DOSAGE PATENTING IN PERSONALIZED MEDICINE

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ABSTRACT

Inventions for dosage regimens often arise after the pharmaceutical product has been dosed in patients and more information is known about the in vivo and pharmacokinetic properties of the medical agent. However, securing patent protection for this type of invention has been difficult because dosage inventions are considered to be simple medical methods whose protection is believed to limit doctors’ choices in clinical practice. Moreover, novel dosage inventions are also considered to involve a process that does not enjoy the same scope of patent protection as new chemical entities despite their superior therapeutic potential. This article examines the nature of dosage inventions under an increasingly personalized clinical setting and argues that traditional patent jurisprudence might not apply to such inventions in personalized medicine. Therefore, more liberal approaches are needed to foster inventions in this field of technology.

I. PERSONALIZED MEDICINE AND DRUG DOSAGE

a. Drug Dosage Defined

Selecting the right dose for a new drug is a crucial step in the development of new pharmaceutical drugs. Without adequate information on dosage, it is not possible for doctors to prescribe a particular drug to patients. Therefore, determining the correct drug dosage is a key question that needs to be addressed in clinical practice.

The main purpose of Phase I and Phase II clinical trial studies¹ is to answer the questions of “How often?” and “How much?”² allowing the determination of the appropriate dose and dose range for a drug candidate that is both effective and safe. Clinicians examine drug concentrations in the body over time at various doses and time intervals. The pharmacokinetic data gathered then allows the design of optimized dosage regimens and the determination of therapeutic ranges.³ However, if the dose or dose range cannot be identified that allows safe and predictable administration; the drug development candidate cannot be a medically useful or commercially viable pharmaceutical product.

Dosage regimens are formalized schedules by which drugs are administered, including the amount of the drug, number of doses in a period of time, and time between doses. As a compound progresses through the various

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² For example, Cubicin is an antibiotic for the treatment of infectious diseases; development of this drug has been not been easy because of the difficulty in avoiding the undesirable side effects observed on skeletal muscles. The dosage was modified to enable this drug to be used against intractable infectious disease. The initial administration interval: 3–4mg/kg, intravenously twice a day for 6–11 days to internal administration 4–6mg/kg, administered by IV drip once 1–2 days for 30 minutes.
⁴ Traditionally, drug information provided by pharmaceutical companies (such as package inserts and the Physician’s Desk Reference) contains data about the pharmacokinetics of drugs and therapeutic ranges.
drug development stages, new insights might emerge into the modes of action, side effects, and patient response. In addition, technologies might also emerge that enable more efficient, effective, or convenient ways to deliver drugs. Based on this information, new dosing regimens can be formulated to improve absorption, prolong a drug’s medicinal effects or improve patient compliance. Patient compliance can be crucial for optimal treatment of various conditions. The more doses required or the more difficult the treatment plan, the less likely a patient is to comply. Although medical agents have the ability to enhance patients’ quality of life (QOL), they can only do so if they are used correctly.  

Today’s drug development is commonly based on a “one-size-fits-all” concept. A drug is prescribed to a group of patients with the same illness regardless of their race, age, or individual genetic compositions. A leaflet inside the drug package provided by pharmaceutical companies to doctors describes usage instructions and the recommended dosages including initial dosage and dosage intervals as gathered from the clinical trials. As a result, side effects or other related issues may appear following the initial dose although other more advantageous dosing regimens may be available. Once discovered, the new regimens are considered a second medical indication under patent law.

Trial and error can sometimes assist doctors in making changes to the dosage of a prescribed drug. When patients return for follow-up visits, the dosage can be adjusted to optimize the effectiveness of the drug and minimize its side effects. However, this manner of dosage alteration in personalized medicine can be an imprecise science. In other situations, drug dosing might be adjusted based on side effects that linger with the initial drug regimen.

During the course of treating patients, doctors may also discover new uses or indications for a drug for which it was not made or tested. By acting as the known intermediary for patients, doctors begin to prescribe drugs to patients for the new use, a practice known as “off-label use.”

b. What is Personalized Medicine

Unlike personalized medicine, the traditional concept of “one-size-fits-all” provides an inadequate dosing paradigm requiring new approaches in order to better identify optimal drug doses. Personalized medicine is based on the belief that different people respond differently to a drug, resulting in positive responses to a drug by some individuals but not others. Today, adverse drug effects are the fifth leading cause of deaths in the US and clinical trial data suggests that more than 2 million serious adverse events occur each year resulting in more than 100,000

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8 Second medical use refers to the situation where it has been found that a known pharmaceutical can be used for the treatment of another known disease.
10 Teva amended an existing Abbreviated New Drug Application (ANDA) and sought FDA approval to market generic versions of Merck’s once-weekly Fosamax® supplement for treating osteoporosis. Fosamax® patients had been suffering from side effects such as esophageal injury or repetitive irritation of the esophagus. Fosamax® also had an additional side effect relating to the size of the dose, where a dose above 20mg was not well-tolerated. The current dosing for Fosamax® is 70mg or 35mg according to a continuous dosing schedule based on a once-weekly dosing interval. However, once-a-week dosing had already been suggested by earlier publications making Merck’s claims for once-weekly dosing of Fosamax® obvious based on the prior art.
11 Off-label prescription of drugs occurs when a doctor prescribes a drug in any manner that varies from drug labeling specifications or for a use that has not been approved by regulatory authorities.
12 See Lesko, supra note 7.
The varying drug responses among patients could be attributed to intrinsic ethnic factors such as genetics, metabolism, or elimination.\textsuperscript{15} Drug responses could also be affected by extrinsic factors associated with environment or culture such as medical practice, diet, or alcohol use.\textsuperscript{16} However, there are currently no known biomarkers or methods that can predict which group of patients will respond positively, which patients will be non-responders, and which patients will experience adverse effects.\textsuperscript{17} Hence, new research is needed to study the effects of an individual’s genetic makeup on responses to various drugs (i.e., pharmacogenetics- investigates the relationship between drug responses and genetic differences; pharmacogenomics- a genome-wide approach that studies the entire spectrum of genes involved in drug responses). This research, if successful, could provide the basis for a rational approach toward improving the effectiveness and safety of prescription drugs.\textsuperscript{18} Therefore, patients could then be classified based on genetic variation into low, intermediate, and high dose groups\textsuperscript{19} allowing doctors to amend the dosage according to each group’s response toward the drug.\textsuperscript{20}

Pharmacokinetic principles may also be used to design dosage regimens for individual patients in order to achieve therapeutic plasma concentrations of drugs. Such designs would require the estimated kinetic data of the drug in the patient and a therapeutic range.\textsuperscript{51} An understanding of the relationship among these major pharmacokinetic parameters would allow modification of dosage regimens when the kinetics of the drug are altered because of drug interaction and/or disease states. Thus, personalized medicine does not mean that individuals require a drug of their own, but rather, require their own personalized suitable dosage regimen. Like choosing the correct clothing size to achieve the best fit in a particular body type, a dosage regimen that achieves the “best fit” or optimal therapeutic effect can be found for each patient.

c. Drug Dosage in Personalized Medicine

It is often standard practice for doctors and pharmacists to design dosage regimens for individual patients based on the reported therapeutic range of the drug and the kinetics of the drug in the patient.\textsuperscript{22} Personalized medicine not only allows the possibility of finding new uses of a known drug, but also allows the correlation of drug dosage to specific patients with a particular genetic makeup. If a correlation can be made, then genetic testing may be used to reveal which patients are suitable to take the particular drug and at what dosage allowing for the elimination of unsuitable test subjects during clinical trials. This correlation might also allow for the amending of the drug dosage according to the patient’s metabolism to find their optimal dosing regimen. Adjustment of dosage based on the particular patient’s metabolism involves three steps: (i) administration of the drug; (ii) determining the testable subject matter (for example, metabolite or enzyme level); and (iii) an adjustment in dosage as required

\textsuperscript{14} See id. at 10.
\textsuperscript{16} See id.
\textsuperscript{17} Barkur S. Shastry, Pharmacogenetics and the Concept of Individualized Medicine, 6 PHARMACOGENOMICS J. 16, 16 (2006).
\textsuperscript{18} See id.
\textsuperscript{19} Mark J. Rieder et al, Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose, 352 NEW ENGL. J. MED. 2285, 2285 (2005).
\textsuperscript{20} Roche Diagnostics has recently developed a genetic test, the AmpliChip CYP450 Test, which combines genotyping with an interpretation table allowing classification of people into groups of slow, medium, high, and ultrahigh metabolizers of certain drug families. These “predictive phenotypes” have the potential to help doctor prescribe the correct doses of drugs known to be metabolized by these selected members of CYP450 family of enzyme. For a detailed description of this test, see Jose De Leon, Margaret T. Susce & Elaina Murray-Carmichael, The AmpliChip(TM) CYP450 Genotyping Test: Integrating a New Clinical Tool, 10(3) MOL. DIAGN. THER. 135,151 (2006).
\textsuperscript{21} Therapeutic range refers to the dosage ranges or plasma concentrations of the drug which are expected to achieve the desired therapeutic effect with minimal toxicity to the majority of patients.
\textsuperscript{22} See Mehvar, supra note 3.
based on the results obtained. Drug dosing could then be subdivided into specific patient groups, specific time intervals, and specific dosage amounts. Therefore, genetic testing must be performed and results must be interpreted by doctors as well as other specialists (i.e., clinical pharmacologists) to allow doctors to correctly design new personalized dosing regimens for individual patients.\textsuperscript{23}

\textbf{II. DOSAGE FINDING CASE STUDY – WARFARIN}

\textit{a. Dosage Regimens Are Difficult to Determine}

Like all new pharmaceutical molecules, dosing regimens must also be verified by clinical trials to assess their therapeutic value. Once a novel and inventive dosing regimen proves effective in clinical trials, it can be added to the drug labels or package inserts.\textsuperscript{24} However, even when a new and inventive dosage regimen is discovered, therapeutic success is not guaranteed and further dosage adjustment by doctors may be required for individual patients. The seminal example is Warfarin, a drug for treating thromboembolism, which has a fixed dose of 5 mg/day and an average maintenance dose of 4-6 mg per day. The dose for different patients can range widely requiring anywhere between 4.5-77 mg per week, placing patients at risk because the correct dose cannot be determined for the vast majority of patients requiring treatment.\textsuperscript{25}

Despite Warfarin’s 60 years of its existence, the problem of dosing lingers. There is a vast difference between discovering a molecule such as Warfarin and knowing how it affects patients and what doses are required for the desired effects. Warfarin is only therapeutically useful if it reaches an appropriate level of anticoagulation, losing its effectiveness at low levels. However, if anticoagulation levels are too high, there could be a significant risk of complications due to increased bleeding or hemorrhaging in patients.

Under the European jurisprudence for patenting second medical indications, dosage regimens are considered selection inventions, where unexpected technical effects are associated with a specific compound known as “a species” that is a member of a larger “genus” of structurally-related compounds.\textsuperscript{26} Novelty, however, is lost because without a new indication, the new dosage invention merely reveals what was not clear to a Person Having Ordinarily Skill in the Art (PHOSITA) and is based on an old, known compound. Nonetheless, the therapeutic value of a new dosage regimen might not be any less than the initial dosage regimen. With evolving new technologies and increased understanding of particular drugs, it is natural for drugs to be “re-invented” and dosage regimens readjusted after initial launching of the product. Therefore, patents should be granted to encourage invention of these better dosage regimens and to foster higher quality therapeutic treatments for patients.

\textit{b. How Warfarin Is Applied in Clinical Practice}

Current patent jurisprudence is based on the belief that compound structure and property should be considered one invention as a whole.\textsuperscript{27} The justifying underlying rationale being that the discoverer of the structure possesses all the known and potential uses of the molecule that comprises their invention. However, as in the case of Warfarin, there may be structural novelty in the discovery of a new compound, but all the properties of the new chemical entity may still be unknown. The true therapeutic value can only be more clearly understood and applied

\textsuperscript{23} Micheline Piquette-Miller & Denis M. Grant, \textit{The Arts and Science of Personalized Medicine}, 81 CLIN. PHARMACOL. THER. 311, 315 (2007).


\textsuperscript{25} Stephen E. Kimmel, \textit{Warfarin Therapy: In Need of Improvement After All These Years}, 9 EXPERT OPIN. PHARMACOTHER. 677, 679 (2008).


\textsuperscript{27} In re Papesch, 315 F.2d 381, 391 (CCPA 1963).
according to empirical experiences, which is far beyond the initial discovery of the novel molecule structure. If this is unknown value is accounted for in the initial molecular discovery, then the requirement for a second indication seems contradictory to clinical practice. A newer and more effective indication should be rewarded and not questioned by the older and less effective use.

Patent jurisprudence has indicated that inventive step can be attained through discovery of an unexpected property which was not foreseeable by a PHOSITA. For example, if the dosage was initially prescribed at 50–60 mg/per day but was reduced to 0.5–0.6 mg/per day, this large decrease could be significant evidence showing the absence of foreseeability to a PHOSITA. This, however, can be a subjective inquiry due to the unpredictability of chemical molecules in different patients. It is much more foreseeable that the current dose as advised by the pharmaceutical company is not the highest quality possible and could vary among patients. Like Warfarin, dosage of various drugs can be affected by several patient factors such as genes, age, sex, bodyweight/body mass index (BMI), as well as environmental factors such as interacting medication, alcohol consumption, and diet. The critical part of dosage studies involves how to achieve the optimal dosage for individual patients.

One way to achieve the optimal dosage for individual patients is to design a dosage algorithm using clinical variables to help improve therapeutic application of drugs. Designing a dosing algorithm requires appropriately developed studies and/or databases that include accurate data and proper use of statistical methods. These activities are typically conducted by the physician but raise several questions. Although a physician has the right to prescribe a drug, should he be barred from designing a new dosage regimen because there is a patent covering its use? If so, is applying the dosing algorithm using the patented dosage regimen an infringing act? The patented dosage regimen does not at all matter to doctors, because once they have the right to use the initial drug and dose, they can design new individual dosage regimens for individual patients. Whether or not a patent covers a novel dosage regimen is unimportant because the patented dosage regimen is one of many possible regimens and is directed to the public and not to specific patients or patient groups. Dosing algorithms provide the opportunity for doctors to prescribe drugs according to the medical needs of individual patients and represents the true spirit of personalized medicine but the grounds for patentability of the algorithm itself have been uncertain (mathematical algorithms may not be considered patentable subject matter under U.S. Patent law). As a result of the importance of dosage adjustment in patient treatment, dosage patenting has been rendered questionable and will be further illustrated in the next section.

III. PATENTABILITY OBSTACLES FOR DOSAGE PATENTING

a. Ethical Concerns

The patenting of drug dosage is controversial because it is often viewed as an evergreen strategy that allows pharmaceutical companies to extend their drug product patent once it expires. It is also controversial because it is considered a form of medical treatment, raising ethical and policy concerns around allowing a patent holder to deny effective treatment to ailing patients. By definition, medical treatment is conducted by or under the supervision of a registered medical practitioner and includes the administration of a drug or other like substance, or any other medical procedure. Therefore, any activities conducted by a doctor during his clinical practice can be considered a

30 James R. Rundell & Gen Shinozaki, Pharmacogenomic Considerations in Patients with Comorbid Medical and Psychiatric Illness, 17 PRIMARY PSYCHIATRY 33, 35-36 (2010).
form of medical treatment. If a doctor is prevented from using the dosage formulation that is optimal for his patient, then the patient will be denied the medical treatment he or she needs. Under the European Patent Convention, Article 52(4) recites that methods for treatment of a human or animal body by surgery or therapy and diagnostic methods practiced on a human or animal body can be barred from patentability. Similarly, international law under the TRIPS Agreement Article 27.2(a) has provided that Members may exclude from patentability diagnostic, therapeutic, and surgical methods for treatment of humans or animals.

The patentability of methods of treatment has been rejected mainly due to public health concerns around not permitting doctors the direct use of these methods in their practice. The unpatentability of medical treatments helps preserve doctor’s therapeutic freedom, and is at the heart of the civil, criminal, and professional regulations that give meaning to medical ethics. As a result, the patenting of medical methods is subject to several criticisms. It is believed that allowing patent protection of medical methods prohibits the open exchange of information and ideas, drives up the cost of health care, impairs the quality of care and human life, may be unnecessary and can be subject to abuse. Similarly, the American Medical Association and Council on Ethical and Judicial Affairs has also raised concerns about patenting medical procedures because of the restriction placed on academic and clinical access to those methods, the increasing financial burdens and the difficulty of enforcing medical process patents when enforcement might compromise patient confidentiality.

However, these concerns can apply equally to all medical products, processes, and diagnostic tools regularly used in clinical practice and fail to answer why medical methods are the exception. One possible rationale could be the fear that patents will prevent doctors in emergency situations from using the patented method if they don't hold the license to do so. However, this is not a highly plausible scenario since the greatest priority of law is the protection of life. Infringement would therefore be justified regardless of whether doctors could obtain permission so that the proper treatment could be provided and the endangerment of patient lives could be avoided.  

b. Inadequacies of Patent Law

Aside from ethical concerns, the pharmaceutical and biotechnology industries have long followed the “one-embodiment doctrine” in patent jurisprudence, a legacy from mechanical inventions where inventors have been known to have near perfect knowledge of the function of their machine. However, this rationale creates obstacles for chemistry and biotechnology because certain properties of the invention might be inherent, unpredictable, and unforeseeable. Biological molecules are both compositions of matter and informational molecules; however, the patentability of the former may prevent the use of the latter. It is particularly difficult to claim biological molecules because the existence of a multitude of structurally and potentially functionally equivalent molecules may not be discovered until after the patent is issued. Hence, the existing system of patent law may never be able to fully appreciate the dual nature of biological molecules and the potentially devastating monopolies these patents create.

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36 See Thums, supra note 33.
40 Mark L. Hayman & Lisa E. Stahl, Homology Claims Face New Equivalents Hurdles; Variations on DNA and Protein Molecules May Be Harder to Protect, 26 NAT’L L.J. 54, 54 (2003).
The patentability of a second medical use is a legal fiction created to compensate for the inadequacies of a product patent which provides the patent holder exclusive rights to all existing and potential uses. However, this rationale of providing a patent holder rights to all uses whether known or unknown is logically perplexing. If the inventor of the molecule only knows certain uses of the product at the time of invention, he should not be entitled to claim rights to all future uses not yet discovered or enabled by the current invention. One successful strategy that has been used by the discoverers of novel second uses of natural products is the isolation of the known product at a greater purity. The higher purity product can then be patented as a new chemical entity. Of course, there is a concern that altering the chemical structure and composition by isolating the higher purity product could also potentially change the properties of the molecule making inadequate for its intended new use.

The insufficiency of patent law in effectively protecting the chemical arts is not a novel issue. Scholars began to question the adequacy of patent law based on the mechanical arts in meeting the needs of the chemical arts as early as 1969. There are an ever increasing number of novel technologies that continue to emerge and challenge our patent law system. As long as the law refuses to recognize the importance of separate protection for both product and process, we will continue to have the all same problems and concerns. Dosage patenting in personalized medicine will cause an even larger emphasis to be placed on these issues as drugs become more personalized making it difficult for patent law to continue to be “one-size-fits all”.

IV. DRUG DOSAGE PATENTING IN DIFFERENT JURISDICTIONS

Recent developments in patent law have allowed the patentability of certain types of medical methods, such as drug dosages, so long as they are novel, inventive, and industrially applicable. However, the patentability of these methods remains controversial when the new dosage regimen for which protection is sought is not for the treatment of a new disease. An invention where the distinguishing or novel feature lies only in a new and inventive dosage regimen, such as a method for optimizing the timing, frequency, or amount of administering a medicament, remains unpatentable. As mentioned earlier, the key goal in drug development is the optimization of drug dosage but a new dosage of a known drug for treating a known disease might not meet the requirement for novelty and inventive step. Since different countries have very different approaches regarding this issue we will now discuss and examine four foreign jurisdictions:

a. The UK

Drug dosage has been barred from patentability in Europe and the UK because a new dosage regimen could not form the basis of a novel and patentable claim unless it involved a new medical indication. The European Patent Convention (EPC) of 1973 (in force until December 12, 2007) did not include any provisions relating to patent protection of a second or further medical use of a substance or composition already known for medicament. Protection of all second medical indication inventions could only be accomplished under the legal fiction of the “Swiss-type claim”, which converts a pure use patent into a manufacturing process (e.g., the use of compound X in the manufacture of a medicament for the treatment of disease Y).

More recently, this position has been changed to help foster research for the development of new and more favorable dosage regimens. In 2007, EPC 2000 went into force containing new Article 54(5) which expressly declares that a newly found, specific further use of a substance or composition already known for use as a...

44 See e.g., Nestle-Le Mur Co. v. Eugene, Ltd., 55 F.2d 854, 858 (6th Cir. 1932).
45 Oksana Mitnovetski & Dianne Nicol, Are Patents for Methods of Medical Treatment Contrary to the Ordre Public and Morality or “Generally Inconvenient?”, 30 J. MED. ETHICS 470, 472 (2004) (the aim of the Swiss-type claim to get patent protection in an indirect way for methods of medical treatment that involve a new medical use of a drug. As a consequence, only pure methods or surgical methods are left unpatentable).
46 This Swiss form of claim disguises use claims as novel manufacturing methods to get around EPC 1973 Art. 54(5) which only allows claims to the first medical use of a known compound, and Art. 52 (4), which prohibits claims to methods of treatment that lack industrial applicability.
medicament in a method for therapeutic treatment can be patentable under EPC 2000 Article 53(c). In addition, significant changes were made to other articles within the EPC that favor the patentability of novel dosage regimens. For example, new Article 52 requires that patents should be granted in all fields of technology. Similarly, Article 53(c) now removes the legal fiction that new medical uses of a known drug have no industrial applicability or utility. Restriction of dosage regimen inventions from patentability would, therefore, prevent patenting in one particular field of technology and be in direct contradiction to the new law.

However, Article 54(5) of the EPC does not define the degree of novelty required for the new use to qualify as a specific use within the meaning of the article. This was only clarified on February 19, 2010 when the Enlarged Board of Appeal of EPO announced in G2/08 (“Dosage Regimen/Abbott Respiratory”),47 that a novel and inventive dosage regime is patentable, even when the dosage regime is the only novel feature of a known drug. Therefore, Article 54(5) of the EPC 2000 does not exclude dosage regimens from being patentable for use as alternative treatment or therapy of the same illness and makes Swiss-type claims unnecessary and impermissible48. The second medical indication can now be autonomously claimed as compound X use in the treatment of disease Y.

Despite these changes in the EPC, UK courts continued to find against the patentability of dosage invention claims after the decision in Bristol-Myers Squibb v Baker Norton Pharmaceuticals49 and this position remained unchanged until the 2008 decision in Actavis v Merck.50 Currently, the UK is in conformity with the European approach of finding novelty in dosage regimen claims even if the sole distinguishing features over the prior art is a new dosing regimen or a new dosage form. However, inventiveness or novelty will not be found unless a clear technical prejudice points away from the claimed dosage regime.51

b. The US

In the US, the dosage invention was considered a medical method and had not been patentable subject matter since 1883. In Ex Parte Brinkerhoff,52 the Board held that granting a patent to “a particular method of treatment would have a tendency to deceive the public that the method therein described and claimed would produce the desired result in all cases.”53 This view was analogous to the European view that method of treatment inventions lack industrial applicability. However, this statement was not entirely accurate and by 1946 medical science had evolved to the extent of not only verifying physiological effects of dosing with accuracy but also rendering them reproducible under properly adjusted conditions.54 In 1954, the Patent Office Board of Appeals in Ex Parte Scherer55 overruled Ex Parte Brinkerhoff to allow the patenting of medical methods. As a result, “Swiss-type” claims for new medical uses were not required in the US as they were in Europe during this time.

Currently, under US patent law, dosage inventions are patentable as a process under 35 U.S.C. 101 if they satisfy the requirements laid down for an “art” within the meaning of §10056 as well as the other patentability requirements including novelty and non-obviousness. Since the only criteria used in determining novelty is that its

48 See id. at 43.
53 See id. at 798.
characterization be done in tangible terms, product patents are not available for dosage regimen inventions and they should, therefore, be claimed as medical methods.

c. Japan

Prior to the 2009 revision of the Japan Patent Office (JPO) patent examination guidelines, Japan shared a very similar view of dosage patenting with Europe prohibiting the claiming of medical methods due to their lack of industrial applicability. While Europe has moved toward alignment with the US practice by allowing the patenting of dosage regimen inventions as medical methods, Japan’s latest revisions allow the patenting of dosage and administration not as “methods of surgery, therapy or diagnosis of humans” but rather as products. In fact, these medical inventions are known in Japan as pharmaceutical products with a medical use limitation.

Under Article 52 of Japan’s Pharmaceutical Affairs Law, it is required that the dosage be shown both on the package and the package insert written instructions. As a result, dosage is considered part of the medicinal agent as one of its constituent parts. When dosage inventions are viewed as medical methods, it can become difficult to recognize them as industrially applicable due to the creation of the potential for infringement by the patient as the end user of the new dosage regimen. Although Japanese law eliminates potential liability for patients, it does not, however, do so for medical agents manufacturing providing the patentee with the right to question indirect infringement by manufacturers under Article 101 Paragraph 5 of Japan Patent Act. This potential for indirect infringement by manufacturers exists even if compounds of a claimed medicinal invention are known and do not possess a new specific use or treat a different disease.

Novelty of the claimed invention is also not denied when the only difference between the claimed medicinal invention and the cited invention is a specific dosage and administration based on specific attributes of the compound. But novelty is not the only requirement for patentability. A new invention must also possess an inventive step. In Japan, dosage inventions are considered inventive if a PHOSITA could not foresee the advantageous effects provided, such as an increase in medicinal effects, the reduction of adverse effects or improvement in drug compliance. However, the JPO does not consider the reduction of toxicity or improvement of efficacy as inventive as these are considered routine experimentation or work of a PHOSITA. Whereas prior to the revision of the patent examination guidelines in 2009, novelty could only be established with new patient groups or with a new specific disease, the current practice in Japan is now more aligned with Europe and their guidelines under the provisions of Article 54 (5) EPC 2000.

d. China

Unlike some of countries previously discussed, applying for dosage patents in China is particularly difficult. As discussed, new secondary uses can be defined as a new quantity or dosage amount, a new form of dosage and formulation, or a use for a different disease. However, in China novelty is still the highest hurdle that

57 See JAPAN INTELLECTUAL PROPERTY HEADQUARTERS, supra note 6, at 5.
59 See JAPAN INTELLECTUAL PROPERTY HEADQUARTERS, supra note 6, at 22.
60 See id. at 23.
61 “The following acts shall be deemed to constitute infringement of a patent right or exclusive license:.. (v) Where a patent has been granted for an invention of a process, acts of producing, assigning, etc., importing or offering for assignment, etc. any product to be used of the said process and indispensable for the resolution of the problem by the said invention, knowing that the said invention is a patented invention and the said product is used for the working of the invention as business.” Japanese Patent Act, Act, No. 151, art. 101 paragraph 5 (1959).
62 See JAPAN PATENT OFFICE, supra note 58 at 8.
63 See JAPAN PATENT OFFICE, supra note 58 at 9.
must be overcome requiring that a new use be substantially different from any known use and not be directly revealed by the mechanisms of action or belong to a genus of a known medical use. Particularly, if the novelty of a feature is embodied only in the administration process (such as administrative routes, pathways, dosage or time intervals), it will not render the uses novel. Hence, unlike the revised European approach, if the only feature of the invention is a difference in dosage, it will not satisfy novelty in China.

e. Summary

Under US patent law, the doctor is considered a beneficiary of the patent who can enjoy the benefits of patent protection as an actively involved partner, while the EPC continues to see the doctor as a victim of patent protection. However, this mentality has been gradually changing in both Europe and Japan due to severe competition within the pharmaceutical industry and to the increasing support for protection of medical use inventions. As a result, the UK and Japan have taken the several steps to liberate the patentability of dosage inventions including lifting the bar on the patenting of medical uses based on lack of industrial applicability, discarding this legal fiction, and eliminating the belief that secondary medical uses lack novelty even when the dosage regimen is the only novel feature of the invention. There are, however, some important points to take into consideration regarding the differences in the patentability of dosage invention between different jurisdictions: (i) in the UK, inventive steps and the involvement of doctors will be the new obstacles in getting patent protection; (ii) the UK and the US are aligned in granting medical use patents to dosage inventions while Japan views dosage inventions as product inventions; and (iii) patenting dosage inventions in China is still not possible.

By allowing novel dosage regimens to satisfy novelty requirements, novelty in the UK means use alone can be patentable despite the fact that the process of designing the molecule and the molecule itself is known. This requirement focuses on the unique property rather than the structure of a particular medicament. However, restricting protection to a particular property limits the scope of protection available for these types of discoveries by only allowing narrow coverage of the claimed dosage regimen and not other closely related dosage regimens. While patenting of dosage regimens is currently possible, the scope, strength and reach of dosage regimen patents are severely limited.

V. DOSAGE PATENTING AND THE INVOLVEMENT OF DOCTORS

In the UK, even if an invention is novel and inventive, it might still be unpatentable if it is directed at the activity of the doctor rather than the manufacturer. In Europe, according to the Board of Appeal in T317/95, paragraph 4.5, the determination of the best individual treatment schedule appears to be part of the typical activities and duties of the doctor in exercising his professional skills in curing, preventing or alleviating the symptoms of suffering and illness. The determination of the best individual treatment schedule includes the prescribing and modification of drug regimens for administering a particular medicament to meet the specific needs of a patient. Therefore, these are the typical noncommercial and non-industrial medical activities which Article 52(4) EPC was intended to free from restraint.

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66 Article 22 of China Patent Law stipulates novelty means that before the date of filling, no identical invention has been publicly disclosed in publications in the country or abroad or has been publicly used or made known to the public by any other means in the country, nor has the person filed previously with the Patent Administrative Authority of the State Council an application which described the identical invention and was published after the said date of filling.

67 See Thums, supra note 33.

68 After all, doctors pursue an activity aimed at making a profit and do so professionally. Therefore, arguing that health care is not categorized as an industry is not possible.

a. The UK

One of the major reasons provided by the court for allowing dosage regimens in Actavis v. Merck in the UK,70 was that the claim at issue was directed at the manufacturer and not the doctor. The claim stated “the use of [finasteride] for the preparation of a medicament for oral administration useful for the treatment of androgenic alopecia in a person and wherein the dosage amount is about 0.05 to 1.0 mg”. Whereas in Bristol-Myers Squibb v Baker Norton Pharmaceuticals,71 the claim was directed at the doctor and stated, “Use of taxol and sufficient medications to prevent severe anaphylactic reactions, for manufacturing a medicamentation for simultaneous, separate, or sequential application for the administration of from 135 mg/m2 up to 175 mg/m2 taxol over a period of about 3 hours or less as a means for treating cancer and simultaneously reducing neutropenia.” According to Aldous LJ, the claim “when analysed it is directed step-by-step to the treatment. The premedication is chosen by the doctor, and administered prior to the taxol according to the directions of the doctor. The amount of taxol is selected by the doctor as is the time of administration. The actual medicament that is said to be suitable for treatment is produced in the patient under supervision of the medical team. It is not part of a manufacture.” Hence, in the UK, if the claim impinges directly on the doctor/patient interaction, and thereby potentially affects the doctor’s professional skill and judgment, then the invention might be unpatentable.72

b. The US

Although there is no limitation to the patenting of medical methods in the US, 35 U.S.C. § 287(c)73 exempts medical practitioners from liability for performance of a medical activity that constitutes an infringement. In other words, the law grants doctors a de facto compulsory license to practice a patented invention without the patent owner’s consent.74

Under 35 U.S.C. § 287(c), the term "medical activity" means the performance of a medical or surgical procedure on a body, but does not include: (i) the use of a patented machine, manufacture, or composition of matter in violation of such patent; (ii) the practice of a patented use of a composition of matter in violation of such patent; or (iii) the practice of a process in violation of a biotechnology patent. Here, (i) protects medical devices and pharmaceutical patents from infringement, while (ii) and (iii) allow for the enforcement of patents on new uses of unpatented drugs (a novel dosage regimen is not a medical activity under this definition) and for the protection of gene therapy patents and similar biotechnological processes. Thus, the statute narrows the definition of protectable medical activities to those generally understood as “pure” medical and surgical procedures and defined by the American Academy of Orthopedic Surgeons as “a medical diagnostic procedure or treatment, a method or process, whether the invention is independent of the use of a medical device and a drug.”75 In other words, the medical community is against patenting methods which doctors use to treat patients. While purely medical and surgical procedures are still patentable, they are not enforceable against medical practitioners in the US unless the patent incorporates pharmaceutical or medical devices.

c. Summary

The UK and US have different approaches for protecting public health. To avoid any restraint on doctors during clinical practice, the UK prohibits claims directed at doctors, while the US prohibits the patenting of purely medical methods. The UK’s prohibition of any claims that may impinge on doctor/patient interactions, as is discussed infra, might, therefore, prohibit the development of personalized medicine. The US, on the other hand, will not find infringement of patented medical or surgical procedures unless the patent incorporates a pharmaceutical or medical device, saving the doctor’s autonomy in their treatment of patients while also promoting the development

70 Actavis UK Ltd., supra note 50.
71 Bristol-Myers Squibb, supra note 49.
72 UK INTELECTUAL PROPERTY OFFICE, supra note 51.
of personalized medicine. The US approach fosters the development of dosage inventions in personalized medicine because in order to prescribe a patented product, doctors must have the right to use it. Typically, the sale of a patented product in the US by a manufacturer will exhaust a patent right. Similarly, the patent rights to a method are also exhausted by the sale of the product in which the method is embodied.\textsuperscript{76} The exhaustion of patent rights, therefore, allows doctors to use patented products to design individual dosing regimens for patients promoting the development of personalized medicine without the worry of potential infringement and liability.

\section*{VI. NEW CHALLENGES FOR DOSAGE PATENTING}

\textit{a. Inventive Step}

The patentability bar has been lowered for dosage inventions—particularly the bar for the novelty requirement. In the past, a medicament directed to a new therapeutic application, such as a dosage regimen, was patentable provided that it was shown to relate to the treatment of a new specific disease, including the treatment of a new patient group, or to a new form of dosage reflecting the new therapeutic application. If the claimed dosage invention did not relate to a new specific disease or to a new form of dosage, it was not considered novel. This rationale was based on the view that if an invention did not meet these criteria, then the invention would be a mere improvement or routine work of a PHOSITA.

However, incremental improvements in the medical field might not be as straightforward as some other areas of technologies might suggest. New specific dosages and new forms of dosage are all improvements but with greater therapeutic value. In order to design a new form of dosage, for example, a complete understanding of the drug substance and its pathways of physiological disposition is required.\textsuperscript{77} Once the physiological and biochemical properties of the drug are determined, scientists can then select and develop the effective dosage form. Generally, it is not possible to study and understand these underlying mechanisms during the drug discovery stage or when the product patent is secured because the actual use of this molecule might still be unknown. Hence, the requirement that a second medical indication be a new dosage form or that it treat a new specific disease to satisfy novelty disregards the therapeutic value and effect they bring. These restrictions do not create a healthy environment for dosage inventions and prevents patients from getting the best possible medical care.

Currently, the UK as well as Japan find novelty in a new dosage regimen if it is original when compared to the prior art even if the new dosage is the only novel part of the invention. However, novelty is not the only hurdle that must be overcome and dosage regimens must also satisfy inventive step to be patentable. This additional requirement is intended to promote truly innovative inventions while preventing the patenting of mere trivial improvements or combinations of prior art. Therefore, novel dosage regimens are only patentable if they are not obvious or foreseeable to a PHOSITA. However, the level of inventiveness of novel dosage regimens required to satisfy the UK courts has yet to be decided. In Japan, because improving the dosage regimen can decrease side effects and increasing compliance is a routine step in clinical studies, an invention can only possess an inventive step if it teaches away from the prior art or shows unexpected results or effects under the PHOSITA standard.

\textit{b. Involvement of Doctors}

Advances in technology allow doctors to amend drug regimens for patients according to how the patients react to the administered drug. For example, a drug for the treatment of depression symptoms may be suggested by the manufacturer to be initially administered at 20 mg but allow for gradual increase with a maximum dose no greater than 60 mg. If the pharmaceutical company discovers that a new dosage regimen consisting of administering the drug at 60 mg one day per week increased patient compliance and increased therapeutic effects, they could

\textsuperscript{76}See e.g., Quanta Computer Inc. v. L.G. Electronics, Inc., 553 U.S. 617, 628-629 (2008) (Supreme Court asserted that if the doctrine was not applied to method claims, it would be rendered useless).

potentially patent the new dosing regimen. However, this patent would merely disclose one specific use and leave the design of patient specific dosing regimens to doctors. Unless the patent is able to cover all possible uses and dosing of the drug, it is hard to argue that other individual dosing regimens designed by a doctor will infringe on a patent. Therefore, a risk of patent infringement could only exist where a doctor merely prescribes the doses and follows the provided administration methods of a drug to which he does not have the right to use in the first place.

The UK attempts to address this potential infringement by suggesting that dosing patents be directed at the manufacturers and not at the doctors. This approach seems questionable since the only difference between BMS and Actavis was the language used in the claims. Dosage regimen inventions are usually patents that arise after the properties of the molecule have been more fully understood. They can be improvements for user convenience, patient compliance or market demand. With the exception of new dosage forms directed at the manufacturer, new medical uses are a constituent of the molecule and are naturally directed at doctors. Therefore, if the involvement of doctors is the limitation, the patenting of dosage regimen inventions could be affected despite the relaxation of the novelty requirement. The UK approach, however, seems to be merely a disguised form of the “Swiss-type” claim, allowing the patenting of the process of manufacture rather than the process of use. Doctors or pharmacists in the UK can now only infringe on dosage regimen inventions if they manufacture the dosage themselves.

As the “one-embodiment” doctrine suggests, all of the uses of a drug are covered by the product patent even if the uses are covered by separate patents owned by different patentees. Once a product is sold, the patent rights in both the product and the method of use are exhausted. Hence, no patent infringement for the use of a drug can exist once doctors purchased the drug unless the product patent has expired or is non-existent and the use is patented. Even if doctors might infringe on the dosage patent by using the one of the claimed dosage regimens for the drug, it is hard to argue that patent infringement would exists on variations of the regimen unless the patent can be claimed to cover all possible optimal uses of the drug inside the human body. Allowing such broad coverage could be seen as trying to enclose the whole field and patent protection of this nature are prohibited by patent law.

In personalized medicine, the involvement of the doctor is essential for avoidance of patent infringement. Since dosage regimen patents involve a particular method of treatment that can be easily averted by doctors, the patenting of dosage regimens seems to be directed at generic competitors rather than the doctors. Generic entry in the US requires that the FDA carefully review and approve a drug label or package insert which the generic company must adopt upon filing for ANDA. This label includes information relating to indications and usage, dosage and administration, forms of dosage and strengths, contraindications, warnings, precautions, special populations, drug interaction, and use among specific populations. As a result, careful attention must be given to the patenting of new, non-obvious methods disclosed in the label.

VII. POLICY RECOMMENDATIONS

Current pharmaceutical patent jurisprudence seems to reward the earlier drug discovery stage, but not the drug development stage. In other words, discovering the new molecule is more important than understanding the nature of its properties and how it interacts with the body. This rationale seems to contradict the actual development of drugs and the aims of patent law to foster technology development for the public good. Achievement of patent law policy goals will require that the law adopt a more flexible approach to assist the progression of technology while also providing sufficient rewards to inventors. In coming up with a solution that will help protect both early

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79 See Feldman, supra note 36, at 9 (once the inventor identifies a single use for the product, the inventor may exclude others from the full spectrum of the product. Thus one embodiment provides an inventor with broad range of rights).
80 See e.g., In re Bilski, 545 F.3d 943, 954 (Fed. Cir. 2008) (unless it satisfies the machine or transformation test which determine whether a process is tailored narrowly enough to encompass only a particular application of a fundamental principle rather than to pre-empt the principle itself)
stage and late stage drug discovery inventions such as dosage regimens, three points should be noted: (i) medical use patents are difficult to enforce; (ii) users of dosage regimens are doctors, not manufacturers; and (iii) dosage regimens could help to optimize the clinical effectiveness of drugs.

This article supports the patenting of dosage regimens because of their innovative contributions to science and technology. Not only should these inventions be protected but they should be protected in the same manner and to the same extent as pharmaceutical inventions. Currently, the trend seems to be moving toward liberating the patentability hurdle for dosage regimen inventions. However, one lingering issue is the value of a dosage patent when it can be easily averted by competitors. This is the one reason Japan protects dosage inventions as a product rather than a process. Although dosage regimens are protected as a process in the US and the UK, once a patent is granted, the use will be afforded protection similar to that provided through product patents in Japan.

When optimizing dosage in different patients, the dosing studies could suggest that a particular dosage range is optimal for patients possessing a particular set of genes. Once a gene specific dosage regimen is developed, it could potentially be patented by pharmaceutical companies and used to get around competitor dosage patents. This approach carries the substantial risk that it will not only allow companies to get around the dosage patent, but also help them expand the scope of their own patent leading to a potential monopoly of the entire field. In the seminal case, Myriad Genetics, the BRCA1 breast cancer gene along with a BRCA1 genetic testing method were claimed in four patents granted by the European Patent Office (EPO). These four patents essentially provided Myriad Genetics the exclusive monopoly over all breast and ovarian cancer diagnostic methods, specific mutations and diagnostic kits in all European countries.\(^2\) The patent, EP0705902, not only protects the isolated gene but also the corresponding protein and all future therapeutic uses of the BRCA1 gene. This new approach of combining both a product and a process patent will help provide stronger protection than any single process patent alone. With the growing reliance on personalized medicine, it may be possible to use this strategy to provide broader patent coverage for dosage regimens. This is an area that needs further attention.

This article recommends the following changes in patent protection of pharmaceutical products and their uses:

1. Patent law should preclude over-rewarding the initial discovery of the new molecular structure and also avoid creating a medical method barrier for new and inventive medical uses. The initial discoverer of the novel molecule should be restricted to the properties known at the time of the invention.

2. Dosing regimens should be allowed to be claimed as a component of the product rather than a single process. This, of course, would be in line with Japan’s approach where dosage inventions are protected as products rather than processes in the form of product patents with use limitations.

3. The bar on directing dosage regimen claims toward doctors could be waived since it is evident that doctors are not affected by dosing regimen patents in making clinical decisions. Therefore, dosage patents directed at either doctors or manufacturers will not jeopardize patient’s rights.

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VIII. CONCLUSION

Unlike mechanical science, chemical science is a field that is unpredictable requiring time to improve and to more clearly understand certain inherent properties of drug molecules. In medicine, better predictability and understanding of these properties in the body is necessary in order to provide the highest benefits to the patients. Although pharmaceutical products come with a single predetermined dosage regimen, this may not be the optimal dosage for all patients. Patients with varying genetic profiles can react quite differently toward the same drug resulting in serious contraindications or other complications. Personalized medicine aims to resolve these issues by using genetic information to prevent patients from receiving the wrong drug or the wrong dose. In clinical practice, doctors have been using empirical dosing and dosing algorithms to calculate the appropriate dosage for patients. Pharmaceutical industries are also now seeking to optimize the effectiveness of drugs and to later patent the results of their studies. As similarly observed with other pharmaceutical inventions, the patenting of dosing regimens has been met with great resistance due to a fear that protection of these inventions will restrict medical sovereignty and jeopardize a patient’s right to access the highest quality of care possible.

This article reveals that personalized dosage regimens are essential to the practice of medicine and that at times these regimens can be as important as the drug molecule itself. Yet, current patent jurisprudence tends to reward the initial discovery rather than the later dosage optimization. This article applauds Europe’s more patent-friendly approach toward dosage regimen patenting reflecting the view that a doctor’s right to adjust dosage is not hindered by dosage patents. However, the protection of dosing regimens as processes may only achieve weak patent protection making the patent easy to get around while also making it difficult to enforce. Therefore, while the patenting of dosage regimens might now be more liberated, its effect and value has yet to be seen. To encourage and foster research and development in new dosage regimens, the rights of the initial discoverer of the drug molecule should be limited, dosage regimens should be protected as product inventions, and limitations on doctors should be waived. These changes will then allow patent law to best serve the interest of patients by providing higher quality dosage regimens and the best possible care.