PATENTS

An administrative fix for manufacturing process patent thickets

Biosimilar manufacturing process patent applications first filed more than a year after the biologic is approved, which represent the largest source of patent assertions in biosimilar litigation, could be addressed without requiring intervention by either the courts or Congress.

As the COVID-19 pandemic has highlighted, strong incentives for biopharmaceutical innovation are critical. While appropriate use of patents serves a salutary incentive role, poor-quality patents granted on information that is not novel or non-obvious, or patents wrongly asserted against non-infringing competitors, deter progress and improperly raise costs on consumers. More specifically, in one category of cases — manufacturing process patent applications first filed more than a year after the drug or biologic is approved — these costs have little to no legal or policy justification. Under black letter patent law, either these patents are invalid or they should not be able to completely thwart competition.

We focus here on branded biologics, which now constitute 43% of US invoice-level biopharmaceutical spending, and for which biosimilar competition has thus far been limited¹. Because complex biologics can be difficult to manufacture, they represent an arena in which manufacturing process patents are pervasive.

We present fresh data on US biosimilar litigation under the Biologics Price Competition and Innovation Act (BPCIA) that show that process patents filed more than a year after US Food and Drug Administration (FDA) approval represent, by a substantial margin, the largest source of patent assertions in such litigation. An antitrust action has recently targeted AbbVie's Humira (adalimumab), citing the company's assertion of certain manufacturing process patents (and other patents) as anticompetitive². The case is on appeal to the US Court of Appeals for the Seventh Circuit. Our data show that the problem is not limited to such isolated cases, but is pervasive.

We also propose a fix that would mitigate the problem at its root without requiring intervention by either the courts or Congress. Under our proposal, information about manufacturing processes submitted to the FDA as part of an originator biologic company's initial application, or in a

subsequent supplement, would be made available to the US Patent and Trademark Office (USPTO) so it could be used in examination of any process application subsequently filed by the originator company in question. As we discuss, this procedure could be executed in a manner consistent with trade secret protection for the information.

Requiring patent examiners, who are already highly time constrained³, to consider more information will impose some costs. However, as we discuss below, costs could be reduced through the creation of a smooth channel of information from the FDA. Moreover, in the case of marketed biologics whose exclusivity term could be substantially extended by additional patents, the social value of considering highly relevant information should be high. Examiners could use this information either to deny the application or to fully clarify its 'metes and bounds' so that it need not be infringed by a potential biosimilar competitor. Savings could accrue both from earlier biosimilar entry and from avoided litigation costs. In the context of small-molecule drugs, for example, studies have estimated that Medicaid alone spends over \$100 million extra annually as a result of delays in generic entry caused by patent litigation⁴. Meanwhile, the cost of district court litigation on the validity of granted pharmaceutical patents can run into the millions of dollars⁵. Even challenging the validity of granted patents administratively at the Patent Trial and Appeals Board can cost hundreds of thousands of dollars. Here, we review the relevant law, discuss our empirical methods and results, and discuss policy implications.

Validity, infringement, and postapproval patents

Validity is fundamental to patent law. We focus here on the dual requirements that granted patents be both novel and non-obvious. As to the former, the invention must not have been known to the world before the priority date of the patent

application (typically the filing date, but sometimes the filing date of an earlier, closely related patent). As to the latter, the invention must also not have been obvious to an ordinary practitioner in the field given what was known as of the priority date (the so-called prior art). We are most concerned here with an inventor's own disclosure. In the United States, an inventor's own disclosure can defeat novelty and non-obviousness, and thus bar patenting, if it occurs more than a year before the priority date.

Notably, under standard US patent law, certain types of secret use by an inventor more than a year before the priority date also represent the type of disclosure that can defeat validity. Since the 1829 Supreme Court case of *Pennock v. Dialogue*⁶, US courts have consistently held that inventors securing commercial advantage through secret use should not be allowed subsequently to layer a patent term onto that secrecy. So if a company — here, a biopharmaceutical company — secretly uses an inventive process to manufacture a commercial product, that manufacturing process is considered to have been used publicly, and be unpatentable, once a year has elapsed since the commercial use began. A 2019 case from the US Supreme Court, *Helsinn v. Teva*⁷, confirmed the continuing viability of this doctrine.

Unlike many requirements of patent law, this black letter law has the virtue of being relatively administrable. Simply put, no patent application filed more than a year after a manufacturing process is put into commercial use may encompass either the process or obvious variations of the process. Nonetheless, this rule does not necessarily translate into practice. Instead, given the time pressure under which patent examiners operate, they may not be aware that prior commercial uses are being made or be inclined to use their adjudicatory powers to ask patent applicants about potential prior commercial uses. Similarly, the relatively remote threat of a subsequent court finding of inequitable

conduct on the part of the patent applicant based on a failure to submit to the USPTO relevant prior art of which the applicant is aware does not appear to have induced voluntary submission of such information. The sample of patent prosecution histories we reviewed in the course of this work indicated that this information was neither submitted nor requested.

For potential competitors facing a patent thicket, manufacturing processes patents are particularly pernicious. When confronted with such a patent, a competitor cannot know whether the examiner simply granted the patent erroneously, lacking knowledge that the process or a related version was already being used commercially, or whether the patent covers a significant, non-obvious postapproval modification that is (by definition) susceptible to being invented around. As a consequence, large numbers of such patents are particularly likely to deter competitive entry. In contrast, with a postapproval patent on (for example) a formulation, the competitor would more clearly know whether the patent covered the therapeutic at the time of approval and would thus have a cleaner path to showing either invalidity or non-infringement.

The case of *Amgen v. Sandoz*⁸ illustrates the dilemma posed by manufacturing process patents. In that case, Amgen filed a patent application on a method of manufacturing its biologic Neupogen (filgrastim) 18 years after filgrastim was approved. Unsurprisingly, this patent was still in force even after Amgen's patent on the filgrastim molecule itself had long since expired. When Sandoz sought approval for its filgrastim biosimilar, Zarxio, it appears to have decided to invent around the patent, using a single purification step instead of Amgen's three.

As it happens, Amgen asserted its manufacturing process patent anyway, arguing that its three-step and the Sandoz one-step method were basically the same. Although the courts rightly rejected Amgen's expansive reading of its patent, the point we make is a more basic one. It is possible that the Amgen patent fell afoul of the novelty and non-obviousness rules mentioned above. But because manufacturing is shrouded in secrecy, it is hard for competitors to know whether they must invent around a process patent, take a risk on challenging it as invalid, or stay out of the market entirely.

Inspired by both *Humira* and the *Amgen v. Sandoz* case, we attempted to ascertain more fully the scope of the problem of postapproval manufacturing process patents.

Methods

We compiled district court litigation from BiologicsHQ⁹ and Big Molecule Watch BPCIA cases¹⁰. We retrieved 28 cases from the Big Molecule Watch listing and 50 cases from the BiologicsHQ listing. We removed overlapping cases manually by cross-referencing between the two lists. The result was a set of 39 unique cases.

To have some level of comparability between cases, we limited ourselves to the standard litigation context of an originator biologic manufacturer suing a follow-on biosimilar approved under the BPCIA. Accordingly, we reviewed the 39 cases manually to identify litigation context. We removed four cases in which this litigation context was not at issue (one case involving molecules approved under the Hatch–Waxman statute, one case involving litigation between biosimilars, one case involving litigation between originator biologics, and one case involving interpretation of the BPCIA). We also removed one case in which the record was under seal. The resulting set contained 34 cases. Although this list may be underinclusive, we know it contains no false positives. We identified the patents asserted in litigation in this set through complaints found on Bloomberg Law (<https://www.bloomberglaw.com>).

For two reasons, we take as our unit of analysis the patent assertion — that is, the assertion of a patent in litigation. First, we want to focus on the amount of potentially avoidable litigation activity associated with patents. Second, because a given patent may be associated with more than one originator product, the question of whether it is a postapproval patent of the type with which we are concerned depends on the biosimilar product against which it is asserted.

The total number of patent assertions in these 34 cases was 552. For each of the patents asserted, we extracted filing dates, priority date, and date of patent grant from Google Patents. We extracted the FDA approval date for each biologic from the Drugs@FDA database¹¹.

Results

Of the 552 patent assertions made in the 34 cases, 349, or 63%, involved patents that had been filed more than one year after the approval of the originator biologic. Thirty-two, or 5.8%, involved patents that had been filed within one year after biologic approval. One hundred and seventy-one, or 31%, involved patents that had been filed before the approval of the biologic.

To further identify the specific type of patent involved, we then examined by hand the titles, abstracts and first claims of all asserted patents. Although a focus on the first claim may unduly simplify the patent (patents can have claims in multiple categories), first claims are typically the broadest and therefore likely to represent what the inventor sees as the most important feature of the patent.

On the basis of this examination by hand, we classified the patents into five categories: active pharmaceutical ingredient, formulation, method of use, manufacturing process and administration device. We were conservative in our use of the manufacturing process classification (for example, in several close cases we called the patent in question a formulation patent).

Nonetheless, by far the largest single category of assertions comprised manufacturing process patents filed over a year after FDA approval (192) (Table 1). In contrast, only 67 assertions of patents filed before FDA approval represented manufacturing process patents. The absolute disparity in assertions was not nearly as high in any other category of patent. In this case, absolute numbers are particularly important as they give a better sense of the magnitude of the thicket created.

Discussion

Better coordination between the USPTO and the FDA could efficiently ensure that manufacturing process patent applications filed more than a year after product approval do not improperly chill competition. In comparison to streamlined information flow from the FDA, the alternative

Table 1 | Patent assertions in district court litigation involving an originator biologic manufacturer suing a follow-on biosimilar approved under the BPCIA

Patent type	Number of assertions: patents filed >1 year after FDA approval	Number of assertions: patents filed before FDA approval
Active pharmaceutical ingredient	0 (0%)	11 (100%)
Composition or formulation	55 (56%)	43 (44%)
Device	29 (100%)	0 (0%)
Method of use	73 (59.3%)	50 (41.7%)
Manufacturing process	192 (74.1%)	67 (25.9%)
Total	349	171

of requiring the examiner to ask the applicant about existing manufacturing processes, and having the applicant itself determine whether it wants to respond fully and accurately, is cumbersome. While inequitable conduct doctrine can be invoked by courts to render unenforceable patents secured through deliberate misrepresentation before the USPTO, defendants alleging inequitable conduct must show strong evidence of specific intent to mislead the USPTO¹².

Importantly, this coordination could be achieved without legislation. In the context of small molecules, the US Department of Health and Human Services is already “authorized and directed, upon request from the [PTO Director] to furnish full and complete information with respect to such questions relating to drugs as the Director may submit concerning any patent application.”¹³ Although this provision does not specifically encompass biologics, it indicates Congressional endorsement of interagency coordination on the issue of biopharmaceutical patent validity. And certainly some level of coordination between agencies is well within the ordinary course of executive branch functioning.

The manufacturing process information that FDA collects in ordinary course could substantially assist the USPTO. Under black letter FDA law, applicants for regulatory approval must provide to the FDA comprehensive information on chemistry, manufacturing and controls (CMC) involved in producing the product. CMC information must also be supplemented to account for any changes to the product that occur after

approval. A memorandum of understanding between the USPTO and the FDA could specify that, for any approved biologic, the FDA would routinely provide to the USPTO the associated CMC information and any subsequent modifications thereto.

Just as the FDA keeps this information a trade secret, the USPTO could establish procedures for keeping the information confidential. While maintaining trade secrecy, the USPTO could profitably use the information to examine subsequent manufacturing process applications by the relevant company. Importantly, because scrutiny using the CMC information would occur at the company level, such scrutiny could not be avoided by attempts to draft process applications without reference to any particular product.

With this system in place, competitors could be confident that any patent that issued did not encompass within its metes and bounds either the process that had been used at approval or obvious versions thereof. Meanwhile, fewer invalid patent applications would issue.

Ultimately, we believe that patents provide important incentives for the development of innovative new biologics — and, for that matter, innovative new biologic manufacturing processes. Those incentives should remain, but where the patents at issue are likely to be inappropriate for completely blocking competition, those weaknesses should be recognized and remedied. Cooperation between the USPTO and the FDA could improve the problematic competitive landscape for biologics and biosimilars, and is worth pursuing.

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Competing interests

The authors declare no competing interests.