PATENTS

Negative innovation: when patents are bad for patients

Incentives in patent law have driven innovation into spaces that are affirmatively harmful to patients, and patentees are discouraged from taking steps to improve the product so as to prevent adverse health outcomes.

Patent law in the United States is historically premised on advancing the interests of society. From the store of productive activity available to all, the government restricts some activities for a limited time in hopes this will redound to the benefit of all by incentivizing innovation[1]. The law thereby restricts competition, forgoing the concomitant advantages of the free market, but only during the patent period. After that time, the law expects that competition will enter, driving down prices and spurring new innovation. From this perspective, US patent law centers on the benefit to the public, with the inventor's reward providing the vehicle for accomplishing this jurisprudential goal.

In the health care space, these incentives have resulted in extraordinary success stories, but the same incentives can also result in a range of undesirable consequences, including excessive development of similar (but not better) products ('me-too drugs'), the focus on drugs for diseases that affect wealthy people and wealthy countries rather than diseases that disproportionately affect the poor and developing nations, and a lack of innovation for types of medicines that may return fewer profits, such as antibiotics[2–4]. Similarly, drug companies will not research the utility of a known (and hence unpatentable) chemical, since the ability to obtain patent protection is central to their business model[5].

Past literature has highlighted these problems but has largely overlooked the problem of 'negative innovation', in which patent law drives innovation into spaces that are affirmatively harmful to patients. By this, we mean scenarios whereby patents create incentives to bring a product to market in a way that is relatively harmful to consumers, and the existence of a patent (and the associated rents) discourages the patentee from taking steps to improve the product so as to prevent the adverse health outcomes.

Of course, there are other patent-driven situations of problematic utility, including scenarios that result in purely financial harms, such as drugs that are no better than existing options but are more expensive; scenarios where a small, heightened risk of direct physical harm is offset by lower prices for the drug in question[6]; and scenarios where there is no existing product on the market and inadequate incentives to develop such a product, so any physical harm is the result of the underlying disease or illness[7]. Finally, there is a general concern that inadequate new information about existing products is generated in the current system[8]. All of these scenarios are different in kind from negative innovation, which results in a harmful (but profitable) product. We focus on this dangerous but overlooked space of the patent landscape, wherein patents themselves lead fairly directly to patient harm.

What does negative innovation look like? We highlight a particularly pernicious example, the case of Imbruvica (ibrutinib); suggest the likelihood of broader problems; and outline various strategies for preventing such outcomes going forward.

The case of ibrutinib

Ibrutinib, a small molecule drug discovered by Pharmacyclics (now a subsidiary of AbbVie), is an irreversible inhibitor of Bruton's tyrosine kinase (BTK), a key regulator of B cell signaling and growth. It is approved by the US Food and Drug Administration for multiple indications and is most commonly used to treat B cell cancers, such as chronic lymphocytic leukemia. While ibrutinib is effective, it, like all anticancer agents, is toxic. It is all the more puzzling, then, that ibrutinib's recommended dosage appears to be substantially higher than necessary to achieve the necessary therapeutic effect—or at least, what evidence is available points to that conclusion[9]. Problematic incentives created by the patent system make this result unfortunately unsurprising.

The basic story is disheartening but simple. Early studies published by Pharmacyclics showed efficacy at low doses (partial response at 1.25 milligrams per kilogram body weight, approximately 40% response at 2.5 mg kg^{-1}, and no relationship of response to dose between 2.5 and 12.5 mg kg^{-1})[10]. These reports were shared by Pharmacyclics in a conference abstract in 2009[11,12] and a press release in 2010[13]. An early patent application by Pharmacyclics (US 2012/0087915 A1) accordingly claimed a full range of doses.

Trials to support approval by the US Food and Drug Administration (FDA) continued. In July 2013, ibrutinib received accelerated approval for mantle cell lymphoma based on a 66% response rate in 111 patients treated at 560 mg daily. Notably, the 2013 FDA review included an analysis of the relationship of ibrutinib dose and trough plasma concentration to both response and toxicity. This analysis demonstrated no relationship with response: "Dose-response relationship for BTK occupancy and clinical response in the phase 1 dose escalation trial showed that maximum BTK occupancy and maximum response were achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg)"[14]—far below the approved dosage of 560 mg.

Meanwhile, the FDA also granted accelerated approval for previously treated chronic lymphocytic leukemia on 12 February 2014 on the basis of a 58% response rate in 48 patients treated at a dose of 420 mg daily. Thus, there were now two different doses approved for ibrutinib, with the labeled dose based solely on the dose that was used in the single-arm studies supporting the accelerated approvals. Furthermore, in the context of that approval, the FDA reiterated its assessment that the labeled dose was higher than necessary and included the explicit suggestion to study lower doses: "However, the proposed dose is 2.4-fold higher than the lowest dose that resulted in maximum BTK occupancy and maximum clinical response. Dose-response relationship for ORR and BTK occupancy from phase 1 study suggested that maximum ORR and maximum occupancy was achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg) [see Pharmacometrics review in DARRTS dated 11/01/2013]. The sponsor should thus consider exploring lower doses in future development programs."[15]

Those lower doses have not, to our knowledge, been rigorously explored in clinical trials—an unfortunate outcome for patients, since if a lower dose is just as effective with lower side effects, treatment would be safer and better. However, if the lower dose were found to provide better patient outcomes and resulted in a change in the labeled dose, it is likely that the labeled dose would not be covered by the patent. Thus, generic competitors might be able to enter the market sooner, once the primary compound patent lost exclusivity. In fact, the process at the US Patent and Trademark Office (USPTO) and the limits of the granted patents encourage the patent holder to avoid such information entirely. The patent examiner evaluating Pharmacyclics' method of treatment patents found lower doses obvious on the basis of the 2009 and 2010 conference and press release disclosures, which occurred more than a year before the relevant patent was filed. Only the highest doses—420 mg and higher—were granted in the issued method of treatment patent[16]. Patent law thus created incentives to pursue a higher, more toxic dose rather than the lower doses the FDA suggested be explored. And, adding insult to injury, once the patent was issued with narrower claims covering the high doses only, the drug sponsor not only lacked incentives to explore the possibility of lower doses, it had an active incentive not to explore those doses because evidence that lower doses were safe and effective would sharply reduce the economic significance of the method of treatment patent it had narrowly managed to obtain. The patent holder already knew it could not get protection on a lower dose––the USPTO had rejected lower doses as obvious–– so any evidence of the importance of lower doses would have undermined the value of the company's patent-protected, higher-dose product.

Broader possibilities

Although ibrutinib is only one example, we are concerned that it may be an indicator of a broader problem, one that either lies ahead or is already lurking. More generally, consider combination products with two drugs at fixed dosages. Many treatment method patents exist in which an independent claim specifies a dose, nominally designed to increase patient adherence but often at a much higher cost[17,18]. The result is that a prescriber cannot adjust the dosage for only one of the two drugs or discontinue only one component. It is possible, perhaps likely, that some of these combination regimens mirror the dosage issue with ibrutinib, in which the incentives of the patent system have encouraged the development of a drug in a form that is suboptimal for patient health in certain circumstances. This would not be the first time in history that combination medications have proven problematic. More than 50 years ago, a US Senate investigation found that certain combination antibiotics products—developed in an effort to bring something 'new' to the market—were useless or dangerous[19]. Nor is ibrutinib the only time in history that medications have been sold at higher dosages than appropriate for safety and efficacy. Millions of women received the birth control pill Enovid (mestranol/noretynodrel), containing ten times the necessary dose, before studies pointed to a concerning risk of blood clots[19]. In another sign of negative innovation, Gilead Sciences is alleged to have intentionally delayed a less-toxic version of its HIV medicine until just a few years before the original version's patent expiration[20].

Unfortunately, the pernicious impact of patent incentives described above means that not only are these situations possible, but it is hard to know how frequent or how serious these situations are. Pharmacyclics did not follow the recommendation from the FDA and others to study lower doses. Because its method of treatment patents were tied to the higher dose, they had no economic incentive to do such research—any information on safer dosing outside the scope of the issued claims would undermine the value of their existing patent, and they would be unable to get a new patent for the safer dose on grounds of obviousness. The safety data are starting to emerge anyway, albeit from sources other than the company[9].

Solutions

Designing the right solution to the problem of negative innovation is tricky. Patents that drive negative innovation look much like patents that drive positive innovation. However, we see three possibilities for potential action.

The first approach lies within existing patent law. Patent law includes a requirement that inventions must be "useful." For well over a century, this requirement has been largely moribund; rather than evaluating whether inventions improve social welfare, courts and the USPTO have largely been content to ask whether an invention does something—anything, really—and then to let the market sort out the bad from the good. This approach works well for most consumer goods, but poorly for medical products: the market is deeply fragmented, regulations limit consumer decisions and product substitution, and the 'consumer' is a confused mélange of physician, patient and insurer[21]. One avenue for reform might be to enforce a more rigorous utility requirement for pharmaceutical patents, demanding that they actually improve social welfare relative to the prior art[3,22]. This would not be trivial—among other things, patents are often filed early, while the jury is still out on the magnitude of any benefits, and that magnitude is often hard to measure—but one could imagine a regime that requires certification of likely improvement, followed by a demonstration that the improvement had materialized, on pain of losing the patent[21]. This approach could be combined with a strengthening of postmarketing surveillance (including a default preference for routine phase 4 trials) to evaluate real-world efficacy and cost-effectiveness.

Second, greater coordination between agencies would reduce the problem of negative innovation[23]. Under the current system, innovators can say one thing to one agency and something different to another. More generally, agencies do not know what other agencies are doing: the USPTO is unlikely to know that the FDA has found an approach predictable (or unpredictable) or a method dangerous, or even that clinical trials are under way or a drug has been approved. The FDA, conversely, may not know whether a patent is truly relevant and should be listed as covering a drug or not. Similarly, on a political-economy level, patent applicants can wear down a patent examiner through repeated filings in a way that they simply cannot wear down the FDA[24]. Greater communication among the agencies (and their parent departments) would help resolve these problems and support socially valuable innovations.

Third, the different forms of exclusivity for pharmaceutical products could be linked—and capped. The current jumbled system of compound patents, method of treatment patents, formulation patents, new chemical entity exclusivity, pediatric exclusivity, orphan drug exclusivity and other incentives creates limitless opportunities for gaming the system. Coordinating incentives and limiting the overall exclusivity associated with any one base product could help limit such gaming, though of course this is easier said than done.

Conclusions

Negative innovation causes real harms. Ibrutinib is a case study of the risks that resulted from the ability of Pharmacyclics to game the patenting and drug approval processes. The costs and health consequences are borne by payers (including large self-insured corporations) and cancer patients, who are subjected to

a patent-protected dosing method far in excess of what is required to obtain the desired therapeutic effects—a point that the FDA noted in its initial 2013 review—which may also result in unnecessary cardiovascular toxicities[9]. If we want to prevent repetition, we need to mandate greater coordination between the FDA and USPTO, create robust incentives (including severe penalties) discouraging drug companies from engaging in such conduct, and fix the regulations that allowed and potentially encouraged this outcome.

Of course, all of our proposals involve difficult and complicated issues of implementation. However, if we want to prevent future negative innovation and the associated harms to patients, we need to make some changes. Promoting the progress of Science and useful Arts—the Constitutional purpose of the patent system—demands nothing less.

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Author contributions

All authors contributed extensively to the work presented in the paper.

Competing interests

D.A.H. and M.J.R. are directors of the Optimal Cancer Care Alliance. M.J.R. is also a consultant for multiple biotechnology and pharmaceutical companies, patent litigation consultant and expert witness on behalf of multiple generic pharmaceutical companies, and a co-inventor on a pending patent for low-dose tocilizumab to treat COVID-19.