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Amgen v. Sanofi: Can an injunction contrary to the public health interest ever properly be granted?

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Frederick Howard Rein, Aviv A. Zalcenstein and Kathleen McGuinness

The recent Federal Circuit decision in *Amgen Inc. v. Sanofi*, 872 F.3d 1367 (Fed. Cir. 2017) raises interesting questions about the role of injunctive relief against an infringing biologic drug. Because the district court enjoined the sale of Sanofi's Praluent® (alirocumab) product despite finding that such a permanent injunction would not serve the public interest, one central issue on appeal concerned the standard for injunctive relief. The question raised was whether all four *eBay* factors[1] should be weighed in a holistic balancing test, or whether one or more of the factors are mandatory in order to obtain the injunction. In dicta, the Federal Circuit suggested that under the facts of the case, the public interest factor, at least, was mandatory, although the decision also cautioned that merely reducing the public's choice of drugs is not enough to foreclose the possibility of injunctive relief. It remains unclear, however, exactly how the public interest (as well as the other *eBay* factors) *should* be analyzed in the context of patent injunctions involving innovative products as opposed to biosimilars or generic drugs. In particular, one question that remains open is whether there is a special, categorical rule that prevents innovative, non-generic, lifesaving drugs from being enjoined because doing so would be contrary to the public health interest.

Background

Amgen v. Sanofi is a patent dispute over claims relating to PCSK9 inhibitor drugs, which treat high levels of low-density lipoprotein (LDL) cholesterol. PCSK9 is a naturally occurring protein which binds to and destroys LDL receptors on liver cells responsible for extracting cholesterol from the bloodstream. In this case, both Amgen and Sanofi[2] independently developed PCSK9 inhibitor biologics—Repatha® (evolocumab) and Praluent (alirocumab), respectively.[3] Both Praluent and Repatha are monoclonal antibodies that bind to PCSK9, preventing it from destroying LDL receptors and enabling these receptors to remove cholesterol from the bloodstream, which lowers LDL levels. Because high levels of LDL cholesterol are associated with higher risk of heart disease, lowering LDL levels is a valuable pharmaceutical research target; while statins are perhaps the best-known class of LDL-lowering drugs, PCSK9 inhibitors represent a newer class of LDL-lowering therapies.

The two companies rushed to be the first to get their products to market. Amgen filed first for product approval with the FDA; in response, Sanofi spent $67.5 million to purchase a third-party priority-review voucher, expediting their review and allowing Sanofi's Praluent to enter the market before Amgen's Repatha. Amgen's Opposition to Defendants–Apellants' Emergency Motion for Stay Pending Appeal and Expedited Briefing ("Opp. to Emergency Mot.") at 2. In response to Sanofi's actions to get its product to market, Amgen filed suit asserting U.S. Patent Nos. 8,829,165 ("the '165 patent") and 8,859,741 ("the '741 patent").

These patents claim a genus of antibodies, which bind to PCSK9 at specific residues and block PCSK9's binding to LDL receptors ("LDLR").[4] For example, Claim 1 of the '165 patent covers "[a]n isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154,... and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR."

Goodwin Procter LLP, New York, NY, USA

Corresponding author:
Frederick Howard Rein, Goodwin Procter LLP, The New York Times Building, 620 Eighth Avenue, New York, NY 10018, USA.
Email: frein@goodwinlaw.com

District Court trial and grant of permanent injunction

The parties agreed to an expedited trial, and Amgen chose not to pursue a preliminary injunction. Corrected Br. for Defendants-Appellants at 11. Sanofi stipulated to infringement, but challenged the validity of the patents on written description, enablement, and obviousness grounds. *Id.* While the litigation was pending, Sanofi launched its Praluent product. Opp. to Emergency Mot. at 1.

In a jury trial, Amgen's patents were not found to be invalid, and the district court denied Sanofi's motions for a new trial and for judgment as a matter of law (which would have the judge overrule the jury verdict). Corrected Br. for Defendants–Appellants at 19. The district court also granted Amgen's request for a permanent injunction against the sale of Praluent, notwithstanding the fact that Praluent was provided in a 75 mg low dose and a 150 mg high dose, compared with Repatha's 140 and 420 mg dosage forms, and according to Sanofi, more than 80% of patients on Praluent were able to hit their LDL target on the low dose. In so ruling, the district court set forth the permanent injunction standard articulated in *eBay*, namely that the party requesting such an injunction must demonstrate (1) irreparable injury, (2) inadequacy of monetary remedies, (3) balance of hardships, and (4) public interest. *See* Memorandum Order, 1:14-cv-10317-SLR (D. Del. 1 January 2017) ("Injunction Op.") at 3 (quoting *eBay*, 547 U.S. at 391.)

The court noted that, *inter alia*, where the companies are direct market competitors or where "the market for the patented technology is volatile or still developing," the argument for irreparable injury and inadequacy of monetary damages is strongest. Injunction Op. at 4. Because both Repatha and Praluent were FDA-approved for the same indication (lowering LDL cholesterol in certain patients), and were the only therapeutics in the still-developing PCSK9 inhibitor market, they were direct market competitors, weighing in favor of an injunction. Injunction Op. at 4–5.

Regarding the first two articulated factors, irreparable harm and remedies at law, Amgen presented evidence of loss of market share. It also argued that Sanofi's marketing of Praluent as "The First U.S. FDA-Approved PCSK9 Inhibitor" was causing unquantifiable harm to Amgen's reputation as the innovator in the PCSK9 market. Amgen also argued that monetary damages would be inadequate because it intended to use its patent to maintain market exclusivity, and because the undeveloped state of the PCSK9 inhibitor market would make monetary damages speculative. Injunction Op. at 5. Sanofi argued that Amgen's status as the first to file with the FDA and the first to receive worldwide regulatory approval mitigated any reputational harm, that Repatha would have faced pricing pressures even without competition from Praluent, and that any reputational harm could be cured by monetary damages. However, the court found that the expert testimony in the case regarding damages did not touch on reputational harm, and that Sanofi did not offer any method of calculation of the same. Accordingly, the court found that these two factors weighed in favor of an injunction. *Id.*

Regarding the balance of the hardships, the court found that both parties had spent "billions of dollars and over a decade of work to bring their respective products to market." *Id.* at 6. If an injunction issued, Sanofi would lose business by being unable to make and market Praluent. And if an injunction did not issue, Amgen would lose market share and face continued competition. Accordingly, the court found that the balance of hardships was neutral. *Id.*

Regarding the last articulated factor, public interest, Amgen relied on "traditional notions of being a patent holder and a verdict winner" while Sanofi emphasized ways in which Repatha might be an imperfect substitute for Praluent especially at certain doses. *Id.* Specifically, Sanofi focused on the facts of this particular case to argue that where, as here, the product at issue was an innovative lifesaving drug, the "public interest" prong implicated concerns of public health, and it would be hard to justify an injunction that deprived the public of a lifesaving drug that exhibited superior properties to what exists on the market. *See* Emergency Motion for Stay Pending Appeal and Expedited Briefing ("Emergency Mot.") at 17, citing *Cordis Corp. v. Boston Sci. Corp.*, 99 F. App'x 928, 935 (Fed. Cir. 2004) (noting that "for good reason, courts have refused to permanently enjoin activities that would injure the public health"). In contrast, Sanofi pointed out that the Federal Circuit in *Apple Inc. v. Samsung Elecs. Co.*, 809 F.3d 633, 647 (Fed. Cir. 2015) recently dismissed an objection to an injunction favoring Apple because "Apple does not seek to enjoin the sale of lifesaving drugs." Emergency Mot. At 17.[5] In a case between two electronics companies such as Apple and Samsung, where the public interest would be in having superior electronics (and not public health), perhaps the public interest prong may just be another factor in the balancing analysis that does not rise to a mandatory level. *See id.* In view of the nature of the technology at issue (i.e., an Food and Drug Administration [FDA]-approved antibody therapy to treat high cholesterol), the district court declined to "substitute its judgment for that of the

FDA" or delve into the issue of the extent to which Praluent patients could seamlessly switch to Repatha. Injunction Op. at 6. Instead, the court noted only that "[t]he public generally is better served by having a choice of available treatments," and held that the public interest "factor weighs in favor of [Sanofi]." *Id.* at 6–7.

Despite finding that the public interest did not support an injunction, the court nevertheless weighed that factor against the other *eBay* factors and granted a permanent injunction against the sale of Praluent. The court, however, delayed enforcement of the injunction for thirty days to allow Sanofi to request expedited review at the Federal Circuit.

Appeal and briefing at federal circuit

Sanofi appealed the issuance of the permanent injunction, as well as several other determinations by the district court. Federal Circuit Opinion at 3. As an initial matter, Sanofi filed an Emergency Motion for Stay Pending Appeal and Expedited Briefing, which the Federal Circuit granted without discussion, preventing the injunction from going into effect while the appeal was ongoing.

In arguing against the injunction (both in its Emergency Motion and its subsequent briefing), Sanofi's position was that the district court had misapplied *eBay*, and that each of the four factors was *mandatory*, not part of a holistic balancing test; in particular, Sanofi emphasized that an injunction against the public interest ought never be granted. Emergency Mot. at 14–15. Amgen, on the other hand, emphasized the flexible nature of injunctive remedies, arguing that no one factor in *eBay* is dispositive, and that no "categorical rules" govern a court's discretion to issue injunctive relief. Opp. to Emergency Mot. at 24.

Arguments on application of the eBay factors

The parties agreed that the Supreme Court's language in *eBay* controlled the analysis of whether to grant a permanent injunction. *eBay* states that "[A] plaintiff seeking a permanent injunction **must satisfy** a four-factor test before a court may grant such relief," and that a plaintiff "**must demonstrate**" the four factors discussed previously. 547 U.S. at 391 (emphasis added). Sanofi's brief focused on the "must satisfy" and "must demonstrate" language of the *eBay* standard, arguing that the language of *eBay* "squarely forbids" any injunction against the public interest. Corrected Br. for Defendants-Appellants at 59–60. It further argued that the nature of equitable remedies prohibits a court from granting an equitable remedy that disserves the public interest, and that the Supreme Court and the Federal Circuit have emphasized the importance of the public interest, particularly in the context of lifesaving drugs. *Id.* at 60–61.[6]

Amgen, on the other hand, argued that *eBay* rejected categorical rules for the issuance of injunctions. It suggested that the sentence from *eBay* that Sanofi quoted should be interpreted as an endorsement of the "traditional four-factor test," which allows the "balancing" of all four factors. Br. of Plaintiffs–Appellees at 81. Because "'flexibility' has always been the 'essence' of the test for injunctive relief," and because several courts had held that no one factor (including the public interest) is dispositive,[7] Amgen argued, the district court's equitable balancing of all four factors should be upheld. Br. of Plaintiffs-Appellees at 81–82 (quoting *Hecht Co. v. Bowles*, 321 U.S. 321, 329 (1944)).

Arguments on the public interest

In addition to their legal dispute over the *eBay* standard, Amgen and Sanofi offered different views over what constituted public interest for purposes of determining whether an injunction should issue. Both parties were supported by *amicus curiae* briefs in support of their factual positions.

Amgen, as the patent holder, argued that "[t]he public interest is served by giving meaning to a patent's exclusionary right" in pharmaceutical cases to encourage innovation, because "[i]f patents are not enforced by injunctions, the business model of an innovative biotech or pharmaceutical company collapses." Opp. to Emergency Mot. at 24–25. AbbVie Inc. filed an *amicus* brief in support of this position, describing the high costs of drug development (particularly for biologics) and the importance of pharmaceutical developers to exercise a "temporary monopoly" on new products in order to generate the funds necessary to develop the next generation of treatments. Brief of *Amicus Curiae* In Support Of Appellees at 24–26.

Sanofi, in contrast, emphasized the ways in which removing Praluent from the market might harm existing patients. In particular, Sanofi emphasized the fact that Praluent (unlike Repatha) is available in a low-dose form preferred by physicians, which can reduce LDL levels to a lesser extent than high-dose Praluent or Repatha. Injunction Op. at 6. According to Sanofi, most doctors treating high LDL cholesterol levels attempt to reduce patients' LDL levels to a target, but also attempt to keep the levels from dropping "too low," which has uncertain medical effects. Emergency Mot. at 5. Accordingly, about 85% of Praluent prescriptions have been for the low dose,

which would avoid the potential complications associated with treatment using too high a dose. *Id.*

Dr. Luis F. Aparicio, MD, a pediatric endocrinologist, submitted an *amicus* brief arguing that all of his patients on a PCSK9 inhibitor, who are currently treated with the low-dosage version of Praluent, would be forced to transition to a higher dosage or stop therapy altogether if the injunction were upheld. Aparicio Amicus Br. in Support of Motion for Stay Pending Appeal at 3. He also argued that "there is no evidence that a patient can safely transition back to the low-dosage version of Praluent after being required to transition to another treatment option," compounding the risks. *Id.* at 3–4. For this reason, his amicus brief urged the Federal Circuit to stay the injunction pending appeal.

Another *amicus* brief in support of the motion to stay was submitted by Dr. W. Ross Davis, MD; Dr. Mary P. McGowan, MD; Dr. Avichai Eres, MD; and Dr. Michael G. Clark, PhD ("Practitioners Who Currently Treat Patients With Praluent" or "Practitioners"). The Practitioners also argued that forcing patients to switch from low-dose Praluent to higher-dose Repatha would be medically unnecessary, and pointed to the "lack of any reliable research" showing that patients who respond to Praluent will respond to Repatha. Response of *Amicus Curiae* Practitioners in Support of Appellants' Motion for Stay Pending Appeal at 7. Dr. Aparicio and the Practitioners also submitted a joint *amicus* brief echoing these arguments in support of the substantive appeal. In that joint brief, they argued also that "[w]hile the public interest will often favor the enforcement of patents, an exception exists where, as here, public health and safety is at stake." Br. for *Amici Curiae* Dr. Luis Aparicio, MD et al. in Support of Defendants-Appellants and Arguing to Vacate The Permanent Injunction at 16.

The AARP and AARP Foundation submitted an amicus brief urging the reversal of the injunction, emphasizing the public importance of access to different treatment options. They argued that because the drugs have different chemical compositions (and are available at different dosage strengths), the variability between individuals in their response to medication constitutes an important public interest that would be disserved by an injunction. Br. for *Amici Curiae* AARP and AARP Foundation in Support of Defendants-Appellants and Arguing for Reversal of Permanent Injunction at 5–6.

Amgen responded that the removal of Praluent from the market would not disserve any members of the public, because Repatha could be substituted. Br. of Plaintiffs-Appellees at 77–80. According to Amgen, because Repatha is approved by the FDA to treat all patients covered by the Praluent label, its product could substitute for the infringing product among all relevant patients. *Id.* at 78. In addition, Amgen argued that the absence of medical evidence that too-low LDL levels have any impact on patient safety showed that Sanofi's was "conjuring an unsubstantiated safety concern" regarding low LDL levels in order to justify the low dose Praluent option. *See* Opp. to Emergency Mot. at 3.

Federal circuit decision

The Federal Circuit ultimately vacated the district court's permanent injunction, granting Sanofi a new trial on the basis of its invalidity arguments. In dicta, the appellate court also appeared to agree with Sanofi that the public interest factor is mandatory in issuing an injunction; that is, where a patentee fails to show that the public interest "would not be disserved by a permanent injunction," no such injunction may issue. Opinion at 22 (quoting *eBay*, 547 U.S. 391.) However, the court also cautioned litigants that "eliminating a choice of drugs is not, by itself, sufficient to disserve the public interest" for the purpose of this analysis, and that there is no blanket policy against issuing injunctions against the sale of infringing drug products. *Id.* at 23.

Conclusion

Although the Federal Circuit's statements on the application of *eBay* were made in dicta and thus not binding on lower courts, they strongly imply that the Federal Circuit will require at least a showing that the public interest would not be disserved by issuance of a permanent injunction. It remains unclear whether the Federal Circuit believes that each of *eBay*'s three other factors—irreparable injury, inadequacy of monetary damages, and balance of hardships—must also be demonstrated independently for an injunction to be appropriate, or whether they may be analyzed more holistically. No subsequent decisions have cited this opinion so far with respect to the question of injunctive relief. As a result, the implications of the Federal Circuit's statement on the proper analysis of the *eBay* factors, and the manner in which future courts choose to interpret its guidance here, remain to be seen.

Indeed, the briefing and decision seem to suggest that the "public interest" prong may fluctuate between being required and being part of a balancing test based on the nature of the product. For example, in a case such as this, where the product at issue was an innovative lifesaving drug, the "public interest" prong implicated concerns of public health, and it would be hard to justify an injunction that deprived the

public of a lifesaving drug that exhibited superior properties to what exists on the market. However, in a case between two electronics companies such as *Apple v. Samsung*, the public interest in having lower-priced or even superior electronics may just be another factor in the balancing analysis that does not rise to a mandatory level. Even enjoining a generic drug would probably not rise to the level of implicating concerns of public health, because all patients who would be receiving that generic could take the branded drug instead. While there would be a benefit to the public in terms of a lower cost, that benefit might not rise to the level of a "public health" concern, and might also be offset by the public interest in encouraging innovation. Accordingly, when the Federal Circuit quoted *eBay* in its decision and said "If a plaintiff fails to show 'that the public interest would not be disserved by a permanent injunction,' then the district court may not issue an injunction," it is possible that the court of appeals may have been referring to this higher level of "public health" concerns, which could have the effect of imposing a categorical rule that an innovative lifesaving drug cannot be enjoined because doing so would be a disservice to public health.

Notes

1. These factors are (1) the existence of an irreparable injury; (2) whether remedies available at law are inadequate to compensate for that injury; (3) the balance of hardships between the plaintiff and defendant; and (4) whether the public interest would not be disserved by a permanent injunction. *eBay, Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006).
2. Sanofi (initially Aventis) and Regeneron Pharmaceuticals, Inc. ("Regeneron") were full partners in developing the pharmaceutical at issue. Corrected Br. for Defendants-Appellants at xi. This article refers to Regeneron and Sanofi together as Sanofi.
3. Both products are the subject of Biologics License Applications (BLAs), used for biologics, as opposed to New Drug Applications (NDAs), used for small molecules. *See* https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf at 2 (Repatha), 1 (Praluent).
4. According to Amgen, the patented monoclonal antibodies "(i) bind to the sweet spot on PCSK9 and (ii) block PCSK9 from binding to LDLR." Br. of Plaintiffs-Appellees at 18.
5. In that case, the appellate court noted: "Given the important public interest in protecting patent rights, **the nature of the technology at issue**, and the limited nature of the injunction, this factor strongly favors an injunction." *Apple*, 809 F.3d at 647 (emphasis added).
6. Sanofi argued that because "the cardinal command of a court of equity is to 'do equity,'" an injunction that the issuing court itself views as contrary to the public interest should be the null set, and that the public interest could hardly be clearer in cases involving public health. *Id.* at 60–61.
7. Amgen cited to, among others, *FMC Corp. v. United States*, 3 F.3d 424, 427 (Fed. Cir. 1993) ("No one factor, taken individually, is necessarily dispositive.") and *Abbott Labs. v. Mead Johnson & Co.*, 971 F.2d 6, 12 n.3 (7th Cir. 1992) ("The public interest is one factor courts must consider in weighing the equities; it is not dispositive.")

Author biographies

Frederick Howard Rein is a partner in the New York office of Goodwin Procter LLP.

Aviv A. Zalcenstein is an associate in the New York office of Goodwin Procter LLP.

Kathleen McGuinness is an associate in the Boston office of Goodwin Procter LLP.