

Inside Views: Why Follow-On Pharmaceutical Innovations Should Be Eligible For Patent Protection

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By Christopher M. Holman *

Despite the important role of intellectual property rights in incentivizing innovation, the patenting of pharmaceutical innovation is frequently accused of impeding access to medicine. Criticism of the prevailing patent regime has focused in particular on patents directed towards follow-on pharmaceutical innovation, i.e., innovation that seeks to improve upon existing pharmaceuticals and their use in treating patients. Patents on follow-on innovation are often derided as “secondary” patents, with the implication that the underlying inventions are somehow lesser in nature than the subject matter claimed in “primary” patents, i.e., the drug active ingredient *per se*. While implicitly acknowledging the legitimacy of primary patents, critics of so-called secondary patents contend that patents on follow-on innovation allow drug innovators to “evergreen” their products, i.e., to extend the period of patent exclusivity beyond the expiration of any original patent on the drug active ingredient, and in doing so contribute to the high cost of drugs, thereby limiting the ability of patients to access the drugs upon which they have come to rely.



In 2015, the United Nations Development Programme (UNDP) issued a document entitled *Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective* (the “Guidelines”), which, in an effort to promote access to medicines, recommends that courts and patent offices implement newly heightened patentability requirements for follow-on pharmaceutical innovation that would be uniquely stringent and largely unprecedented.[1] In 2017, I challenged many of the assertions made in the

Guidelines in an article entitled *In Defense of Secondary Pharmaceutical Patents: A Response to the UN's Guidelines for Pharmaceutical Patent Examination ("Defense of Secondary Patents")*, which provides numerous examples of so-called secondary patents that have withstood validity challenges in the courts and patent offices throughout the world and which were directed towards follow-on pharmaceutical innovation clearly meriting patent protection.[2] More recently, I teamed up with legal scholars Timo Minssen and Eric Solovy in authoring *Patentability Standards for Follow-on Pharmaceutical Innovation ("Patentability Standards")*, an article that reiterates the important role of follow-on pharmaceutical innovation in addressing compelling human health concerns, and which proposes what we consider to be the appropriate standards and criteria to be applied in assessing the patentability of this sometimes underappreciated aspect of medical innovation.[3]

Why Protect Follow-On Innovation?

The attack on secondary pharmaceutical patents is based in part on the flawed premise that follow-on innovation is of marginal value at best, and thus less deserving of protection than the primary inventive act of identifying and validating a new drug active ingredient. In fact, follow-on innovation can play a critical role in transforming an interesting drug candidate into a safe and effective treatment option for patients. A good example can be seen in the case of AZT (zidovudine), a drug ironically described in the *Guidelines* as the "first breakthrough in AIDS therapy." AZT began its life as a failed attempt at a cancer drug, and it was only years later that its potential application in the fight against AIDS was realized. Follow-on research resulted in a method-of-use patent directed towards the use of AZT in the treatment of AIDS, and it was this patent that incentivized the investment necessary to bridge the gap between a promising drug candidate and a safe, effective, and FDA-approved pharmaceutical. Significantly, because of the long lag time between the first public disclosure of AZT and the discovery of its use in the treatment of AIDS, patent protection for the molecule *per se* was unavailable. In a world where follow-on innovation is unpatentable, there would have been no patent incentive to invest in the development of the drug, and without that incentive AZT might have languished on the shelf as simply one more failed drug candidate.

Other examples of important drugs that likely never would have been made available to patients without the availability of a "secondary" patent include Evista (raloxifene, used in the treatment of osteoporosis and to reduce the risk of invasive breast cancer), Zyprexa (olanzapine, used in the treatment of schizophrenia), and an orally-administrable formulation of the antibiotic cefuroxime.

Pharmaceutical development is prolonged and unpredictable, and frequently a safe and effective drug occurs only as a result of follow-on innovation occurring long after the initial synthesis and characterization of a pharmaceutically interesting chemical compound. The inventions protected by secondary patents can be just as critical to the development of drugs as a patent on the active ingredient itself.

The Benefits of Follow-On Innovation

The criticism of patents on follow-on pharmaceutical innovation rests on an assumption that follow-on innovation provides little if any benefit to patients, and merely serves as a pretense for extending patent protection on an existing drug. In fact, there are many examples of follow-on products that represent significant improvements in the safety-efficacy profile. For example, the original formulation of Lumigan (used to treat glaucoma) had an unfortunate tendency to cause severe hyperemia (i.e., redevye), and this adverse event often lead patients to stop using the drug, at times resulting in blindness. Subsequent research led to a new formulation which largely alleviated the problem of hyperemia, an example of the type of follow-on innovation that significantly benefits patients but that which would be discouraged by a patent regime that does not reward follow-on innovation.

Follow-on pharmaceutical innovation can come in the form of an extended-release formulation that permits the drug to be administered at less frequent intervals than the original formulation. Critics of secondary patents downplay the significance of extended-release formulations, claiming that they represent nothing more than a ploy to extend patent protection without providing any real benefit to patients. In fact, the availability of a drug that can be taken once a day has been shown to improve patient compliance, a significant issue with many drugs, particularly in the case of drugs taken by patients with dementia or other cognitive impairments. Extended-release formulations can also provide a more consistent dosing throughout the day, avoiding the peaks and valleys in blood levels experienced by patients forced to take an immediate-release drug multiple times a day.

Other examples of improved formulations that provide real benefits to patients are orally administrable formulations of drugs that could previously only be administered by more invasive intravenous or intramuscular injection, combination products that combine two or more active pharmaceutical agents in a single formulation (resulting in improved patient compliance), and a heat-stable formulation of a lifesaving drug used to treat HIV infection and AIDS (an important characteristic for use in developing countries with a hot climate).

“Evergreening” – an Incoherent Concept

Drug innovators are often accused of using secondary patents to “evergreen” the patent protection of existing drugs, based on an assumption that a secondary patent somehow extends the patent protection of a drug after the primary patent on the active ingredient is expired. As a general matter, this is a false assumption — a patent on an improved formulation, for example, is limited to that improvement and does not extend patent protection for the original formulation.

Once the patents covering the original formulation have expired, generic companies are free to market a generic version of the original product, and patients willing to forgo the benefits of the improved formulation can choose to purchase the generic product, free of any constraints imposed by the patent on the improvement. Of course, drug innovators hope that doctors and their patients will see the benefits of the improved formulation and be willing to pay a premium for it, but it is important to bear in mind that ultimately it is patients, doctors, and third-party payers who determine whether the value of the improvement justifies the costs.

Of course, this assumes a reasonably well-functioning pharmaceutical market. If that market breaks down in a manner that forces patients to pay higher prices for a patented new version of a drug that provides little real improvement over the original formulation, then it is the deficiency in the market which should be addressed, rather than the patent system itself.

For example, if a drug company is found to have engaged in some anticompetitive activity to block generic competition in the market for the original product once it has gone off patent, then antitrust and competition laws should be invoked to address that problem. If doctors are prescribing an expensive new formulation of a drug that provides little benefit compared to a cheaper, unpatented original product, then that is a deficiency in the market that should be addressed directly, rather than through a broadside attack on follow-on innovation. In short, if it is found that secondary patents are being used in a manner that creates an unwarranted extension of patent protection, it is that misuse of the patent system which should be addressed directly, rather than through what amounts to an attack on the patent system itself.

Compatibility with TRIPS

The heightened requirements of patentability proposed in the *Guidelines* not only pose a threat to important follow-on pharmaceutical innovation, but if they were to be adopted could constitute noncompliance with certain international treaties, including

in particular the Agreement on Trade-Related Aspects of Intellectual Property Rights ("TRIPS Agreement"), which the 164 Members of the World Trade Organization (WTO) have agreed to abide by. The TRIPS Agreement requires WTO Members to provide certain minimum levels of protection for patentable inventions, thus placing substantive limitations on the ability of WTO Members to raise the bar for patentability. The TRIPS Agreement in no way sanctions subject matter-specific heightened requirements of patentability; to the contrary, the antidiscrimination provision in the TRIPS Agreement affirmatively precludes such measures. Unfortunately, this point is all too often lost in discussions of international and domestic patent policy.

Best Practices for Evaluating the Patentability of Follow-On Pharmaceutical Inventions

Patentable Subject Matter

In *Patentability Standards* my co-authors and I endorse what we believe to be the proper standards for assessing the patentability of follow-on pharmaceutical innovation, which are essentially the same standards currently being applied in the US, Europe and other nations in compliance with the TRIPS Agreement.

As a general matter, inventions arising out of follow-on pharmaceutical innovation, and in particular the categories of "secondary" invention identified in the *Guidelines*, should be deemed patentable subject matter so long as the various substantive requirements of patentability, including novelty, non-obviousness, and practical utility are satisfied. Although the US Supreme Court's 2012 *Mayo* decision appears to have rendered many diagnostic inventions patent ineligible in the United States, the Court explicitly noted that the decision was not intended to adversely affect the patent eligibility of new methods of using drugs, and the patent eligibility of drugs and drug improvements remains generally noncontroversial in the US. In particular, the *Guidelines'* recommendations that new methods of using a drug should be presumptively treated as patent ineligible "discoveries," and that drug metabolites are not patent eligible because they can be produced by physiological processes, should be rejected. An inventive method of using a drug to treat disease is a significant advance in medicine, not a mere "discovery," and it is a mistake to conflate naturally-occurring metabolites with drug metabolites, which as a general matter are not naturally-occurring molecules and which can in many instances constitute important contributions to medicine in and of themselves.

Utility / Industrial Application

The requirement of utility/industrial application likewise should generally not be an issue for follow-on pharmaceutical innovation, since by their nature these inventions involve a new form or mode of use of a pharmaceutically active chemical entity of known therapeutic potential. It is important to emphasize that compliance with the utility requirement does not require a showing that the follow-on invention provide some beneficial utility not otherwise provided by the prior art. If a follow-on pharmaceutical invention does not provide any significant benefit over the prior state-of-the-art, regulatory authorities and a well-functioning market should ensure that the patent will not significantly impact access to medicine.

Novelty

Under the TRIPS Agreement, an invention can be denied patent protection if, as of the effective filing date, it is not novel (i.e., new) relative to the "prior art," as defined by statute and case law in domestic systems. The prior art consists of publications and other public disclosure of the invention, and under some circumstances encompasses certain non-public uses and offers for sale. Significantly, in order to have effect the prior art generally must enable one skilled in that field of technology to make and use a claimed invention without engaging in undue experimentation.

For example, the generic disclosure of a large group of molecules comprising some common structural core does not necessarily destroy the novelty of each and every molecule encompassed by that disclosure. The rationale behind this approach, which is well-established in jurisdictions such as the US and Europe, is that while a generic disclosure can easily be defined so as to encompass millions and even billions of individual molecules, it does not meaningfully enable the identification, synthesis, and clinical use of a specific molecule falling within the genus that is later found to provide some specific utilitarian benefit not shared by other members of the group.

The *Guidelines* would upset the status quo by declaring patents directed to inventions of this type (referred to in the *Guidelines* to as "selection patents") as generally invalid for lack of novelty. But if a paper disclosure encompassing a large group of molecules, the vast majority of which have never been made or tested, is deemed sufficient to render every molecule falling within the group unpatentable, the incentive for drug companies to invest in identifying and developing a potentially safe and effective pharmaceutical compound falling within the group will be severely dampened. Identifying a specific molecule with the safety and efficacy profile required of a successful human therapeutic is a veritable search for a needle in a haystack, and without the potential for patent protection in cases in which a valuable needle is recovered too many haystacks will remain inadequately searched.

Nonobviousness

This brings us to what most would consider to be the most fundamental and important requirement of patentability, the nonobviousness requirement (i.e., the requirement that an invention embody an inventive step). Not surprisingly, the *Guidelines* focus heavily on the nonobviousness requirement, recommending that patent offices interpret and apply the requirement in a manner that would effectively render most follow-on pharmaceutical innovation presumptively unpatentable; some categories of follow-on innovation, such as a new polymorph with improved properties, or an isolated enantiomer that does not cause the adverse effects associated with the racemate, would be treated as per se obvious and thus entirely excluded from patent protection. These recommendations are based on an oversimplified and highly abstract understanding of pharmaceutical research, and fail to take into account the unpredictability and technical challenges inherent to the research and development of follow-on pharmaceutical innovation.

The criterion for compliance with the nonobviousness requirement is straightforward when stated in the abstract: a claimed invention satisfies the requirement if, and only if, as of the relevant date, i.e. the effective filing date, the invention would not have been obvious to a person of skill in that area of technology, given the state-of-the-art at that time. In practice, the nonobviousness/inventiveness inquiry is highly fact-specific, decided on a case-by-case basis in view of the state-of-the-art at the time of the invention, the knowledge and skill of those working in the field at that time, the extent to which those working in the field would have been motivated to try to make the invention, and the unpredictability associated with that area of technology during the relevant timeframe. The question of compliance with the nonobviousness requirement must focus on the specifics of the invention at hand, rather than relying on the broad categorization of entire categories of invention as either per se or presumptively obvious, the approach advocated by the *Guidelines*.

In assessing whether an invention would have been obvious at the time it was made, it is important to avoid the well-established tendency towards hindsight bias. In retrospect, once an invention has been made and proven successful, there is an inherent tendency of humans to look back and think "I could have thought of that." This is particularly problematic in the context of follow-on pharmaceutical innovation, where it is tempting to assume that a new formulation or new method of using a drug would have been "obvious to try," once that formulation or method has been made, tested, and proven safe and effective. When viewed in the abstract, by a person not actually engaged in pharmaceutical research and development, follow-on pharmaceutical innovation can appear deceptively simple. However, the path to

meaningful follow-on innovation is tremendously challenging, unpredictable, and more often than not results in failure. This explains why so many courts and patent offices around the world have explicitly found patents directed to follow on pharmaceutical innovations nonobvious and patentable.

An invention should only be deemed obvious if the prior art would have motivated one of skill in the art to attempt that invention and would have created a reasonable expectation of success in the attempt. It is not enough to merely show that the skilled person *could* have attempted the invention; the question is whether that person *would* have been motivated to make the attempt. In some cases, invention can lie in the identification and solution of a previously unidentified problem. In other cases, the problem is well known, but the solution requires the inventor to overcome technical challenges that stymied contemporaries in their attempts to solve the problem. Sometimes an invention occurs when the inventor tries an approach that runs entirely counter to conventional wisdom, ultimately proving that conventional wisdom to have been wrong. *Defense of Secondary Patents* provides numerous examples of inventions of this type, explaining how courts have determined such inventions to be nonobvious based on the specific factors at play in each individual case.

Concluding Thoughts

Patent law is primarily concerned with rewarding and enhancing the creation of useful inventions. It is not an instrument that has been specifically designed to address crucial problems relating to ethics, access, health, competition and human rights policies. This is particularly true for the bio-pharmaceutical sector.

It is therefore crucial that patent offices and courts continue to assess the inventiveness of all inventions, including inventions arising out of follow-on pharmaceutical innovation, based on the specific features of that invention when compared to the relevant prior art, rather than adopting the sort of technology-specific presumptions against patentability endorsed by the *Guidelines*. In cases where there are legitimate concerns that patents are being misused in a manner that restricts access to medicine, then that misuse should be addressed directly, rather than through a broadside attack on the patenting of follow-on pharmaceutical innovation *in toto*.

If the patent system is being misused in a manner that is anticompetitive, then antitrust and competition laws should be invoked to address the problem directly. If certain specific types of patent enforcement activities are deemed problematic, they too can be addressed directly. The US patent statute, for example, already provides an

exemption from liability for doctors who use a patented method of medical treatment. This addresses concerns about doctors potentially being sued without depriving medical innovators of patents (which would still be enforceable against a competing medical device company, for example). It would be a mistake to upset the delicate balance of innovation policy embodied in the current consensus patent regime – to do so poses a grave risk of greatly diminishing the pipeline of future medicinal breakthroughs.

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[1] Carlos M. Correa, *Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective*, UNDP (2015) [hereinafter *Guidelines*].

[2] Christopher M. Holman, *In Defense of Secondary Pharmaceutical Patents: A Response to the UN's Guidelines for Pharmaceutical Patent Examination*, 50 *Indiana Law Review* 759 (2017) [hereinafter *Defense of Secondary Patents*].

[3] Christopher M. Holman, Timo Minssen, and Eric Solovy, *Patentability Standards for Follow-on Pharmaceutical Innovation*, 37 *Biotechnology Law Report* 131 (2018) [hereinafter *Patentability Standards*].



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