent 21, Mr O also explained in the context of application of section 3(d) of Patent Amendment Act 2005, the word 'known' which is important in restricting evergreening patents.

The examples provided by respondent 18, an academician indicates that improvement of dosage can constitute as evergreening patent. Respondent 18 gave an example of an evergreening patent drug named Janumet, a combination of sitagliptin and metformin to treat diabetes. Merck a pharmaceutical branded company released once a daily prescription of Janumet (xr) tablets containing Sitagliptin in Januvia (R) and extended release Metformin once-a day tablet where its patent will be in force for another 20-25 years.

The second use of the unintended purpose of the drug can also be considered as evergreening patent. The insulin injection used to treat type 2 diabetes can be further used for very skinny diabetic patient to enable them to put on weight. The further use of helping diabetic patient to put on weight can be considered as evergreening patent according to respondent 1, Mr.R. Metformin is given to obese people suffering from diabetes or even normal people to reduce weight. The metformin medicine for instance for reducing weight though considered as evergreening patent is an example of off label prescription for treating to reduce weight.

The concept evergreening patent was discussed by Respondent 22 in the case of Novartis AG vs Union of India.

II. CONCLUSION

The legality aspect of off label prescription can be addressed with improvise interpretations under Section 14(4) (d) of the Patents Act 1983. It is important to realise merely recognising new uses of known substances which impliedly allowing patentability of second medical use under the section 14(4) (d) of the Patents Act 1983 does not contribute to the advancement in the field of pharmaceutical and medicine. Off label practice has been pertinent in the medical field which is unavoidable, however careful consideration by physicians and medical practitioners are essential in ensuring the safe practice of off-label prescription. Despite the scarcity of medicine and off label prescription the undesirable side-effect from the first-use to treat another disease is still worrying on the impact of the health of the patients. For instance, as discussed above the second medical use of sulfonamides used on certain class of

populations who do not have diabetic can be harmful as the glucose level in the blood could drastically be lowered. The practice of off-label medications especially in treating cancer must be carefully considered by doctors. In dealing with patentability of second medical use indications related to cancer drugs, the Patent Office must take stringent steps to require information on evidence based clinical trials and the undesirable adverse drug reactions of the first indications must be disclosed in the patent specification.

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