

The Patent Landscape of Nanomedicines

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1. Introduction

The number of United States (U.S.) Food and Drug Administration (FDA) approved nanomedicines continues to grow at surprising rates, with one firm projecting the global market to reach \$US334 billion within the next decade [1]. While this outlook most likely depicts the rosier possible view of nanomedicines' future, it has been proposed that this projected growth will be due to first generation nanomedicines coming off patent, "follow on" nanomedicines entering the market, and the maturation of second generation nanomedicines in the marketplace [2]. Every one of these potential markets for nanomedicines is inextricably linked with the efficient functioning of the patent system and a smooth patent landscape for nanomedicines. This linkage may spell trouble for the potential for a booming market for nanomedicines, though, as potential pitfalls lurk on the horizon. Many of the issues that plague nanotechnology as a whole have also followed nanomedicines through the patent system, including the U.S. courts. While old problems that were thought to hamper innovation either never materialized or found market solutions, the legislatively crafted solutions these problems have created new potential snags for nanomedicines that were unintended. Even worse, the administrative morass created by a functioning patent system itself can potentially bog down drug development and innovation for years while firms wait to obtain a patent on their novel drug.

2. Nanodrugs: Who is patenting what?

One of the key issues with nanotechnological inventions has been an inability for the U.S. Patent and Trademark Office (USPTO) and other national stage patent offices to define inventions on the

nano-scale. This is no truer for nanotechnology as a whole than nanomedicines specifically. One recent development, though, is that these types of controversies have moved from national stage patent offices into the courts. In 2008, Elan Pharmaceutical International, Ltd. (Elan) filed what has come to be known as the first nanodrug patent infringement suit against Abraxis Bioscience, Inc. (Abraxis) [3]. In this case, Elan claimed that Abraxis' cancer treatment drug Abraxane infringed on U.S. Patents 5,399,363 and 5,834,025, which are respectively drawn to "crystallized anticancer agents" with compounds surrounding them that maintained the average particle size of less than 1000 nm and techniques for intravenous injection of nanoparticles. The crux of this case focused on whether Abraxane contained a "crystalline" formulation of paclitaxel or, as Abraxis claimed in their FDA filings, an "amorphous" formulation of the drug. In the end, the jury sided with Elan, and awarded them \$US55.2 million in damages after 10 days of trial [3]. While Abraxis publicly stated that they would appeal the ruling, they eventually settled out of court for a lump sum of \$US78 million for all past and future infringement [4].

Not all the issues surrounding nanotechnology are doom and gloom. One universal characteristic of innovation in today's world is the interdisciplinary and international character of the teams needed to develop a commercially viable and profitable product. Nowhere is this truer than nanotechnology, and especially with nanomedicines.

In 2016, we searched the specification of patents in the USPTO's Full Text and Image Database for the word "nano" to get a rough estimate of how prevalent international teams of inventors are [5]. Our results covered mostly electronic and semiconductor patents, and showed that

The Patent Landscape of Nanomedicines

roughly 20% of these patents (50 within the first 250) contained internationally diverse groups of inventors. These patents also showed inventors from Korea, the U.S., Germany, Japan, Taiwan, China, Canada, France, and Russia collaborating on patents involving nanotechnology. In 2017, we replicated this study with patents drawn to FDA approved nanomedicines as identified by Tinkle et al. in 2014 [6]. Here, we both consulted the FDA's Orange Book and performed cursory patent searches in Google Patents and Free Patents Online to assemble our list of applicable patents. Our results show that the nanomedicine sphere seems to have a slightly different character of collaboration between internationally diverse inventors. Within the 59 unique patents we identified as drawn to nanomedicines, 49 had used a team of inventors [5]. Out of those 49 patents, 8 of them (16%) had internationally diverse teams of inventors.¹ Furthermore, our nanomedicine patents showed collaboration between inventors from Israel, France, the U.S., Ireland, Canada, Italy, Germany, and South Korea. The slight differences in this data correspond with trends identified in the international biomedical industry as a whole by the Milken Institute in 2011 [7]. While the U.S. still dominates the industry, and has at least one inventor on every diverse team, industrialized countries across the European Union (E.U.), Asia, and even the Middle East are present in a sizable portion of the marketplace [5].

The U.S. Constitution states that the goal of the patent system is to “promote the progress of science and the useful arts,” but history has shown us that this is not always the case [8]. Time and again, critics have decried the patent system as operating

¹ A total of 103 patents were found drawn to nanomedicine patents. Patents with duplicate inventors and disclosures were counted as one patent for this analysis.

contrary to this constructional imperative by throwing up barriers to innovation [9]. Two modern culprits are normally cited as being behind these barriers: patent trolls and patent thickets. Patent trolls, the more infamous of the two, are named after the mythical trolls who lived under bridges and either demanded payment for crossing or attacked travelers. In the same vein, patent trolls are entities who do not practice or produce their patented invention, but instead either extract licensing revenue or sue companies practicing the patent in the marketplace. While many commentators have envisioned the arrival of nanotechnology patent trolls [10], the anxiety surrounding this possibility seems to have been overblown. Extensive searching of the news media, where the majority of stories of patent trolls surface, has turned up absolutely zero incidences of patent trolls attempting to extract their tolls from nanotechnology companies.

This lack of evidence of nanotechnology trolls could be for a couple of reasons [5]. First, a large part of the patent troll business model is based upon remaining hidden. Thus, patent trolls may be out there, but may be structuring licenses in ways that forces licensees to keep them confidential. A confidential license enables the troll to sign licenses from individual companies while at the same time avoiding alerting the industry as a whole. If the industry is put on notice that a troll is actively licensing, they may pool their resources into a unified defense group and challenge the troll's patents. To analogize this to the mythical bridge troll, it's better for the troll to remain hidden under the bridge and demand a payment from smaller groups of travelers because if the travelers band together into a larger group they are harder to fight.

Another reason nanomedicine patent trolls have yet to materialize may be due to the high cost of developing a patentable nanotechnology invention. Patent trolls, who

The Patent Landscape of Nanomedicines

primarily use a speculative patenting strategy, are unable to meet the enablement requirements of § 112 of the U.S. Patent Act, which requires that the inventor disclose in their patent how to “make and use” the invention. Enablement in the nanomedicine sector is an especially high bar to overcome, as it requires the disclosure of what are known as working examples, and working examples are impossible to include in a patent application without including the results of experiments. The result of this is that, in order to file a patent application on a nanomedicine, a patent troll would have had to actually create the nanomedicine in a laboratory and conduct experiments to show that their nanomedicine was operating in the way they claimed. For the vast majority of patent trolls, who are primarily focused on minimizing cost so that they can fund the eventual litigation over their patent, development to the point of producing working examples is just too large of a cost to bear.

Thickets are another classic example of a barrier to innovation created by the patent system, and exist when multiple patents claim rights that are overlapping and can be drawn to the same invention. The theory is that, since no one person can claim sole exclusive rights in an invention, companies who want to bring a product incorporating the invention to market must get licenses from many individuals. This type of barrier is especially prominent in nanotechnology due to the lack of a standardized nomenclature surrounding nano-sized substances, and thus allows clever patent attorneys to obtain patents on the same or substantially similar inventions by simply describing them in a different way. While our previous work has focused on identifying the rough outlines of patent thickets surrounding nanostructures such as buckeyballs, carbon nanotubes and fullerenes [5], we have yet to turn our sights

on identifying a thicket in any type of nanomedicine. Thankfully, the Initiative for Medicines Access and Knowledge (IMAK) identified one for us in 2013 [11].

PEGylation of protein therapeutics was one of the very first methods of producing nanomedicines, and provides a number of benefits including increased solubility, increased stability, reduced immunogenicity, and reduced toxicity. It is no surprise, then, that a thicket has arisen around one of the more profitable PEGylated proteins: PEGinterferon alfa. IMAK’s 2013 patent landscape search discovered no less than 37 U.S. patents and patent applications divided between Roche and that would stand as barriers to a biosimilar PEGinterferon entering the U.S. marketplace [11]. These patent cover everything from the molecular weight of the attached PEG residues, location of the covalent attachment of the PEG residues, methods of producing PEGinterferon, formulations for different routes of administration, combination therapies with other drugs, different PEGylated isomers of interferon, and methods of treatment using PEGinterferon [11]. Given the thickness of the thicket surrounding PEGinterferon, it is not surprising to see patent litigation occurring in an attempt to sort it out.

In 2001, drug makers Schering-Plough and Hoffmann-La Roche settled wide ranging patent infringement suits surrounding the PEGinterferon drugs Pegasys and Peginteron that covered marketing and distribution of the drugs in both the U.S. and the E.U [12]. What is significant about this is not that the two companies settled instead of testing the strength of their patents by going to trial, but that they decided to enter into a cross licensing agreement to settle their dispute. We have previously postulated that the use of cross licensing and patent pools may be one method that nanotechnology companies can use to untangle a patent thicket [5]. Not

The Patent Landscape of Nanomedicines

only does a cross license or patent pool lower the transaction costs of entering the market for the firms involved, but it also is an amazing way to create value for both sides during a testy negotiation surrounding patent infringement litigation. In the end, though, it seems that this deal benefited the newcomer to the market more than the owner of the previous standard of care. Subsequent studies have since shown that Pegasys, owned by Hoffman-La Roche, provides for better outcomes than Peginteron in patients with chronic hepatitis-c [13]. These studies may not have been possible if the patent infringement case had gone to trial, and Hoffman-La Roche was found to be infringing.

While thickets may seem like a purely modern problem, they are actually not new to the patent system. The first identified thicket occurred during the mid-1800's in what has been come to be known as "The Sewing Machine Wars" [14]. In the past, one would have had to resort to the courts to truly untangle a thicket and sort out who owns what rights to a complex invention, but more recently Congress has been taking steps to trim and de-bramble existing thickets before a federal judge gets involved while at the same time fighting patent trolls. In 2011, President Obama signed into legislation the first major patent reforms since the 1905s in America Invents Act (AIA). One of the more significant portions of the AIA was the creation of the Inter Partes Review (IPR) system before the Patent Trial and Appeals Board (PTAB) within the USPO. In an IPR, parties completely unaffiliated with a patent can present some type of disclosure, such as another patent, a scientific paper, or poster presentation, to the PTAB that predates the filing date of the patent in an effort to invalidate the patent. Overall, IPRs were intended to provide a cheaper, mini-trial that

could be performed prior to an infringement suit to test the viability of a patent.

The IPR procedure, while it may have seemed like a good idea in the abstract, has turned into a place where patents go to die due to the lower standards of proof required. During the first three years of filings, IPRs invalidated a little over half of challenged patent claims [15]. Within the biotechnology and nanomedicine landscape, IPRs have been cast in a more sinister light. The Coalition for Affordable Drugs (CFAD) has a noble mission in the abstract: target companies who have weak patents and challenge those patent in an IPR in the hopes of invalidating the patent. Diving below the surface shows that the public interest may not be the only motive behind the CFAD's mission. Run by a notorious hedge fund manager, Kyle Bass, the CFAD has faced accusations of using IPR filings to short sell drug company stocks since its founding. While Bass has not targeted nanomedicines specifically, his penchant for suing over time released formulations has inadvertently drawn PEGylated formulations into his orbit [16].

3. Conclusions

Overall, the patent landscape for nanomedicines looks bountiful when looking at the potential economic benefits, but at the same time perilous when looking at the potential legal issues. Positive aspects, such as international diversity of inventorship, lack of established trolls, and receptiveness of the market to cross licensing may be outweighed by the uncertainty inherent in the IPR system. Further, the next parties who's nanomedicine patents are entangled in a thicket may opt to duke it out in the courts or before PTAB instead of entering a cross licensing agreement, thus throwing the landscape into further tumult. Change may

The Patent Landscape of Nanomedicines

be on the horizon, though, as calls for reform of the IPR system are growing louder by the day [17]. Only time will tell how the patent landscape for nanomedicines unfolds in light of this potential for reform, but if the past is any indication of the future, then

reform will be slow to arrive and the nanomedicine industry will conform to best accommodate the existing patent landscape.

The Patent Landscape of Nanomedicines

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The Patent Landscape of Nanomedicines

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