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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, vs. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, Defendants.	Case No. 3:14-cv-04741-RS **NOTICE OF MOTION AND MOTION BY AMGEN FOR A PRELIMINARY INJUNCTION** Date: March 2, 2015 Time: 1:30 PM Location: Courtroom 3, 17th Floor

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NOTICE OF MOTION

TO ALL PARTIES AND THEIR COUNSEL: PLEASE TAKE NOTICE that on March 2, 2015, at 1:30 PM (Dkt. No. 55), Plaintiffs Amgen Inc. and Amgen Manufacturing, Limited (together, "Amgen"), will move this Court for a preliminary injunction under Rule 65 against Defendant Sandoz Inc. ("Sandoz"), based on the Federal Rules of Civil Procedure, the Local Rules of this District, this memorandum, the record and hearing of this proceeding, and any matters of which the Court takes judicial notice.[1]

ISSUE TO BE DECIDED AND RELIEF SOUGHT

As soon as March 8th, Sandoz may begin marketing a copy of Amgen's successful Neupogen® (filgrastim) product. Sandoz is waiting only for FDA approval. It is not, however, waiting to comply with the law. Sandoz will launch its product even though it has not complied with the provisions of the Biologics Price Competition and Innovation Act ("BPCIA") that are designed to protect Amgen, the sponsor (and innovator) of the reference product for Sandoz's biosimilar product. The BPCIA required Sandoz to provide Amgen with a copy of its Biologics License Application ("BLA") and manufacturing information and to participate in a detailed information exchange designed to allow Amgen to commence a patent infringement suit and seek a preliminary injunction before Sandoz's commercial entry. Amgen alleges that Sandoz's use of the FDA license for Neupogen®—which is allowing Sandoz to greatly shortcut the time for development and approval of its own product—while denying Amgen the benefits that the law requires is an unlawful business practice under California Business & Professions Code § 17200 et seq. ("section 17200") and an act of conversion. On March 2nd, the Court will hear argument on the parties' cross-motions for judgment on the pleadings, which will resolve whose reading of the BPCIA is correct. Sandoz has refused to refrain from launching its biosimilar filgrastim until the Court can resolve those motions. As set forth in the accompanying Proposed

[1] Amgen refers to Sandoz Inc. as "Sandoz" in this motion. The Complaint is also against Sandoz International GmbH and Sandoz GmbH, which with Sandoz Inc. is alleged to have acted in concert. Nothing herein is intended to waive claims against the foreign defendants.

Order, Amgen now seeks a preliminary injunction restraining Sandoz from launching its product until the Court decides the pending motions for judgment on the pleadings and, if the Court rules in Amgen's favor on those motions, further restraining Sandoz from commercially manufacturing, using, selling, offering for sale, or importing its biosimilar product until the parties have been placed in the position they would be in had Sandoz complied with the BPCIA. Given the immediacy of Sandoz's proposed unlawful commercial marketing, the irreparable harm that Amgen faces, the public's interest in ensuring compliance with laws, and the equities strongly favoring Amgen, should the Court grant a preliminary injunction?

PRELIMINARY STATEMENT

Amgen brings this motion for a preliminary injunction to prevent Sandoz from entering the U.S. market with a biosimilar filgrastim product, which could happen as soon as March 8th. Because Sandoz's market entry will be unlawful and will irreparably harm Amgen, and because the public interest and the equities favor an injunction to stop that unlawful entry and prevent that irreparable harm, the Court should enter an injunction. That injunction should last until the Court decides the parties' pending motions for judgment on the pleadings, set to be argued along with this motion on March 2nd, and should continue thereafter if the Court agrees with Amgen's reading of the plain text of the applicable law.

This case is about what may be the first FDA approved "biosimilar," roughly akin to a generic but for a biologic product, not a small-molecule drug. Sandoz's estimated FDA approval date for its biosimilar filgrastim product is March 8th, and Sandoz has said it will enter the U.S. market—and compete directly with Amgen's Neupogen® (filgrastim) product—as soon as it obtains FDA approval. The law forbids this. Sandoz seeks FDA licensure under a new statute, the BPCIA, that created an abbreviated approval pathway for "biosimilar" copies of previously licensed biologic products in which the biosimilar applicant references another's pre-existing biologics license, a reference that would otherwise be impossible without the license-holder's permission. *See* 42 U.S.C. § 262(k)(2)(A)(iii)(I); 21 C.F.R. 314.420. That statute imposes obligations on Sandoz and protections for Amgen: contemporaneous with the start of

FDA's consideration of Sandoz's application for biosimilar licensure, Sandoz was required to give Amgen a copy of Sandoz's BLA and information about how it manufactures its biosimilar filgrastim product, and thereafter to engage in a series of detailed exchanges to identify patents that would be at issue if Sandoz were to gain licensure and commence commercial activity in the U.S. *See* 42 U.S.C. § 262(l)(2)-(5). The information exchanges include detailed contentions regarding infringement, validity, and enforceability, and ultimately ensure that Amgen would have adequate time and information to seek a preliminary injunction after FDA licensure and before commencement of commercial activity. That exchange would have proceeded, concurrent with FDA's review of Sandoz's BLA, over some 230 days, culminating in a patent infringement action if necessary. Even after this 230-day period, the obligation to continue the exchanges for newly issued or licensed patents persists. If FDA licenses Sandoz's biosimilar product, the statute affords a further 180-day period before first commercial marketing to give the reference product sponsor (here, Amgen) time to seek preliminary injunctive relief. *See* 42 U.S.C. § 262(l)(8).

Sandoz has refused to comply with the Act. It intends to enjoy the full advantage of the BPCIA's abbreviated pathway and launch its product without having met any of its information-disclosure exchange and timing obligations under the Act. To be clear, Sandoz made a choice: it could have conducted the full complement of pre-clinical and clinical trials for all therapeutic uses on which it seeks FDA licensure, submitted the data from these trials to FDA in its own, full application, and thereby sought licensure without reference to Amgen's license. But Sandoz chose instead the advantages of the abbreviated pathway, including savings of time and cost, and less uncertainty. That decision had consequences, however, that Sandoz refuses to accept, and thus Sandoz has simply decided it does not have to comply with the BPCIA because, it says, the statute's information exchanges are "optional."

For the reasons set forth below and in the accompanying papers, the Court should enter an injunction restraining Sandoz from commercially manufacturing, using, offering to sell, or selling its biosimilar filgrastim product until the Court decides the parties' pending motions for

judgment on the pleadings and, if the Court resolves those motions in Amgen's favor, further restraining Sandoz until the parties are in the same position they would be in had Sandoz complied with the BPCIA (which steps are spelled out in detail in the accompanying Proposed Order). All of the factors favor the grant of an injunction here.

Likelihood of Success: Amgen seeks this preliminary injunction based on its contention that the BPCIA means exactly what it says. The information exchanges in 42 U.S.C. § 262(l)(2)(A) through (l)(5) are not, as Sandoz says, optional. They are mandatory, phrased repeatedly as what Sandoz "shall" do (but did not do) and what Amgen "shall" do (but could not do, because Amgen was denied that opportunity when Sandoz unilaterally determined not to comply with those portions of the BPCIA it found disadvantageous to it). The details of the parties' dispute are explored in the pending motions for judgment on the pleadings. In this brief we merely summarize for the Court's convenience, and address those elements of Amgen's section 17200 and conversion claims that are not addressed in those motions.

Irreparable Harm: The harm here is recognized in the BPCIA itself. Congress expressly forbade biosimilar applicants from putting reference product sponsors in the position in which Sandoz's lawlessness puts Amgen: facing entry of a biosimilar into the marketplace without the ability—the information and the time—to seek a preliminary injunction on the full and relevant breadth of its patent portfolio. That is why the Act specifically directs the disclosure of otherwise confidential information, directs the exchange of patent contentions, and provides time to seek a preliminary injunction before the marketplace is changed by commercial entry of the biosimilar product. As set forth in the accompanying declaration of Amgen's Stuart Watt, Amgen and its subsidiaries are the owners by assignment of more than 1,400 United States patents that have issued since 1998, many of which are directed to manufacturing and purification processes for recombinant proteins. Watt Decl. ¶ 3. Over 400 of Amgen's patents fall into U.S. Patent and Trademark Office's classes and subclasses that could include patents that might be relevant to the recombinant production and purification of filgrastim. *Id.* ¶ 4. While not all of the 400 patents would apply to Sandoz's biosimilar product, some of them

could cover the recombinant manufacture and purification of filgrastim in bacterial cells. *Id.* And there could be even more Amgen patents in other classes and subclasses that could be relevant to the production of Sandoz's biosimilar product or its use. *Id.* ¶ 5. Without reviewing Sandoz's BLA and manufacturing information, Amgen cannot assess which of its patents may apply (including Amgen's manufacturing patents) in order to assert those patents against Sandoz. *Id.* ¶ 6. That is exactly why subsection 262(l)(2)(A) required Sandoz to provide Amgen with not only its BLA but also "information that describes the process or processes used to manufacture the biological product that is the subject of such application." Sandoz, having withheld that information from Amgen for more than six months in the face of Amgen's assertion that Sandoz was in violation of the BPCIA and in the face of this lawsuit, continues to seek the benefit of the abbreviated regulatory approval pathway at Amgen's expense. Specifically, as alleged in Amgen's conversion claim, Sandoz is unlawfully using the safety, purity, and potency determination represented in Amgen's biological license for Neupogen® to gain licensure of Sandoz's own filgrastim product without Amgen's permission or compliance with the BPCIA. *See* Compl. ¶¶ 87-97. If Sandoz is permitted to launch its product without having provided the information and time to Amgen as the statute provides, Amgen will be irreparably harmed by losing the opportunity afforded it under the BPCIA to exercise its exclusionary patent rights and seek a preliminary injunction before Amgen is injured by the entry of Sandoz's biosimilar product. As alleged in Amgen's Complaint, the result of Sandoz's violating the BPCIA is the entry of Sandoz's biosimilar product to directly compete with Amgen, which causes Amgen's injury to its business and property. *Id.* ¶¶ 77-86.

The harm that Amgen faces is irreparable, as often befalls an innovator when a generic (or, here, a biosimilar) version of its product improperly comes on the market. As set forth in the declaration of University of Chicago economist Tomas Philipson, the harm that Amgen faces takes several forms, each irreparable and sufficient to support an injunction:

- **Harm to Research and Development:** Revenue from Amgen's commercial products funds Amgen's research into and development of potentially lifesaving

new treatments, which would be immediately, significantly, and irreversibly harmed if Sandoz's biosimilar filgrastim product were to draw sales away from Amgen's products. The delay or missed opportunity to conduct research or advance development of a product cannot be remedied by a later issued injunction or damage award. Sandoz's entry into the market also could cause the research and development projects of Amgen's highly skilled scientists to go unfunded, compounding the harm by creating risk of losing the scientists. *See* Philipson Decl. Ex. B ("Philipson Report") ¶¶ 20-59, 83-101. The law recognizes this as irreparable harm.

- **Harm to New Products In Their Infancy:** Amgen has recently launched or is poised to launch three new products that are all handled by the same salesforce that markets Neupogen®: (i) an on-body injector for Amgen's Neulasta® product (a long-acting version of filgrastim), which will eliminate the need for chemotherapy patients to return to the clinic the day after chemotherapy to receive their filgrastim treatment (i.e., Neulasta®, Neupogen, or Sandoz's biosimilar filgrastim product), but which requires significant time and effort to train doctors and nurses in its use; (ii) Tvec, a cancer-killing virus currently being studied for the treatment of melanoma and other cancers; and (iii) a new, first-line indication for Vectibix®, a treatment for colorectal cancer. *Id.* ¶¶ 53-54; Azelby Decl. ¶¶ 26-28. If Sandoz launches its biosimilar filgrastim product now, Amgen's sales force will be diverted to competing against Sandoz. They will not be able to devote their attention to these three new products, which are in the critical/sensitive launch stages and need their attention.

- **Price Erosion:** Sandoz's public statements about its pricing plans for its biosimilar filgrastim product suggest that Sandoz plans to harm the public interest while lining its own pockets, irreparably harming Amgen in the process. Sandoz may actually increase the amount that Medicare and private insurance pay, but in a way that also requires Amgen to cut its own prices to maintain market share. And Sandoz's pricing could cause oncologists to prescribe biosimilar filgrastim rather than Amgen's long-acting filgrastim product Neulasta®, causing Amgen to have to lower prices on Neulasta® as well. The price erosion for Neupogen® and Neulasta® would be effectively permanent and irrevocable. If Sandoz were

later compelled to leave the market to comply with the BPCIA, Amgen would be left in the position to accept effectively permanent and irrevocable price erosion, or to damage Amgen's ongoing relationship with its customers by taking a precipitous price increase resulting in irreparable loss of goodwill. *See generally* Philipson Report ¶¶ 49-105; Azelby Decl. ¶¶ 14-25.

- **Damage to Customer Relationships and Loss of Goodwill:** Sandoz's entry into the market may damage Amgen's ongoing relationship with its customers and result in an irreparable loss of goodwill. If Sandoz launches its biosimilar filgrastim and then the Court enters an injunction, Amgen's efforts to enforce its rights will be portrayed as trying to take a medicine off the market. And if Amgen then tries to raise its prices to where they were prior to Sandoz's wrongful entry, Amgen will further harm its goodwill in the market, particularly under reimbursement rules that would likely leave doctors without full reimbursement after the price increase. *See* Phillipson Report ¶¶ 51, 57-59, 93-105.

The Public Interest: We are a nation of laws. The public has no interest in permitting lawlessness. The BPCIA requires an orderly and predictable process for the resolution of patent disputes with the least disruption to the treatment of patients and the ongoing businesses of the companies involved. Sandoz's game of catch-me-if-you-can is a violation of federal and state law, and the uncertainty and disruption it injects into the process is not in the public interest. The public interest lies instead in a stable and predictable process (as set forth in the BPCIA) for resolving patent disputes so as to encourage the continued investment in R&D that produce such patents while also allowing for biosimilar applicants to launch their products after the process for resolving patent disputes has been followed. The public interest also lies in Amgen's successful introduction of new therapeutics, which Sandoz's unlawful activities threaten to impede. *See* Philipson Report ¶¶ 106-128.

Further, Sandoz has repeatedly suggested its biosimilar product is "lower-cost" and a "less expensive version" than Neupogen®. (Dkt. No. 45 at 1, 4, 7, 9, 20.) This is inconsistent with how Sandoz has indicated it may price its products. In the media, Sandoz has suggested it may not price biosimilar filgrastim product below Neupogen®. *See, e.g.*, Winters Decl. Ex. 1,

at 5. If Sandoz prices its product at or above Neupogen®, then Sandoz will be reimbursed at a higher cost to the government than Amgen's reference product. There is no public interest to lining Sandoz's pockets at the expense of the American public.

Balance of Equities: Amgen asks that Sandoz be compelled to follow the federal statute before they engage in commercial activity. The risk to Amgen of an unlawful launch by Sandoz is enormous and irreparable. Sandoz's purported interest, on the other hand, is in launching its product and making money. The risk to it of an injunction until, in the first instance, the court decides the motions it is currently scheduled to hear on March 2nd, is comparatively minor. If the Court rules in Amgen's favor, the risks to Sandoz of a further injunction are simply that it will have to do what the law requires it do. The balance of equities tips strongly in Amgen's favor.

STATEMENT OF FACTS

The parties' pending motions for judgment on the pleadings, (Dkt. Nos. 35, 45), describe in detail Sandoz's refusal to comply with the BPCIA, beginning with Sandoz's submission of its BLA to FDA under 42 U.S.C. § 262(k), the notification by FDA of acceptance of that BLA on July 7, 2014, Sandoz's immediate proposal that Amgen accept terms other than those set forth in 42 U.S.C. § 262(l) as a precondition to Sandoz providing a copy of its BLA to Amgen, Sandoz's July 25, 2014 declaration that it had opted not to provide Amgen with that BLA and manufacturing information within 20 days of FDA's notification of acceptance, as would have been required by 42 U.S.C. § 262(l)(2)(A), and Sandoz's repeated assertions that it provided notice of commercial marketing to Amgen under 42 U.S.C. § 262(l)(8)(A) in the summer of 2014, and thus that the 180-day period under that statute had already run, even though the statute provides that such notice may not be provided until the FDA has issued a license for the biosimilar product, which has not yet happened. (Dkt. No. 35 at 6-7.)

Rather than repeating that chronology, Amgen lays out below where the parties would be at this point in the Subsection 262(l) exchanges had Sandoz complied with the law at the time those obligations accrued, and responds to Sandoz's accusations of delay.

The But-For World in Which Sandoz Complied With the Law

This is what would have happened if Sandoz had complied with the BPCIA. While the FDA was, in parallel, reviewing Sandoz's BLA, and prior to Sandoz's anticipated date of FDA approval on March 8, 2015, all of this would have occurred:

- Sandoz would have provided Amgen with a copy of its BLA and manufacturing information on or before **Monday, July 28, 2014**. *See* 42 U.S.C. § 262(l)(2)(A).
- Amgen would have reviewed that information and provided to Sandoz a list of patents for which Amgen reasonably believes a claim of patent infringement could be asserted, as well as a list of those patents it would be willing to license, within 60 days, or on or before **Friday, September 26, 2014**. *See* 42 U.S.C. § 262(l)(3)(A).
- Sandoz would then have had until **November 25, 2014** to, if it chose, supplement the list of patents with others it believes could reasonably be asserted against it, and to provide for each patent (whether listed by Amgen or Sandoz) either a statement that it would remain off the market until the patent expires or a detailed statement describing, on a claim by claim basis, why the patent is unenforceable, invalid, or will not be infringed by the marketing of Sandoz's biosimilar filgrastim. *See* 42 U.S.C. § 262(l)(3)(B).
- Amgen would then have had sixty days, or until **January 26, 2015**, to respond with a claim by claim assertion of why Amgen believes that each patent will be infringed by Sandoz's biosimilar product and to respond to Sandoz's statements of invalidity and enforceability. *See* 42 U.S.C. § 262(l)(3)(C).
- Thereafter, the parties would have negotiated in good faith which listed patents, if any, should be the subject of an action for patent infringement under 42 U.S.C. § 262(l)(6). *See* 42 U.S.C. § 262(l)(4). If commenced immediately after the exchange above had been completed, the negotiations would have ended **February 11, 2015**.
- If the parties agreed, then Amgen would have had to bring—the statute says "shall bring"; the lawsuit is mandatory—a patent infringement suit on the agreed-on patents within 30 days, or approximately **March 13, 2015** depending on the start date of negotiations. *See* 42 U.S.C. § 262(l)(6)(A).

- If the parties had not agreed on the list of patents to be included in the (l)(6) lawsuit within fifteen days of negotiations commencing, then the parties would have followed the dispute-resolution procedures of subsection 262(l)(5), and would have arrived at a list of at least one patent to be included in the lawsuit within 5 additional days (**by February 16, 2015**), *see* 42 U.S.C. § 262(l)(5), and Amgen would have been compelled to bring the subsection (l)(6) lawsuit on the listed patents **by approximately March 18, 2015**.
- Once the FDA licensed Sandoz's biosimilar filgrastim, then Sandoz would have given notice to Amgen 180 days before the date of first commercial marketing under 42 U.S.C. § 262(l)(8)(A) and Amgen could have used that period to bring a preliminary injunction motion on any patent that was included in the parties' early exchanges of patents under 42 U.S.C. § 262(l)(3), as supplemented in accordance with 42 U.S.C. § 262(l)(7), but not designated for inclusion in the subsection (l)(6) lawsuit. *See* 42 U.S.C. § 262(l)(8)(A), (B).

The most remarkable thing about this but-for-world chronology is how it plays out in the real world: the parties would be almost done by now, before Sandoz's anticipated date of FDA approval on March 8, 2015. They would currently be negotiating the list of patents to be included in the subsection (l)(6) lawsuit. And if the FDA gives Sandoz a license for its product on March 8th, as may happen, Sandoz would give notice to Amgen 180 days before the date of first commercial marketing, and Amgen could seek a preliminary injunction in that period rather than imposing on the Court's limited resources for a preliminary injunction that gives force to the BPCIA in the first place. For each of those patents, Amgen would have received detailed non-infringement, invalidity, and unenforceability contentions from Sandoz, and would have prepared detailed infringement and validity/enforceability positions of its own. The preliminary injunction practice would have been orderly and informed and focused on the patents rather than the BPCIA.

Instead, Sandoz has sandbagged Amgen. It has refused to provide its BLA and manufacturing information, frustrating Amgen's ability to determine which of its many patents it can assert against Sandoz. And Sandoz intends to launch its product immediately upon FDA

licensure, rather than waiting the 180 days required by the law. That is why Amgen brings this motion for a preliminary injunction.

The Timing of Amgen's Motion

Sandoz has complained that Amgen has delayed filing this motion, and should have filed the motion in 2014. The fervor of the charge is exceeded by its inaccuracy. On January 15, 2015, the parties submitted a Joint Case Management Statement in which Sandoz states that it "expects that FDA approval of Sandoz's biosimilar product may occur as early as March 8, 2015, and Sandoz anticipates launch of its biosimilar product immediately thereafter." (Dkt. No. 40 at 4.) It was only in the negotiation of that joint statement, and specifically in an email the previous day, that Sandoz identified March 8th as a specific potential launch date. (Dkt. No. 51-1 ¶ 5.) By then, Amgen had already moved for partial judgment on the pleadings (which it did on January 6, 2015, *see* Dkt. No. 35), and that motion had a hearing date of February 12, 2015, nearly a month before Sandoz's proposed launch. The parties also discussed a preliminary injunction application with the Court at the CMC on January 22nd, and the Court expressed a desire to hear a preliminary injunction application simultaneously with the motion for judgment on the pleadings. But Sandoz not only opposed Amgen's motion on January 23, 2015, it cross-moved for judgment on the pleadings too (Dkt. No. 45.) The parties discussed the possibility of obviating the need for preliminary injunction proceedings by Sandoz agreeing to postpone the launch of its biosimilar product pending resolution of the BPCIA issues by this Court. (Dkt. No. 51-1 ¶ 8.) Those efforts were unsuccessful. (*Id.*) Amgen also asked if Sandoz would provide Amgen and the Court with five business days' notice before launch so that Amgen could seek emergency relief if needed. (*Id.* ¶ 11.) Sandoz did not agree. Accordingly, Amgen now brings this motion, seeking in the first instance a preliminary injunction until the Court can decide the parties' motions for judgment on the pleadings, and thereafter—if the Court agrees with Amgen's reading of the BPCIA—an injunction, as set forth in the accompanying Proposed Order, putting the parties where they would be had Sandoz

complied with the BPCIA. The Court ordered that the parties' motions for judgment on the pleadings and this motion for preliminary injunction be heard on March 2nd. (Dkt. No. 55.)

ARGUMENT

"A plaintiff seeking a preliminary injunction must establish [1] that he is likely to succeed on the merits, [2] that he is likely to suffer irreparable harm in the absence of preliminary relief, [3] that the balance of equities tips in his favor, and [4] that an injunction is in the public interest." *Winter* v. *Natural Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008). The Federal Circuit applies the law of the regional circuit (here, the Ninth Circuit) in reviewing the grant or denial of an injunction, which is an issue not unique to patent law. *See Allergan, Inc.* v. *Athena Cosmetics, Inc.*, 738 F.3d 1350, 1354 (Fed. Cir. 2013).

I. Amgen Is Likely to Succeed on the Merits of Its California Business and Professions Code and Conversion Claims

Counts One and Two of Amgen's Complaint rest in the first instance on an allegation that Sandoz has violated the BPCIA, by refusing to provide its BLA and manufacturing information under 42 U.S.C. § 262(l)(2)(A) and by providing notice of commercial marketing not after FDA approval, as the statute requires, *see* 42 U.S.C. § 262(l)(8)(A), but when it filed its BLA, rendering the 180-day notice period meaningless. *See Sandoz Inc.* v. *Amgen Inc.*, No. C-13-2904, 2013 WL 6000069, at *2 (N.D. Cal. Nov. 12, 2013). The parties' briefing on the cross-motions for judgment on the pleadings fully explores the statute, its plain text, and Sandoz's striking argument that it is free not to comply with the law because it does not want to comply. Amgen does not repeat that briefing here, and instead addresses its likelihood of succeeding at the remaining elements of its section 17200 claim (Count One) and its conversion claim (Count Two) if the Court agrees with Amgen's reading of the BPCIA.

A. Amgen Is Likely to Succeed on its California Business and Professions Code Claim

Sandoz's unlawful refusal to provide the information called for by 42 U.S.C. § 262(l)(2)(A) and premature notice of commercial marketing under subsection 262(l)(8)(A) are acts of unfair competition under section 17200. Unfair competition is "any unlawful, unfair or

fraudulent business act or practice[.]" Cal. Bus. & Prof. Code § 17200. As described in Amgen's motion for judgment on the pleadings, the "unlawful" prong of section 17200 "'borrows' violations of other laws and treats these violations, when committed pursuant to business activity, as unlawful practices independently actionable under section 17200 et seq . . . ." *Farmers Ins. Exch.* v. *Superior Court*, 2 Cal. 4th 377, 383 (1992). "Virtually any law-federal, state, or local-can serve as a predicate for a section 17200 action." *State Farm Fire & Casualty Co.* v. *Superior Court*, 45 Cal. App. 4th 1093, 1102–03 (1996) (abrogated on other grounds by *Cel–Tech Commc'ns, Inc.* v. *Los Angeles Cellular Tel. Co.*, 20 Cal. 4th 163, 180 (1999)).

If the Court agrees with Amgen that Sandoz has violated the BPCIA and that this violation is sufficient to support a section 17200 claim, Amgen will also have to demonstrate standing under Cal. Bus. & Prof. Code § 17204 by proving that Amgen has "(1) suffered an injury in fact and (2) lost money or property as a result of the unfair competition." *Birdsong* v. *Apple, Inc.*, 590 F.3d 955, 959 (9th Cir. 2009). Lost money or property may be shown in "innumerable ways" including "hav[ing] a present or future property interest diminished" or "be[ing] required to enter into a transaction, costing money or property, that would otherwise have been unnecessary." *Kwikset Corp.* v. *Superior Court*, 51 Cal. 4th 310, 323 (2011). Here, Sandoz has diminished Amgen's present and future property interests and required the needless expenditure of funds. Sandoz made clear that it would not provide Amgen with its BLA and manufacturing information pursuant to 42 U.S.C. § 262(l)(2)(A) and said that Amgen would have to file suit in order to protect its rights. Amgen then did so, incurring the cost of this lawsuit, and the cost of this injunction motion, all of which would have been (and should have been) avoided by Sandoz's compliance with the law. And Amgen's future property interests are further reduced by the elements of irreparable harm (detailed below) that will befall Amgen if Sandoz launches its product without giving Amgen the time and information the BPCIA affords it to commence enforcement of its patents and to seek an injunction on any applicable patents before first commercial marketing of Sandoz's biosimilar filgrastim. Sandoz will harm Amgen

through premature competition, price erosion, loss of goodwill, lost research & development opportunities, the risk of losing uniquely qualified employees, and simply lost revenue. Any one of those is sufficient to sustain Amgen's burden of proving a likelihood of success on its Business and Competition Law claim.

B. Amgen Is Likely to Succeed on its Conversion Claim

To succeed on its conversion claim, Amgen must prove (1) its "ownership or right to possession of personal property," (2) Sandoz's "disposition of the property in a manner that is inconsistent with" Amgen's "property rights," and (3) "resulting damages." *Fremont Indem. Co.* v. *Fremont Gen. Corp.*, 148 Cal. App. 4th 97, 119 (2007). Three criteria must be met to recognize a property right: "First, there must be an interest capable of precise definition; second, it must be capable of exclusive possession or control; and third, the putative owner must have established a legitimate claim to exclusivity." *G.S. Rasmussen & Assocs., Inc.* v. *Kalitta Flying Serv., Inc.*, 958 F.2d 896, 903 (9th Cir. 1992).

Amgen's FDA license for Neupogen® meets these requirements: Amgen owns the biological product license to NEUPOGEN® (filgrastim). Winters Decl. Ex. 2, at 2; Winters Decl. Ex. 3. While the BPCIA permits Sandoz to make use of Amgen's FDA license for Neupogen® by reference to it, the right to this use comes with the obligation to provide Amgen with the information at the times dictated by 42 U.S.C. § 262(l). By instead using Amgen's BLA under the BPCIA without also complying with the information-exchange and timing provisions of that very statute, Sandoz used Amgen's FDA license in a manner inconsistent with Amgen's property rights.

In *Rasmussen*, the Ninth Circuit confirmed that this type of act is an act of conversion. There, Rasmussen held a Supplemental Type Certificate (STC) that allowed "an airplane owner to obtain an airworthiness certificate for a particular design modification [of an airplane] without the delay, burden and expense of proving to the FAA that a plane so modified will be safe." 958 F.2d at 903. The defendant, Kalitta, decided to modify a used passenger airplane to cargo use, "a use that would be uneconomical without the modification described in

Rasmussen's STC." *Id.* at 899. Kalitta, however, neither generated nor submitted the requisite information showing that modifications to his planes were safe, nor did Kalitta license the STC from Rasmussen. *Id.* at 899-900. Instead, Kalitta relied on Rasmussen's STC in his application to the FAA to secure an airworthiness certificate for itself, which the FAA then granted. *Id.*

The Ninth Circuit held that Rasmussen stated a claim for conversion based on Kalitta's improper use of Rasmussen's certificate to its own advantage because Rasmussen had a property right in the STC even though it "has value only because it helps secure a government privilege to do something that would otherwise be forbidden." *Id.* at 900-01 (emphasis omitted). "The time, money and effort Rasmussen devoted to obtaining his STC would largely be wasted but for the fact that they generated the data necessary to satisfy the requirements of the Federal Aviation Act and the Code of Federal Regulations." *Id.* at 901. Having determined that the government-issued STC was a property right, the Court found that Rasmussen asserted a valid claim for conversion. So, too, here, where Sandoz improperly uses Amgen's FDA license, Amgen has a valid claim for conversion.

The damages from Sandoz's violation of the BPCIA began immediately upon Sandoz's refusal to comply. Sandoz used Amgen's FDA license to its own advantage, but did not provide Amgen with a copy of its BLA or with information about how it manufactures its biosimilar filgrastim, depriving Amgen of the information needed to assess how to protect its patent rights and thus devaluing those patent rights. Amgen was forced to bear the cost of this lawsuit and this preliminary injunction motion to secure a ruling that Sandoz has to comply with the law, an expense that the existence of a system of laws is intended to avoid. And the damages to Amgen will only continue to grow and accelerate, as it suffers all of the forms of irreparable harm that are described below in Point III. Coupled with the expense that Sandoz's lawlessness has already cost Amgen, any one of these many categories of harm is sufficient to make out a likelihood of Amgen prevailing on its conversion claim.

II. The Balance of Equities Tips Strongly in Amgen's Favor

The balance of the equities strongly favors a preliminary injunction. If Sandoz launches before this Court can decide whether that launch is unlawful under the BPCIA, Sandoz will have unleashed the cascade of harms that the statute was designed to avoid and that Dr. Philipson details. Worse, from the perspective of the judicial system, Sandoz will have deprived this Court of the ability to provide a meaningful remedy. If, on the other hand, this Court grants the preliminary injunction requested but soon finds on the motion for judgment on the pleadings that Amgen's interpretation of the BPCIA is wrong, then the BPCIA will no longer be a bar to Sandoz launching its product. It will have been delayed to permit the Court to rule, but then it will get to launch. Given that the statute itself imposes such a delay, Sandoz should not be heard to complain about complying with the law. The equities all favor Amgen.

III. Amgen Will Be Irreparably Harmed if Sandoz Enters the Market in Violation of the BPCIA

Provided FDA licensure is obtained and maintained, Sandoz will eventually enter the market. But the entire purpose of section 262(l), "Patents," is to ensure that reference product sponsors like Amgen receive the information and the time they need to enforce their patent rights. Sandoz has hidden from Amgen its BLA and its manufacturing information, frustrating Amgen's ability to identify those patents in its portfolio that could reasonably be asserted against Sandoz's manufacture, use, offer for sale, sale, or import into the U.S. of its biosimilar filgrastim product. (The one patent that Amgen has asserted reads on a method of treatment, and Amgen does not yet know the indications for which Sandoz's product will ultimately be licensed.) The irreparable harm question here, then, is whether Amgen will be harmed by Sandoz marketing its biosimilar product now, rather than after (a) the statutory periods inherent in the BPCIA, which together total over 400 days, and (b) expiration of any patents that Sandoz infringes and Amgen could have asserted had Sandoz provided its BLA and manufacturing information.

Sandoz seeks to whitewash its disregard of the statute by asserting that the patents that cover Neupogen®'s composition of matter have long expired. That tells only the smallest part

of the story. As set forth in the accompanying declaration of Amgen's Stuart Watt, over 400 of Amgen's patents fall into U.S. Patent and Trademark Office's classes and subclasses that could include patents relevant to the recombinant purification or production of filgrastim. Watt Decl. ¶ 4. While not all 400 patents would apply to Sandoz's biosimilar product, some could cover the recombinant manufacture and purification of filgrastim in bacterial cells. *Id.* There could also be other Amgen patents in other classes and subclasses that could be relevant to the production of Sandoz's biosimilar product or its use. *Id.* ¶ 5. Without reviewing Sandoz's BLA and manufacturing information, Amgen cannot assess which patents it can assert against Sandoz. *Id.* ¶ 6. If Sandoz unlawfully launches its product without having provided the information and engaged in the processes that the BPCIA required, Amgen will be irreparably harmed by losing the statutory right to assess and enforce its patents for injunctive relief prior to commercial entry. "[T]he essence of a patent grant is the right to exclude others from profiting by the patented invention." *Dawson Chem. Co.* v. *Rohm & Haas Co.*, 448 U.S. 176, 215 (1980) (citing multiple Supreme Court cases). The harm to Amgen is more than monetary, it comes in all the forms the cases recognize, and it is irreparable.

A. Disregarding the BPCIA Timeline Causes Irreparable Harm

The BPCIA expressly forbids Sandoz from putting Amgen in its current position. Sandoz is poised to launch a biosimilar version of Amgen's product, but Sandoz has hidden away the information that Congress mandated Sandoz provide so that Amgen could act against Sandoz, if necessary to protect Amgen's patent protected inventions.

Concurrent with FDA review of a biosimilar application, the BPCIA contemplates an orderly process to resolve patent disputes, starting with the subsection (k) applicant (here, Sandoz) providing its BLA and manufacturing information to the reference product sponsor (here, Amgen) within 20 days of the FDA's acceptance of the BLA. Without that information, the reference product sponsor is in the dark about fundamental facts needed to identify and select the patents that could reasonably be asserted against the biosimilar applicant: what are the

specific and relative amounts of the biologic's formulation? How is it made? How is it purified? How is it intended to be administered?

That is why the BPCIA mandates this early disclosure, followed by an exchange of the parties' respective patent positions, negotiations, and a lawsuit—a process that concludes with a 180-day period, after the FDA approves the application, for the reference product sponsor to seek a preliminary injunction, if warranted. The entire purpose of subsection 262(l) is to drive communication, negotiation, and—in the absence of resolution—orderly litigation with time for injunction practice.

If Sandoz launches its product without giving Amgen the required notice and without participating in the required information exchanges, Amgen is harmed—irreparably—by being foreclosed from seeking preliminary injunctive relief on its patents before the exclusionary right has been infringed. To be sure, Sandoz will have to produce its BLA and manufacturing information in discovery. But that is inherently too late for preliminary injunctive relief, and it works the very harm the statute is designed to avoid.

The Court should enjoin Sandoz from launching its product until it determines whether Amgen's or Sandoz's reading of the BPCIA is correct. If Amgen is correct, then Sandoz should be compelled to follow all of the provisions of that statute prior to commencing commercial marketing of its biosimilar filgrastim product. To permit Sandoz to launch without giving Amgen the protections of the BPCIA would irreparably harm Amgen. Once a "statutory entitlement has been lost, it cannot be recaptured." *Apotex, Inc.* v. *FDA*, Civ.A. 06-0627 JDB, 2006 WL 1030151, at *17 (D.D.C. Apr. 19, 2006), *aff'd*, 449 F.3d 1249 (D.C. Cir. 2006).

B. Premature Competition From Sandoz Will Harm Amgen Irreparably

The accompanying report of Tomas Philipson substantiates the irreparable harm that Amgen faces if Sandoz enters the marketplace in violation of the BPCIA. *See generally* Philipson Report ¶¶ 15-19 (summary of opinions), 20-128. The result of Sandoz's unlawful conduct is that Amgen faces each of these independent forms of irreparable harm:

1. Irreparable Harm to Research and Development

Amgen—unlike Sandoz—is an innovator. It invests substantially to develop novel, potentially life-saving products through primary research and development. Revenue for that research comes from Amgen's commercial products, including Neupogen® and Neulasta®. That research will be immediately and irreversibly harmed if Sandoz's biosimilar filgrastim draws sales from Amgen's products. *See* Philipson Report ¶¶ 20-59, 83-101. The missed opportunities in research or development of a product could not be remedied later by an injunction or an award of damages. In addition, Sandoz's entry into the market could cause Amgen to have to lay off the highly skilled research and development scientists whose projects would now go unfunded. This is irreparable harm: "[D]amage caused by a loss in personnel and the impact this would have on [a] company are indeed significant and unquantifiable." *AstraZeneca LP* v. *Apotex, Inc.*, 623 F. Supp. 2d 579, 612 (D.N.J. 2009), *supplemented*, 623 F. Supp. 2d 615 (D.N.J. 2009) and *aff'd*, 633 F.3d 1042 (Fed. Cir. 2010).

In the preliminary injunction context, the law must guard against that outcome. In *Bio-Technology Gen. Corp.* v. *Genentech, Inc*., the Federal Circuit affirmed the finding of irreparable harm based in part on Genentech's being "required to reduce its research and development activities" and because of the loss of revenue that would occur absent an injunction. 80 F.3d 1553, 1566 (Fed. Cir. 1996). Another court noted that "a significant disruption or loss of research that otherwise would have been sponsored or completed by [plaintiff] as well as a scaling back of investment in research and development which otherwise would not have occurred" are losses that cannot be "adequately compensated by a monetary payment." *Eli Lilly & Co*. v. *Teva Pharm. USA, Inc.*, 609 F. Supp. 2d 786, 812 (S.D. Ind. 2009). Irreparable harm has also been found in the context of a permanent injunction when "a reduction of revenue would subsequently impact [a pharmaceutical company's] ability to allocate its resources to product development." *Pozen Inc.* v. *Par Pharm., Inc.*, 800 F. Supp. 2d 789, 824 (E.D. Tex. 2011) *aff'd*, 696 F.3d 1151 (Fed. Cir. 2012).

2. Irreparable Harm to New and Emerging Products

Amgen is launching or poised to launch three new products that, like Neupogen® and Neulasta®, are all handled by Amgen's Oncology Salesforce: (i) an on-body injector for Amgen's Neulasta® product, which launched last month and will allow chemotherapy patients not to have to return to the clinic the day after chemotherapy to receive Neulasta®; (ii) Tvec, a genetically-engineered cancer-killing virus currently being studied for the treatment of melanoma and other cancers, a product that is expected to launch later this year; and (iii) Vectibix®, which received approval for first-line treatment of colorectal cancer within the past year. The sales, marketing and educational support for products at the beginning of their lifecycle is crucial to the success, revenues and profits of these products, and is handled by the same salesforce that supports Amgen's Neupogen® and Neulasta® products.

In response to unlawfully premature Sandoz sales, Amgen would have to divert sales, marketing and educational support from these products to Neupogen® and Neulasta® to mitigate the risk of share loss and additional erosion in price. The on-body injector, for example, requires in-person training of the nurses who will put the injector on chemotherapy patients, training that will be hindered by the diversion of Amgen's sales force. Tvec, too, is expected to involve significant provider training. This diversion means that the new Amgen products will not be as successful as they otherwise would have been had there been an effective launch. The harm to Amgen from reduced revenues for the new products would likely be long-lasting. And, to the extent that the diversion of support from these new products to Neupogen® and Neulasta® would result in the ineffective use of these new products, or the failure of providers to adopt these products, public health could be harmed. *See* Philipson Report ¶¶ 49, 53-59, 83-93; Azelby Decl. ¶¶ 26-28.

The outcome that Sandoz's gambit seeks to achieve is particularly perverse given the enormous expense and risk that bringing a new therapeutic to market entails. As Dr. Philipson explains, only two out of every ten approved drugs ever recoup their R&D costs; it is the "blockbuster" therapeutics, such as Neupogen®, that enable biopharma companies to fund the highly uncertain R&D to bring new products to market. Philipson Report ¶¶ 32-36. The

funding for that effort will in part come from Neupogen® revenues streams. *Id.* ¶¶ 37-43. Sandoz's proposed course of action would divert those revenue streams, just as they were about to have their most pronounced effect: to introduce new therapeutics into the market.

In short, Sandoz's use of Amgen's biological license for Neupogen® to gain an FDA license to enter the marketplace in competition with Neupogen® would reallocate Neupogen® revenue to Sandoz not only at the expense of Amgen, but at the expense of patients awaiting the innovating new therapies Amgen seeks to provide. That is not an outcome the law should encourage, particularly in the preliminary injunction context.

3. Irreparable Price Erosion

Sandoz has not publicly stated precisely how it will price its biosimilar figrastim product. If Sandoz were to price lower than Neupogen®, this pricing would raise the concerns about price erosion that courts recognize as irreparable harm where generic drugs launch in contravention of patent rights and are later enjoined. *See Abbott Labs.* v. *Sandoz Inc.*, 544 F.3d 1341, 1361-62 (Fed. Cir. 2008). *See generally* Philipson Report ¶¶ 49-105; *see* Azelby Decl. ¶¶ 14-25. But during the Advisory Committee meeting with FDA in January, FDA reportedly asked Sandoz to confirm that it would price below Neupogen® and Sandoz refused: "Sandoz would not state it would price the product, . . . below Neupogen[®]." Winters Decl. Ex. 4, at 2. Instead, Sandoz equivocated with "[w]e can't say that the price will be less because in some situation[s] the price will be at parity." Winters Decl. Ex. 1, at 5. Sandoz has elsewhere suggested that it would not make the "mistake" it has previously made pricing follow-on biologic Omnitrope below the reference innovator's therapeutic. Winters Decl. Ex 5, at 1-2.

If Sandoz intends, as it has suggested, to price its product at the level of Neupogen®'s Wholesale Acquisition Cost, or WAC price, and then offer doctors discounts or rebates from that price, Sandoz will harm the public interest and irreparably harm Amgen in the process. As Professor Philipson explains, Medicare (and most private payors') reimbursement to doctors for oncology medications is at Average Selling Price ("ASP") plus 6% rather than the WAC price. However medications newly introduced into the marketplace won't have an ASP for 6-9 months

after launch, so Medicare uses the WAC price to set reimbursement in the meantime. If the WAC price of the newly introduced product is greater that the ASP price of the incumbent, Medicare pays more for the newly introduced product.

As an illustrative hypothetical, assume that Amgen's WAC for a vial of Neupogen® is $100 and its ASP is $85. A doctor pays Amgen $85 for a vial, and the doctor is paid $90 by Medicare to reimburse the doctor (because $90 = 106% of $85), and thus profits $5. Because Sandoz's product is new to the market, however, it will have no ASP for six to nine months. In the meantime, Medicare (and most private payors) will reimburse doctors at Sandoz's listed WAC price plus 6% of Amgen's ASP. If Sandoz prices at Amgen's WAC price, the doctor will pay Sandoz $100 for a vial, and receive $105 dollars from Medicare (because $100 + (6% of $85) = $105). The doctor will thus make the same $5, but Medicare will have to pay $15 more for Sandoz's product ($105) than for Neupogen® ($90). Then, to drive sales over the crucial first six months, Sandoz could offer rebates to the doctor of, hypothetically, $10. Now the doctor pays Sandoz $100 for the filgrastim biosimilar, receives $105 from Medicare to reimburse the cost of the medicine, and gets a $10 rebate back from Sandoz. The doctor has made $15 rather than the $5 she would get for prescribing Amgen's Neupogen®, while the government and the public (in the form of Medicare) have paid $15 instead of $5, and the patient has seen no additional therapeutic benefit for the added cost to Medicare. Amgen would then have to cut its own prices on Neupogen® or risk losing sales to Sandoz.

Indeed, as Professor Philipson explains, Amgen may also have to cut its prices on Neulasta®, the long-acting form of filgrastim. Philipson Report ¶¶ 71-78. Right now, Amgen strives to provide pricing and discounts that leave healthcare providers to make choices between Neulasta® and Neupogen® based on clinical considerations. Sandoz, lacking a long-acting product, will have the incentive to price its short-acting product in a manner that draws sales from patients currently receiving Neulasta®. To counteract the risk of losing share Amgen could have to cut the price of Neulasta® as well. The price erosion for Neupogen® and Neulasta® would be permanent and irrevocable, as Professor Philipson explains. *Id.* ¶¶ 94-97.

The law recognizes this price erosion as irreparable harm to Amgen. As one court noted, "price erosion" is a "type[] of harm that traditionally [has] qualified as not easily compensable by money damages." *Antares Pharma, Inc.* v. *Medac Pharma, Inc.*, Civ.A. 14-270 SLR, 2014 WL 3374614, at *8 (D. Del. July 10, 2014) *aff'd*, 771 F.3d 1354 (Fed. Cir. 2014). Another district court elaborated on this principle by describing "irreversible effects" when the introduction of a generic product led to less favorable tier pricing, including "difficulty persuading third-party payors to restore the original tier placement." *Sanofi-Synthelabo* v. *Apotex Inc.*, 488 F. Supp. 2d 317, 342-43 (S.D.N.Y. 2006) *aff'd*, 470 F.3d 1368 (Fed. Cir. 2006).

4. Irreparable Damage to Consumer Relationships and Goodwill

Sandoz's premature entry into the market may irreparably damage Amgen's relationship with its customers and goodwill. *See* Philipson Report ¶¶ 51, 57-59, 93-105. If Sandoz launches its biosimilar filgrastim and the Court then enters an injunction, Amgen's enforcing its rights will be portrayed as taking a medicine off the market. If Amgen tries to raise its prices to their level before Sandoz's wrongful entry, Amgen's goodwill in the market will be further harmed, particularly where reimbursement rules would likely provide doctors less than full reimbursement for the new cost of Medicare after the price has been restored. In the context of patent litigation, "[t]here is no effective way to measure the loss of sales or potential growth—to ascertain the people who do not knock on the door or to identify the specific persons who do not reorder because of the existence of the infringer." *Celsis In Vitro, Inc.* v. *CellzDirect, Inc.*, 664 F.3d 922, 930 (Fed. Cir. 2012). Here too, there is no effective way to quantify the effect of Sandoz's entry into the market on Amgen's reputation—all the more reason to conclude the harm is irreparable.

IV. The Public Interest Favors the Entry of an Injunction

Sandoz wants to disregard a statute enacted to govern commercial behavior in an area as important to the national economy as healthcare. There is an overriding public interest in barring Sandoz from doing so that should be dispositive. *See* Philipson Report ¶¶ 106-128.

Makers of generic drugs argue that the public interest weighs against an injunction because lower priced generics are good for society. Sandoz has continued that tradition in this case by repeatedly suggesting that its biosimilar product is "lower-cost" and a "less expensive version" than Neupogen®. (Dkt. No. 45 at 1, 4, 7, 9, 20.) Courts actually reject that argument because, as the Federal Circuit observed in affirming a preliminary injunction, there is a strong public interest in encouraging investment in drug development, and that fact that a copyist may sell at a lower price does not override that important concern. *Sanofi-Synthelabo* v. *Apotex, Inc.*, 470 F.3d 1368, 1383-84 (Fed. Cir. 2006). Likewise, just as selling a lower-priced copy does not justify the disregard of the statutory ability to exclude that a patent confers, *Pfizer, Inc.* v. *Teva Pharm., USA, Inc.*, 429 F.3d 1364, 1382 (Fed. Cir. 2005), selling a lower-priced copy cannot justify the wholesale disregard of the federal statutory scheme that provides the innovator with the right to assess and then assert the appropriate patents—and provides the court with the ability to assess those patent disputes in orderly fashion.

Here, though, Sandoz should not be heard to argue anything about the public interest. It has suggested publicly that it will price its biosimilar filgrastim product at or above Amgen's Wholesale Acquisition Cost for Neupogen®. Offering a biosimilar copy of an existing product at a higher cost to Medicare is not benefitting the public.

Finally, there are additional important equitable considerations in this case: Sandoz's unlawful activities threaten to impede Amgen's successful introduction of therapeutics into the market, including an on-body injector for Neulasta® which can be implanted on chemotherapy patients at the time of their chemotherapy, thus removing the need for patients to return to oncology clinics the day after chemotherapy. Surely the public interest favors the use of the Court's equitable powers to allow new therapeutics to come to market unimpeded.

V. Amgen Should Have to Post At Most a Nominal Bond

The Court has wide discretion in setting a bond amount, including no bond at all. Sandoz bears the burden of showing that it will suffer damages from a wrongfully entered preliminary injunction. *See Conn. Gen. Life Ins. Co.* v. *New Images of Beverly Hills*, 321 F.3d

878, 882-83 (9th Cir. 2003). The Ninth Circuit has recognized that in cases involving the public interest, it is appropriate to require only a nominal bond or no bond at all. *See Save Our Sonoran, Inc.* v. *Flowers*, 408 F.3d 1113, 1126 (9th Cir. 2005); *Van De Kamp* v. *Tahoe Reg'l Planning Agency*, 766 F.2d 1319, 1325-26 (9th Cir. 1985). A bond provides a remedy for defendants if an injunction is improperly issued, and the defendant's remedy is then limited to the amount of the bond.

This case involves a public interest: it is about the willful violation of federal law. The biosimilar industry is waiting to see the outcome of this case, as the Court's decisions on this motion and the co-pending 12(c) motions may affect and perhaps set strategy for that industry.

Moreover, Amgen asks for very limited relief: that Sandoz not be permitted to launch its biosimilar filgrastim product while the Court considers the co-pending 12(c) motion, and if the Court resolves those motions in Amgen's favor, thereafter until Sandoz has completed the information exchanges and commercial-marketing notice required by the BPCIA. For at least the period until the Court rules on the pending 12(c) motions, Sandoz can articulate no damages; it has not even received FDA licensure yet, nor publicly announced its selling price, nor lost so much as a single sale. For that period, then, Amgen respectfully submits that the injunction should issue without bond, or with a nominal bond. Amgen will of course be prepared to discuss a larger bond should the Court issue a longer injunction and should Sandoz demonstrate harm that would befall it from such an injunction.

CONCLUSION

The Court should grant a preliminary injunction restraining Sandoz from engaging in the commercial manufacture, use, offer to sell, sale within the United States, or importation into the United States of its biosimilar filgrastim product:

(1) until the Court decides the parties' motions for judgment on the pleadings and,

(2) if the Court resolves those motions in Amgen's favor, until, as set forth in detail in the accompanying Proposed Order, the parties have been placed in the position they would be in had Sandoz complied with the BPCIA.

Date: February 5, 2015

/s/ Vernon M. Winters

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, vs. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, Defendants.	Case No. 3:14-cv-04741-RS **DECLARATION OF STUART WATT IN SUPPORT OF AMGEN'S MOTION FOR A PRELIMINARY INJUNCTION**

I, Stuart Watt, declare and state as follows:

1. I am an attorney and Vice President, Law and Intellectual Property Officer at Amgen, Inc. ("Amgen"). I submit this declaration in support of Amgen's Motion for a Preliminary Injunction against Sandoz, Inc. ("Sandoz"). I am personally knowledgeable about the matters set forth in this Declaration and, if called upon to do so, I could and would competently testify to the following facts set forth below.

2. I understand that Sandoz is poised to enter the oncology market with a biosimilar version of Amgen's Neupogen® (filgrastim) product, which Sandoz has said will be named Zarxio. I further understand that Sandoz has not provided Amgen with a copy of the Biologics License Application ("BLA") and, as set forth in 42 U.S.C. § 262(l)(2)(A), "such other information that describes the process or processes used to manufacture the biological product that is the subject of such application."

3. Amgen and its subsidiaries are the owners by assignment of more than 1,400 United States patents that have issued since 1998. A good number of those issued patents are directed to manufacturing and purification processes for recombinant proteins. The United States Patent and Trademark Office classifies and subclassifies patents based on subject matter. Using that classification system, I located several classes and subclasses that could include patents that might be relevant to the recombinant production and purification of filgrastim, including the following:

- 435/69.1 Recombinant DNA technique included in method of making a protein or polypeptide
- 435/243 Micro-organism, … process of propagating, maintaining or preserving micro-organisms or compositions thereof; … culture media therefor
- 435/252.1 Bacteria or actinomycetales; media therefor
- 435/252.3 Transformants (e.g., recombinant DNA or vector or foreign or exogenous gene containing, fused bacteria, etc.)
- 530/412, 416, 417 Separation or purification of protein

4. Amgen has more than 400 patents issued since 1998 that fall within the above-listed USPTO classes and subclasses. While many of those patents would clearly not apply to the production of Zarxio, because they are either specific to proteins or classes of proteins other than filgrastim (including, for example, patents on purification of antibodies) or are specific to recombinant production of proteins in eukaryotic (for example, mammalian) cells as opposed to the bacterial cell production which Amgen uses to produce filgrastim and I suspect is used by Sandoz to produce Zarxio, some of those 400 Amgen patents could cover the recombinant manufacture and purification of filgrastim in bacterial cells.

5. Further, there could be additional Amgen patents in other classes and subclasses that could be relevant to the production of Zarxio or its use.

6. If Sandoz had provided its BLA and manufacturing information required by the statute, Amgen could have made a determination whether a claim of infringement of such patents could reasonably be asserted if Sandoz engaged in making, using, offering to sell, selling or importing into the United States, the filgrastim product that is the subject of its BLA. Without that BLA and manufacturing information, on the other hand, Amgen cannot assess which of its patents may apply in order to assert those patents against Sandoz.

7. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed the 5th day of February, 2015, at Thousand Oaks, California.

Stuart Watt

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC. and AMGEN MANUFACTURING, LIMITED,

Plaintiffs,

vs.

SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH,

Defendants.

Case No. 3:14-cv-04741-RS

DECLARATION OF ROBERT AZELBY IN SUPPORT OF AMGEN'S MOTION FOR A PRELIMINARY INJUNCTION

I, Robert Azelby, declare and state as follows:

1. I am Vice President and General Manager Oncology at Amgen Inc. ("Amgen"). I submit this declaration in support of Amgen's Motion for a Preliminary Injunction against Sandoz, Inc. I am personally knowledgeable about the matters set forth in this Declaration and, if called upon to do so, I could and would competently testify to the following facts, below:

Amgen's Filgrastim Products

2. Amgen has two filgrastim products: Neupogen® (filgrastim) and Neulasta® (pegfilgrastim).

3. Generally speaking, Neupogen® is approved by FDA for use to treat patients in five indications: (1) cancer patients receiving myelosuppressive chemotherapy; (2) patients with acute myeloid leukemia receiving induction or consolidation chemotherapy; (3) cancer patients receiving bone marrow transplants; (4) patients undergoing peripheral blood progenitor cell collection and therapy; and (5) patients with severe chronic neutropenia. The current prescriber information for Neupogen® can be found at http://pi.amgen.com/united_states/neupogen/neupogen_pi_hcp_english.pdf

4. Neulasta® is approved by FDA for use in treating cancer patients receiving myelosuppressive chemotherapy. The current prescriber information for Neulasta® can be found at http://pi.amgen.com/united_states/neulasta/neulasta_pi_hcp_english.pdf

5. In my role as Vice President and General Manager Oncology at Amgen, my responsibilities include the sales and marketing of Amgen oncology business unit products and services in the United States. I am therefore familiar with both Neupogen® and Neulasta®, the channels through which they are sold and paid for, the patients they serve, how they are used by health care providers, and considerations that influence purchasing decisions. The same sales force that sell Neupogen® and Neulasta® also sell other of Amgen's oncology products such as Vectibix®. This sales force reports indirectly through to me in my role as Vice President and General Manager Oncology.

6. Both Neulasta® and Neupogen® are administered to patients most commonly by subcutaneous injection. A cancer patient receiving myelosuppressive chemotherapy who is treated with Neupogen® or Neulasta® in accordance with the prescribing information would receive the first dose of Neupogen® or the only dose of Neulasta® no earlier than 24 hours after receiving a dose of chemotherapy. Typically, this has meant that a patient receives a dose of chemotherapy and then must return to the treatment center on the following day to receive an injection of Neupogen® or Neulasta®. Treatment with Neulasta® requires only a single injection, while Neupogen® is generally injected daily for a number of days.

7. Each of Neupogen® and Neulasta® is a highly successful product. Each has achieved "blockbuster" status, an industry term used to denote products with over $1 Billion in total sales, and each has become incorporated into the standard of care for cancer patients receiving certain myelosuppressive chemotherapy regimens. While Amgen does not publicly report the precise profitability of these products, the contribution margins on Neupogen® and Neulasta® are significant.

The Market For Filgrastim Products

8. Healthcare providers have a choice of filgrastim products: Neupogen®, Neulasta®, and Teva's Granix® (tbo-filgrastim), which is not biosimilar to Neupogen®. In my experience, decisions about which product to prescribe are made based on a desire to maximize successful treatment outcomes, ensure safety and efficacy, and address patient convenience, while also being sensitive to the economics of healthcare.

9. Any company selling products or services in the oncology market will strive to understand the details of that market, which is complicated and ever changing. Neupogen® and Neulasta® are each paid for, for example, by both public payers (for example, Medicare/CMS) and private payers (for example, private health insurance). Although there is substantial overlap among them, the medications are generally administered in three principal market "segments": oncology clinics, hospitals, and pharmacy purchasers. How healthcare providers are reimbursed

for their out-of-pocket expense to purchase and administer filgrastim products varies by segment and often by payer.

10. To take an example Medicare in the hospital segment: For many inpatient treatments, hospitals are reimbursed by Medicare based on a patient's Diagnosis-Related Group, or "DRG," which includes a fixed payment amount in return for a bundle of related therapies and pharmaceuticals. Some private insurers similarly reimburse certain types of hospitals for specific inpatient treatments.

11. In the oncology clinic segment, the Medicare reimbursement system is different. Medicare reimburses doctors based on a product's Average Selling Price, or "ASP," which is the pharmaceutical's net selling price in recent quarters including rebates and discounts. In oncology, for example, Medicare reimburses doctors at ASP + 6% (currently lowered to 4.3% because of the federal sequester).

12. A new entrant wishing to sell a filgrastim product in competition with Amgen's Neupogen® and Neulasta® products, like Sandoz, could choose from at least four basic strategies: (1) target the hospital segment; (2) target the clinic segment; (3) target the pharmacy segment; or (4) target all three.

Sandoz's Proposed Entry into the Filgrastim Market and the Potential Harm to Amgen

13. I am aware that Sandoz is poised to launch a biosimilar version of Neupogen®, which it will call Zarxio, upon FDA approval. I also understand that Amgen has asserted through the filing of a lawsuit that Sandoz's anticipated launch is premature and unlawful.

14. I am very concerned that Sandoz's premature launch of its biosimilar filgrastim product in the United States will severely and permanently harm Amgen.

15. As an initial matter, I anticipate that sales of Zarxio will reduce Amgen's revenue from Neupogen® and Neulasta® sales. The market research I have seen suggests that the population of patients who need filgrastim treatment are currently getting it. Therefore, sales of Zarxio will likely and largely come at the expense of Neupogen® and possibly Neulasta® sales.

16. Customers of filgrastim products are fairly price-sensitive. Even though Granix is approved for only one indication, as compared to Neupogen®'s five, Teva gained roughly 8 to 9% of the short-acting filgrastim market over 2014, with a share as high as 14% over the past four weeks, by offering lower prices.

17. It is unclear to me how Sandoz will price its product. I have seen statements attributed to Sandoz executives that describe Zarxio as a lower-cost product, but I have also seen statements attributed to Sandoz executives that say that Zarxio will be priced at parity with or above Amgen's Wholesale Acquisition Cost (or "WAC") for Neupogen®, which is similar to a list price. New market entries do not have an established ASP because they have not accumulated sales from which to do the ASP calculation over the requisite period of time, so until they have accumulated such a track record their WAC is their ASP. By offering discounts off the WAC price to health care providers, it would be possible for Sandoz to set a WAC price above Neupogen®'s WAC price and increase the difference between the provider's acquisition cost and the amount of Medicare reimbursement. If Sandoz were to pursue that strategy, Medicare would pay more for Zarxio than for Neupogen® (which has an ASP lower than WAC), and doctors would keep more money from prescribing Zarxio than Neupogen®, resulting in increased profits to Sandoz and the prescribing physicians, increased costs to Medicare, its patients, and to society as a whole, and lost sales to Amgen.

18. The sequester further complicates the situation. As noted in the trade press, because of the details of how it is implemented, the 2% federal sequestration cut in Medicare reimbursement can make "the biosimilar reimbursement more attractive than the innovator." [1] As that article shows, a discount in the biosimilar list price can result in an even higher difference between the amount that doctors pay to acquire the biosimilar and the amount that they are reimbursed. While this may not have been Congress's intent, "the sequester in Medicare will have the unintended impact of making Part B payments more attractive for

[1] Ex. A (Michael McCaughan, *Biosimilar Reimburssement Under the Sequester: The Lower the Price, the Bigger the Spread,* "THE PINK SHEET" DAILY, August 8, 2014).

biosimilars than they would have been."[2] That article cites Sandoz's Mark McCamish "highlighting the reimbursement formula as a key reason why the company" used the biosimilar approval route for Zarxio.

19. Because of the intricacies of the Medicare reimbursement formula, Amgen could lose sales to Sandoz whether Sandoz prices Zarxio initially above or below Amgen's WAC.

20. For example, Sandoz might also compete with Amgen on acquisition cost in the inpatient hospital segment, where the incentives can be different. If Sandoz comes in below Amgen's average selling price for Neupogen®, cost-sensitive hospitals, in order to maximize economics under fixed, DRG-based reimbursements, could switch to Sandoz's product.

21. If Sandoz chose to target both hospitals and clinics, Sandoz could seek a balance between desire for low prices and desire for higher reimbursement.

22. At the right price, Sandoz's Zarxio could draw sales not just from Neupogen® but also Neulasta®. Assuming that Zarxio is dosed like FDA-approved filgrastim products, one advantage of Neulasta® over Sandoz's Zarxio would be that an appropriate treatment is achieved in a single injection, whereas once-a-day filgrastim treatments over a number of days depends on the patient returning each day for a new injection. With sufficient economic incentives, however, providers might switch to Zarxio not only from Neupogen® but from Neulasta®. Amgen might then be forced to lower its prices on Neupogen® and Neulasta® to retain market share.

23. If Amgen were forced to lower its prices for Neupogen® or Neulasta® to compete with Zarxio in the current ASP reimbursement system, it would be very difficult if not impossible for Amgen to simply raise its prices back to what they were before Zarxio competition, particularly with the existence of another competing filgrastim product, Teva's Granix. Because of the way the ASP reimbursement formulas and timing work, a price increase could lead to a greater cost for our products than doctors would be receiving in reimbursement.

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[2] *Id.*

If that were to occur, healthcare providers may be reluctant to prescribe Neupogen® or Neulasta® to patients in need, fostering animosity towards Amgen.

24. In my view, then, Sandoz's entry in the market will therefore not just harm Amgen through lost sales, but may also harm Amgen through permanent erosion of its prices.

25. Sandoz's entry in the market will also have significant adverse effects on Amgen's sales force. Amgen's sales force consists of highly sophisticated, valuable employees, whose loss would have adverse impacts on Amgen's ability to effectively sell its products. Indeed, in recent weeks Amgen has learned that former Amgen sales representatives now working for Sandoz have improperly been trying to hire away Amgen sales representatives to join them at Sandoz.

26. Further, Amgen oncology sales representatives will necessarily be diverted away from what they would otherwise be doing in order to address Sandoz commercial marketing of its filgrastim. This, too, could cause irreparable harm to Amgen. There are currently two, and perhaps three, significant tasks for the Amgen oncology sales force besides the day-to-day sale of Neupogen® and Neulasta®. First, Amgen has just introduced an on-body injector for Neulasta®. A doctor or nurse attaches the on-body injector to the patient's arm on the day that chemotherapy is delivered. The next day, the on-body injector delivers a full dose of Neulasta® into the patient, without the patient needing to return to the clinic. The on-body injector has the potential to revolutionize patient care in this area, as returning to the clinic the day after chemotherapy can be very arduous for a patient population that is very sick, often elderly, and may not live near the health care provider. The on-body injector also has a significant in-service education component: doctors and nurses need to be taught how to use it, a process that can take several hours and involve several applications of the on-body injector through test kits before applying the on-body injector on a patient. If Amgen's Neulasta® and Neupogen® salesforces are diverted to addressing Sandoz's marketing of Zarxio because Sandoz has not waited the time required by the BPCIA before entering the market, then Amgen may miss or severely harm the chance to educate the provider population about the new on-body injector. In

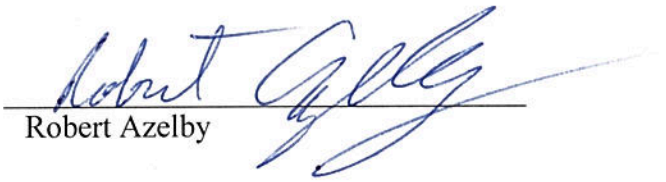
my experience, products like this need sustained, daily attention early in their life cycle or fewer patients will benefit and revenues will be lost. This loss of revenue (which would have been obtained had there been effective launch) is permanent and harmful to Amgen.

27. Similarly, Amgen has recently received approval to use its Vectibix® product as a first-line treatment for colorectal cancer in combination with Folfox, a chemotherapy regimen. Vectibix® is sold by the same sales representatives who sell Neupogen® and Neulasta®. These sales representatives must spend time, now, educating oncologists about the new approval for this product. Diverting them to address the marketing of Zarxio will cause them to also spend less time on Vectibix®, likely causing that franchise lasting and irreparable harm.

28. Finally, Amgen is pursuing approval of a new therapeutic product, talimogene laherparepvec, or "Tvec," that not only destroys certain cancer cells, but also stimulates the immune system to fight those cells elsewhere in the body. If Tvec is approved, which is expected later this year, and Amgen's oncology sales and marketing resources have been diverted to address Sandoz's filgrastim marketing, Amgen's ability to support Tvec during its all-important first 6-12 months on the market may be impaired, permanently harming that franchise.

29. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed the 5th day of February, 2015, at Thousand Oaks, California.



Robert Azelby

EXHIBIT A

2 of 3 DOCUMENTS

The Pink Sheet Daily

August 8, 2014

SECTION: Vol. 14 No. 80

LENGTH: 765 words

HEADLINE: Biosimilar Reimbursement Under The Sequester: The Lower The Price, The Bigger The Spread

BODY:

FDA finally has a biosimilar application to review.

On July 24, **Novartis AG** announced that it has a BLA for a version of Amgen's *Neupogen* (filgrastim) pending at FDA. It will thus set all kinds of precedents as the first biosimilar reviewed under the new 351(k) pathway (unless someone else has snuck an application in without announcing it, which seems unlikely).

Upon approval, it will also test a novel Medicare Part B reimbursement formula, intended to put biosimilars on a more equal footing when it comes to competing in that key segment. In an interview with "The Pink Sheet" DAILY, Mark McCamish, head of Global Biopharmaceutical and Oncology Injectables Development at Novartis' **Sandoz Inc.** subsididary, highlighted that reimbursement formula as a key reason why the company opted to use the 351(k) route rather than file for a full BLA - as **Teva Pharmaceutical Industries Ltd.** did, getting approval in 2012 for its version of filgrastim ("Sandozs Filgrastim Biosimilar Relies On Data Extrapolation" "The Pink Sheet Daily" Jul. 24, 2014).

The Medicare reimbursement formula may in fact be even more attractive than intended, thanks to the 2% across-the-board payment cut in Medicare triggered by the sequester in 2013.

The sequester is nobody's idea of rational public policy. But it just might end up working in a manner that makes the "spread" on biosimilars larger than on innovator products, with the size of the "spread" collected by physicians actually increasing as the price of the biosimilar decreases.

Like most issues involving Medicare reimbursement, the explanation is convoluted - and like everything involving biosimilars, there is no precedent to cite yet to show how it actually works in the real world. But here is what we know:

Under Section 3139 of the Affordable Care Act, biosimilars approved by FDA under the 351(k) pathway will be reimbursed under Medicare Part B using a unique formula: average sales price plus 6% of the innovator's ASP (rather than 6% of the biosimilar ASP).

The intention was to assure that biosimilars would not be hampered by the paradoxical way that Part B pricing works. In general, a lower price in Part B means a smaller "spread" for physicians and therefore an incentive to choose

higher priced products. So, if a product like Teva's *Granix* (tbo-filgrastim) is sold at an ASP of $80 versus Neupogen's $100, a physician would collect a spread of $4.80 for using Granix (6% of $80), compared to $6 for using Neupogen. And if Teva discounts even more steeply, the spread just gets smaller.

That obviously isn't much of an incentive for the doctor to choose the lower cost option.

As written, the biosimilar law would mean that a physician choosing Novartis' 351(k) version of filgrastim would still collect a $6 spread, no matter what the ASP is. That would assure a level playing field.

The sequester, however, changes those formulas - and does so in a way that actually makes the biosimilar reimbursement more attractive than the innovator.

When the 2% payment cut took effect last year, CMS applied it both to the ASP and to the 6% spread. Thus, providers are receiving a net payment of ASP+4.3%. That by itself is a complicated calculation because the sequester only impacts the federal government's portion of the payment (80% of the charge); patients - or their supplemental insurance policies - pay the other 20%, and that is not reduced by the sequester. (The American College of Rheumatology explains the formula here.)

Thus, in this hypothetical examples, a provider using Neupogen at an ASP of $100 would receive a $4.30 spread. Granix at $80 ASP would be reimbursed at a total of $83.44 - still the smaller amount.

However, a 351(k) biosimilar priced at $80 would produce a total reimbursement of $84.62 - a spread of $4.62 that is a smidge higher than the $4.30 provided for the brand. And, in a hypothetical case of an even more deeply discounted biosimilar, say at $50, the spread actually goes up: the total reimbursement would be $55.10 in that instance.

All of this, of course, assumes that CMS agrees with this way of calculating the formula for biosimilars under the sequester. It also assumes the provider purchases the product at ASP; the real market is much more dynamic than that, and innovator companies will of course be testing different discounting models to maintain the most attractive reimbursement they can.

Still, it appears clear that the sequester in Medicare will have the unintended impact of making Part B payments more attractive for biosimilars than they would have been.

By Michael McCaughan

LOAD-DATE: August 8, 2014

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, vs. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, Defendants.	Case No. 3:14-cv-04741-RS **DECLARATION OF TOMAS PHILIPSON, PH.D. IN SUPPORT OF AMGEN'S MOTION FOR A PRELIMINARY INJUNCTION**

I, Tomas Philipson, Ph.D. declare and state as follows:

1. I am the Daniel Levin Professor of Public Policy Studies in the Irving B. Harris Graduate School of Public Policy Studies at the University of Chicago and a founding partner of the economic consulting firm Precision Health Economics LLC, a firm engaged in quantitatively assessing the returns to innovation of its clients and the effects of public policies upon them.

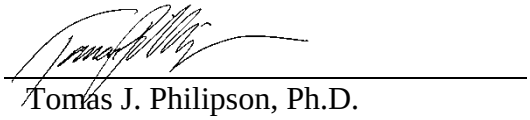
2. In this matter, I have been retained by Paul, Weiss, Rifkind, Wharton & Garrison LLP, counsel to Amgen, to perform economic analysis regarding the factors that I understand the Court will consider to determine whether an injunction against the unlawfully premature manufacture and importation, sale, offer to sell, and/or use of Sandoz's biosimilar product Zarxio in the United States should be granted.

3. Attached as Exhibit B is my February 5, 2015 expert report that accurately reflects my opinions in this case.

4. If called upon to testify about the matters set forth in the expert report, I could and would competently testify as to the conclusions and analyses set forth therein.

5. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed the 5th day of February, 2015, at Los Angeles CA.



Tomas J. Philipson, Ph.D.

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC., and AMGEN MANUFACTURING, LIMITED, Plaintiffs, v. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, Defendants.	Case No. 3:14-cv-04741-RS

EXPERT REPORT OF TOMAS J. PHILIPSON, PHD

February 5, 2015

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A. Overview

A.1. Qualifications

(1) I am the Daniel Levin Professor of Public Policy Studies in the Irving B. Harris Graduate School of Public Policy Studies at the University of Chicago and a founding partner of the economic consulting firm Precision Health Economics LLC, a firm engaged in quantitatively assessing the returns to innovation of its clients and the effects of public policies upon them. I received my BS in mathematics from Uppsala University in Sweden and my MA and PhD in economics from The Wharton School and The University of Pennsylvania.

(2) My research focus is on health economics, and I teach masters' and doctoral-level courses in microeconomics and health economics at the University. My research has been published in the leading academic journals of economics such as *American Economic Review, Journal of Political Economy, Quarterly Journal of Economics, Journal of Economic Theory, Journal of Health Economics, Health Affairs,* and *Econometrica.* I have twice (in 2000 and 2006) been the recipient of the Kenneth Arrow Award of the International Health Economics Association, which is awarded for best paper in the field of health economics. In addition, I was awarded the Garfield Award by Research America in 2007 for best paper in the field of health economics and the Distinguished Economic Research Award from the Milken Institute in 2003 for best paper in any field of economics.

(3) I was on leave from the University to serve as the senior economic advisor to the head of the Food and Drug Administration (FDA) during 2003 and 2004. During my term at the FDA, I was involved in policy deliberations regarding Canadian drug reimportation, reauthorization of the Prescription Drug User Fee Act, and the redrafting of the Abbreviated New Drug Application (ANDA) under which the generic drugs enter the market. In 2004, I was also on leave from the University to serve as the senior economic advisor to the head of the Centers for Medicare and Medicaid Services (CMS). During my term at CMS, I was involved in the implementation of the Medicare Part D rules which provide prescription drug coverage. I have also been appointed by the Speaker of the U.S. House of Representatives to serve on the Commission on Key National Indicators.

(4) I am a co-editor of the journal *Forums for Health Economics & Policy* of Berkeley Electronic Press and am on the editorial boards of the journals *Health Economics* and *The European Journal of Health Economics.* In addition, I write a monthly column related to health care topics for *Forbes* magazine.

(5) Additional information about my professional experience as an economist, including publications, affiliations, and work experience can be found on my curriculum vitae, which is attached as Appendix A. My curriculum vitae also includes a list of matters on which I have testified as an expert witness at any time during the past 10 years.

(6) In this matter, I am being compensated for my work at a rate of $950 per hour. I was assisted in my work in this matter by Compass Lexecon staff who performed work at my direction. All opinions expressed in this report are my own.

A.2. Scope of analysis

(7) In this matter, Amgen alleges that Sandoz did not comply with provisions of the Biologics Price Competition and Innovation Act (BPCIA). In particular, Amgen alleges that Sandoz violated the BPCIA by refusing to provide information about its proposed biosimilar product, Zarxio, in the form of its Biologics License Application and information about manufacturing processes for that product, and by refusing to provide 180 days' notice of commercial marketing after FDA licensure. Amgen alleges that Sandoz's violations of the BPCIA have prevented Amgen from being able to assess whether Sandoz's proposed biosimilar filgrastim product, Zarxio,[1] infringes Amgen's patents, thus depriving Amgen of the ability to seek an injunction against Sandoz's sale of products that may infringe Amgen's patents. Amgen has asked for an injunction to restore it to the position it would be in had Sandoz provided the information under the BPCIA that would have allowed Amgen to better determine whether the manufacture, importation into the U.S., sale, offer to sell, and/or use of Zarxio in the United States by Sandoz will infringe Amgen's patents.[2] [3] Additionally, Amgen alleges that Sandoz infringes on at least one of Amgen's patents, U.S. Patent No. 6,162,427 ('427).[4]

(8) I understand that the purpose of the BPCIA is to establish a biosimilars pathway that balances innovation and consumer interests.[5] While the BPCIA allows products to be approved as biosimilar or interchangeable with existing, or "reference" products, it also establishes a process that permits firms that sponsor the reference product to defend their patent rights. Specifically, I understand that the BPCIA requires that:[6]

- Within 20 days of the FDA accepting the biosimilar application, the applicant must provide the reference product sponsor with a copy of the biosimilar application and information on the manufacturing process for the biosimilar product;

- Within 60 days of receipt of the biosimilar application and information on the manufacturing process for the biosimilar product, the reference product sponsor must provide the applicant with a list of all patents the it believes are infringed;

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1 Zarzio is the brand name for Sandoz's biosimilar filgrastim product in Europe. "Novartis Biosimilar of Amgen's Neupogen Wins U.S. Panel Backing," Washington Post, January 7. 2015. I understand that it will be marketed in the United States under the brand name Zarxio. http://www.medscape.com/viewarticle/837725

2 Throughout this report I will refer to Amgen Inc. and Amgen Manufacturing Limited or AML collectively as "Amgen." I will refer to the Amgen patent at issue in this case (U.S. Patent No. 6,162,427 ('427)) as "Amgen's Patent." Finally, I will refer to Sandoz Inc., Sandoz GmbH, and Sandoz International GmbH collectively as "Sandoz." See Complaint for Patent Infringement, Conversion, and Unfair Competition (Cal. Bus. & Prof. Code § 17200), Amgen Inc. and Amgen Manufacturing, Limited, Plaintiffs, vs. Sandoz Inc., Sandoz International GmbH, and Sandoz GmbH, Defendants, United States District Court Northern District of California, Case 3:14-cv-04741-EDL, October 24, 2014 ("Amgen Complaint").

3 Amgen Complaint, at 30, 33, 35.

4 Amgen Complaint, at 30, 33, 35.

5 Amgen Complaint, at 52.

6 Amgen Complaint, at 98-106.

- Within 60 days of the receipt of the list of patents the reference product sponsor believes are infringed, the applicant must provide a list of those patents that it believes would be infringed and, for all patents identified, a statement of the legal and factual basis for its opinion that the patents are invalid, unenforceable, or will not be infringed;

- Within 60 days of receiving the list of patents the applicant believes are infringed, the reference product sponsor must provide the applicant a statement regarding the factual and legal basis for an opinion that each patent will be infringed upon as well as a factual and legal basis regarding the validity and enforceability of these patents;

- The parties must then engage in a good faith negotiation regarding which patents, if any should be subject to patent infringement litigation. The reference product sponsor is then compelled to bring an immediate patent infringement lawsuit against either an agreed upon list of patents, or a list of patents identified by the applicant.

(9) I understand that the BPCIA further requires the biosimilar applicant to provide the reference product sponsor notice at least 180 days before first marketing of the biosimilar.[7]

(10) These patent provisions of the BPCIA serve to protect an important public interest in innovation. The patent provisions protect innovation by giving force to the exclusionary rights granted by a patent. As the BPCIA recognizes, the reference product sponsor may have patents from a variety of sources. Some of those patents may arise from the same risk-based investment that generated the data that supported FDA licensure of the reference product, such as patents on the molecule itself. Some patents may come from follow-on research into and improvements on the use of that molecule in therapeutic treatments, such as patents on therapeutic indications other than the one for which the product was first approved. Some patents may come from innovation by the reference product sponsor in unrelated areas of science that nevertheless could apply to the proposed biosimilar, such as patents that address the manufacture of a range of molecules that improve the purity or safety of such molecules, or the efficiency of those manufacturing processes. Given the complexities in the manufacture of biologic products, the protections the BPCIA affords to manufacturing and process patents, including the requirements regarding disclosure of the biosimilar manufacturing process, are an important safeguard to protect the intellectual property of innovators. The BPCIA more broadly serves to protect and thereby support the innovation incentives that patents create, beyond the specific patent-protected inventions that stem from the research and development on which the reference product received approval for its first therapeutic indication.

(11) I have been retained by Paul, Weiss, Rifkind, Wharton & Garrison LLP, counsel to Amgen, to perform economic analysis regarding the factors that I understand the Court will consider to determine whether an injunction against the unlawfully premature manufacture, importation into the U.S., sale, offer to sell, and/or use of Zarxio in the United States should be granted. In performing my analysis, I have been asked to assume that the legal interpretation of the BPCIA is as alleged by Amgen. I have been further asked to assume that Amgen has one or more patents that could be infringed by the manufacture, importation into the U.S., sale, offer to sell,

[7] Amgen Complaint, at 50.

and/or use of Zarxio in the United States but that Amgen needs a copy of Sandoz's Biologics License Application and manufacturing information to determine whether, in fact, Amgen's patents would thus be infringed. My analysis focuses on whether an injunction is economically appropriate given these assumptions.

(12) Specifically, I have been asked by counsel to analyze:

i. How Sandoz's failure to comply with the requirements of the BPCIA, by making it more difficult for Amgen to determine whether Sandoz is infringing Amgen's patents, impacts the analysis of whether the injunction is justified.

ii Whether Sandoz's commercial manufacture, importation into the U.S., sale, offer to sell, and/or use of Zarxio in the United States prior to the time that Sandoz could have entered the market had it complied with the BPCIA and prior to the expiration of any applicable Amgen patents would cause irreparable harm to Amgen.

iii. Whether money damages adequate to compensate Amgen for the harms that Sandoz's unlawfully premature, and possibly patent-infringing sales are likely to cause to Amgen can be determined with reasonable confidence at this time.

iv. How the burden an injunction would impose on Sandoz compares with the harms Amgen would suffer if Sandoz's sale of products in violation of the BPCIA and, if appropriate, sales that infringe Amgen's patents, are not enjoined.

v. Whether the public interest would be disserved if the injunction Amgen seeks were entered by the Court.

A.3. Materials considered

(13) A list of materials I considered in forming the opinions expressed in this report appears in Appendix B as well as in the citations noted throughout this report.

(14) I reserve the right to supplement and/or amend this report to the extent that additional information becomes available through the course of discovery or otherwise, and to replace interim estimates with final calculations; conduct additional research or analyses in response to opinions and reports offered by other experts in this case and to respond to those opinions and reports; and update this report with continuing analysis.

A.4. Summary of opinions

(15) I have been asked to assume that: (a) Sandoz is attempting to market a product as biosimilar to one of Amgen's most successful therapeutic products, Neupogen® (filgrastim), piggybacking on Amgen's innovative research and Amgen's investment to develop and gain FDA licensure of Neupogen®, and (b) despite availing itself of the advantages provided by the BPCIA, Sandoz has refused to comply with the obligations created by the BPICA. In my expert opinion, the sale of a

biosimilar filgrastim product without complying with the BPCIA will cause irreparable harm to Amgen that, as a matter of economics, warrants the grant of an injunction.

(16) Specifically, Sandoz's refusal to comply with the requirements of the BPCIA has three effects, each of which provides economic grounds for granting an injunction. First, I have been informed that Amgen has many patents that might be relevant to the recombinant production and purification of filgrastim, and Sandoz's actions have made it more difficult or impossible for Amgen to determine whether Sandoz is infringing those patents. Sandoz's refusal to comply with requirements in the BPCIA that protect patent rights creates uncertainty that threatens to undermine the value and effectiveness of Amgen's patents, and is inconsistent with the efficient operation of the patent system and the BPCIA. In particular, one aspect of determining whether a preliminary injunction should be issued in a patent infringement case is to examine the likelihood of success on the merits. However, Sandoz's refusal to comply with requirements in the BPCIA has made it difficult for Amgen to determine which patents are infringed or how, justifying – from an economic perspective – the issuance of an injunction. That is, Sandoz should not be rewarded for any difficulties Amgen faces in demonstrating infringement or likelihood of success created by Sandoz's unlawful lack of transparency. Allowing Sandoz to evade the patent protection requirements in the BPCIA and launch a product that may well have been found to be infringing had Sandoz followed the requirements would be contrary to the public interest. Once launched, irreparable harm to Amgen would occur even if the products were later proven to be infringing Amgen's patents and Sandoz were later enjoined.

(17) Second, if Sandoz had complied with the requirements of the BPCIA and Amgen had determined that Sandoz's manufacture, importation into the U.S., sale, offer to sell, and/or use of Zarxio infringed upon Amgen's existing patents, I understand that compliance with the procedures mandated by the BPCIA would have required as many as 410 days before Zarxio entry could occur. For convenience, I will refer to this 410 day period, plus any additional period in the event that Sandoz is infringing Amgen's patents, as the "Restricted Period." The entry of Zarxio prior to when it would otherwise would have if Sandoz had complied with the requirements of the BPCIA would have resulted in the same kinds of irreparable harm to Amgen as if Sandoz entered and was later determined to have infringed on Amgen's patents.

(18) Finally, the fact that Zarxio would be the first biosimilar product to be approved under the BPCIA creates a potential further societal harm should Sandoz's interpretation of the BPCIA become accepted. This harm would flow from the increased patent uncertainty that other firms would have over their patent protected biologic products, and the incentives provided to entrants to introduce biosimilar products that could infringe upon the patents of incumbents, and to attempt to conceal any such infringement. This would create a reduction in the incentives to invest in R&D and innovate throughout the industry, thus harming society.

(19) Based on my analysis and experience, I conclude that:

- The patent uncertainty created by Sandoz's failure to comply with the requirements of the BPCIA provides economic grounds for granting an injunction
- Sandoz's unlawfully premature sales of Zarxio would cause irreparable harm to Amgen

- Monetary damages would be inadequate and difficult to estimate with reasonable accuracy

- The burdens an injunction would impose on Sandoz are minimal compared with the harms to Amgen if Sandoz were not enjoined

- The public interest would not be disserved if Sandoz is enjoined from not complying with the requirements of the BPCIA and from launching its filgrastim product prior to the expiration of any applicable Amgen patents

B. Amgen's business

B.1. Amgen's business model: a cycle of innovation and commercialization

B.1.1. Amgen is a leader in biological innovation

(20) Amgen is a leading biotechnology company that discovers, develops, and markets innovative human therapeutics. Founded in 1980 as Applied Molecular Genetics, Amgen is headquartered in Thousand Oaks, California. As a result of its successful innovation and development of numerous therapeutic products, Amgen has grown into a leading biotech innovator as well as a pharmaceutical manufacturer. Currently, the company has approximately 20,000 employees and facilities or subsidiaries in the United States and more than 75 other countries, including Japan, China and other emerging markets.[8] Almost 80% of Amgen sales are in the United States.[9]

(21) Amgen's business focuses on (a) discovering and developing new treatments for diseases where limited or no alternative drugs currently exist, (b) teaching the safe and effective use of its therapies for the benefit of patients and the science behind its medicines, and (c) reinvesting the proceeds from its sales of therapeutic products in the discovery and development of still further new therapies for significant unmet medical needs. Because the discovery and development of new biological products has a very low probability of success, yet entails substantial and sustained exploratory research and clinical investigation, external funding for such research and development is generally very costly and difficult to obtain. Instead, Amgen relies on revenues almost entirely generated under patent protection by its successful products to fund its ongoing and future innovation. Amgen's business model depends on being able to maintain this cycle of innovation and commercialization.

(22) Since its founding, Amgen has become a leading innovator in the identification, isolation, production, and use of human proteins as therapeutic agents that are generally referred to as biological drugs or biologic products.[10] Amgen's research team achieved its first major breakthrough in 1983, three years after its founding, when it succeeded in cloning the gene for human erythropoietin (EPO), a hormone involved in controlling red blood cell production in humans.[11] The discovery eventually resulted in the development and FDA approval of Epogen® (epoetin alfa), one of the first biological products sold in the United States, for treating anemia caused by kidney failure.[12] Two years later, Amgen's scientists cloned the gene for human G-CSF, laying the groundwork for the development of Neupogen®. Over the years that followed, Amgen discovered, developed, and gained FDA approval for a number of other new treatments, some attaining large revenues like Neupogen® and others attaining far more modest revenues. Examples include Aranesp® for treatment of anemia associated with chronic renal failure, Neulasta®, an innovation on Neupogen® for treating neutropenia, Vectibix® for colorectal cancer, Enbrel® for arthritis and psoriasis, Blincyto® for certain forms of acute lymphoblastic leukemia,

8 Amgen 2013 10K, at 19 and 39.
9 Amgen 2013 10K, at F-48.
10 Biological drugs are derived from living matter and have a much more complex molecular structure compared to small molecule drugs, such as Tylenol or aspirin, which are chemically synthesized.
11 Amgen, "Milestones," http://www.amgen.com.au/milestones.html
12 Joshua W. Devine, Richard R. Cline, and Joel F. Farley, "Follow-on Biologics: Competition in the Biopharmaceutical Marketplace," *Journal of the American Pharmacists Association,* 46 (2006): 193.

Kyprolis® for refractory multiple myeloma, Nplate® for the treatment of chronic immune thrombocytopenia, Prolia® for treating osteoporosis in postmenopausal women, Sensipar® for treatment of hyperparathyroidism and hypercalcemia in certain patients, and Xgeva® for treatment of patients with bone metastases from solid tumors, in addition to establishing other indications for Epogen® and Neupogen®.[13]

(23) Amgen's products provide innovative new treatment options for patients whose medical needs were not adequately met by any other treatment. In fact, a number of Amgen's products were granted "fast track" approval by the FDA,[14] a status intended to expedite the review of drugs "intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs."[15] Epogen® and Neupogen® were both named "Product of the Year" by *Fortune* magazine (in 1989 and 1991, respectively),[16] and their inventors received such nationally recognized awards as the Distinguished Inventor Award and the Pharmaceutical Research and Manufacturers Association Discoverer's Award.[17] In 1994, Amgen was awarded the National Medal of Technology by the President of the United States for its leadership in developing innovative and important commercial therapeutics based on cellular and molecular biology for delivery to critically ill patients throughout the world.[18]

(24) In addition to developing innovative new products for the treatment of patients in need, Amgen is an innovator of methods for the manufacturing, purification, and administration of biologic products. These innovative manufacturing methods are particularly important because they can often be applied broadly, not only to the safe, pure and efficient manufacture of existing products, but to future products as well.

(25) Amgen's level of innovation can be demonstrated, in part, by the number of patents it has been granted.[19] As shown in Figure 1, Amgen has received over 1,100 patents on its inventions since its founding.

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13 http://www.amgen.com/patients/products.html

14 FDA, "Fast Track Approvals," http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/drugandbiologicapprovalreports/ucm082380.htm
FDA, "Fast Track Designation Request Performance," http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm122932.htm

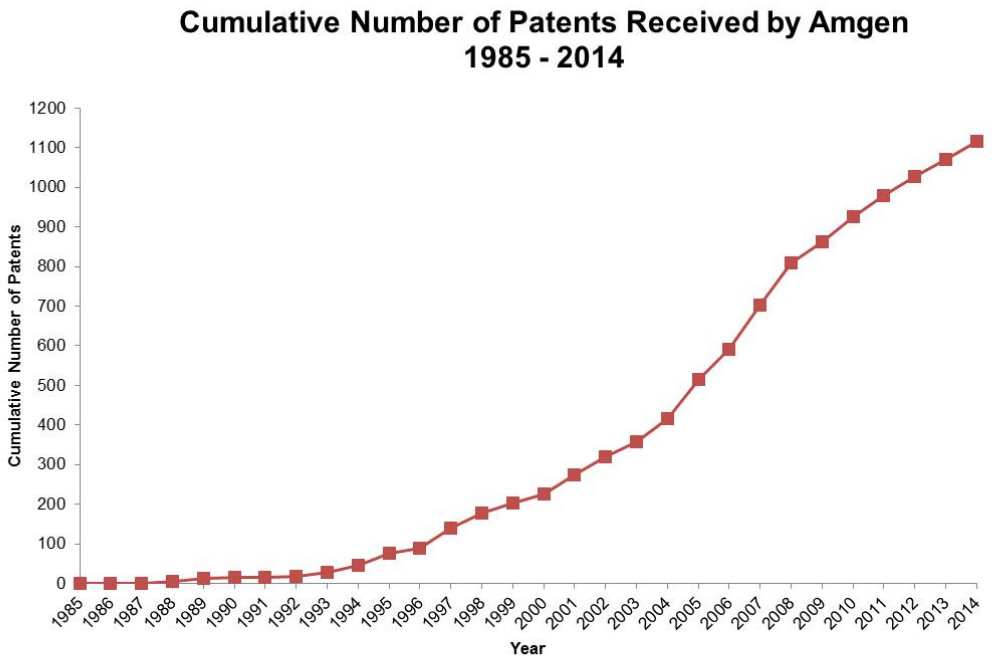
16 Amgen, "Milestones," http://www.amgen.com.au/milestones.html

17 Intellectual Property Owners Education Foundation, "2010 IPO Education Foundation Awards Dinner, Thirty-Seventh National Inventor of the Year Award & Third Distinguished IP Professional Award," page 11, http://www.ipo.org/wp-content/uploads/2013/03/06AM10_IOY_Pgm_FINAL.pdf. "Amgen Scientist Receives PhRMA 1995 Discoverers Award; Dr. Fu-Kuen Lin Honored for EPOGEN," Business Wire, October 11, 1995

18 U.S. Patent and Trademark Office, "The National Medal of Technology and Innovation Recipients," http://www.uspto.gov/about/nmti/recipients/index.jsp

19 The number of patents received by a company is a well-accepted metric for that company's level of innovation. See, for example, Gerald Silverberg and Bart Verspagen. "The size distribution of innovations revisited: An application of extreme value statistics to citation and value measures of patent significance." *Journal of Econometrics* 139 (2007): 318-339; see also Adam B. Jaffe, "Real Effects of Academic Research," *The American Economic Review* 79, 5 (1989): 957-970.

Figure 1



Source: U.S. Patent and Trademark Office (www.assignment.uspto.gov).

(26) The development of new biological treatments at the core of Amgen's business is uncertain and risky, very time consuming, and extraordinarily expensive. As described in more detail below, these factors drive Amgen's level of R&D investment and its continuing need to generate revenues and profits to support this investment.

(27) To fuel its continued innovation, Amgen invests heavily in advanced scientific research and development. Amgen's annual R&D expenditures have averaged over $3 billion since 2007.[20]

B.1.2. Biological innovation is uncertain and expensive

(28) When Amgen's exploratory research identifies a therapeutically promising new molecular compound, the compound goes through an FDA-regulated process to obtain approval for sale in the United States. This process generally entails five stages, beginning with pre-clinical research, continuing through three stages of increasingly detailed human clinical trials, and the final regulatory review

[20] Amgen Inc. Income Statement, S&P Capital IQ.

stage.[21] The average time required to complete the clinical trial and regulatory review stage for biologicals is between nine and 11 years, and this has more than doubled since the early 1980s.[22]

(29) The investment required to establish the clinical safety and efficacy of an innovative biological product is enormous. Recent research estimated that the total capitalized R&D cost per approved biological product is between $1.24 billion and $1.33 billion, compared to between $454 million and $1.32 billion for a small-molecule drug.[23] During the 1990s, total capitalized costs for developing new drugs increased at an annual rate of 7.4% above the rate of inflation.[24]

(30) Only a small percentage of the drugs that undergo pre-clinical research complete clinical trials and are approved for commercial sale. For each drug approved by the FDA, on average 5,000 to 10,000 molecular compounds are explored in the discovery stage; 250 begin pre-clinical trials; and only five enter clinical trials.[25] The success rate is lower for biological products than for small-molecule drugs because of the additional challenges of biological molecules to be resolved during the R&D process, including the molecular complexity, the source of biological molecules in living cells, and the challenges of the manufacturing and engineering process.[26]

(31) By contrast, the research efforts conducted by a firm like Sandoz to market a biosimilar product are qualitatively different. Sandoz begins with an existing product and copies it, then attempts to demonstrate that the copy is an accurate one.[27] However, Sandoz knows from the beginning that the product is feasible, effective and profitable, and Sandoz is able to take advantage not only of the fundamental research conducted by Amgen and other innovative firms, but of the effort invested in clinical trials and FDA licensure.

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[21] The five stages are:
1. Pre-clinical research: demonstrates the safety of administering the drug to humans in initial, small-scale clinical studies, often using lab or animal testing. After pre-clinical testing is completed, the company files an Investigational New Drug Application (IND) with the FDA.
2. Phase I clinical studies: begin after an IND is approved and are designed to gain early evidence on drug characteristics associated with increasing doses (e.g., mechanism of action, efficacy, side effects).
3. Phase II clinical studies: obtain preliminary data on the efficacy of the drug for a particular indication in patients with the disease or condition.
4. Phase III clinical studies: gather additional information about the drug (e.g., efficacy, safety) to evaluate the overall benefits and risks to the general population with the disease or condition.
5. Final regulatory review phase by the FDA.

[22] The total approval time is on average about 8% longer for biologicals than for small molecule drugs, with a large portion of the difference coming in Phase I of clinical trials. Development times have grown steadily over time as the complexity of biological products under development has increased. See Henry Grabowski, "Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition," *Nature Review Drug Discovery,* published online May 12, 2008.

[23] Joseph DiMasi and Henry Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 28 (2007): 469; Henry Grabowski, "Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition," *Nature Review Drug Discovery,* published online May 12, 2008. For estimates of small-molecule drug research and development, see also Christopher Adams and Van Brantner, "Estimating the Cost of New Drug Development: Is It Really $802 Million?" *Health Affairs* 25, no. 2 (2006): 426.

[24] Joseph DiMasi, Ronald Hansen, and Henry Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics,* 22 (2003): 151-185 at 180.

[25] Pharmaceutical Research and Manufacturers of America, "Pharmaceutical Industry Profile 2010," Washington, DC: PhRMA, March 2010 at 27.

[26] Todd Wallack, "FDA Rejects Genzyme Request for Myozyme," *The Boston Globe,* June 1, 2008.

[27] http://www.sandoz-biosimilars.com/biosimilars2/development_of_biosimilars.shtml

B.1.3. Only a small fraction of approved drugs are commercially successful, and only after a costly and lengthy effort

(32) Once Amgen gains FDA approval for a new, innovative biological product or files for expansion of an FDA-approved label for an existing product, there is a significant need to educate physicians, nurses, and other healthcare providers and payors about the disease state and how to safely and effectively use the new product for optimal patient benefit. This educational and commercialization effort entails an important and extensive effort given Amgen's focus on innovative medicines and the treatment of disease states for which no similar treatment has previously existed.[28] For example, within days of receiving FDA approval for Prolia® (denosumab) in June 2010, Amgen deployed as many as 1,000 sales representatives and medical personnel to educate healthcare providers on the novel mechanism of action of Prolia and the benefits this provides.[29] Building and supporting such an infrastructure is a key part of Amgen's business and is vital to the company's continued success. It also adds substantial costs to the business beyond the investment needed to complete the R&D process.

(33) The time and investments required to develop and bring to market new therapeutic products have multiple implications for pharmaceutical companies. First, only two out of every 10 approved drugs ever recoup their own R&D costs.[30] Therefore, a large fraction of the revenues generated by innovative drug companies comes from a small number of commercially successful drugs.[31] For a pharmaceutical company to be successful, the revenue generated by each commercially successful drug needs to cover not only that drug's costs of development and commercialization, but also (a) the R&D expenses for the drug candidates that never result in an FDA approved drug and (b) the R&D and commercialization costs for those drugs that are approved but are less commercially successful.

(34) For those drugs that do receive FDA approval, a considerable amount of time is commonly required after a drug is launched to generate demand sufficient to generate substantial revenue. Most of the revenues earned by patented drugs typically accrue towards the end of the patent term after the market for the patented drug is fully developed and mature.[32]

(35) Viewed in isolation, the revenue from highly successful biologic products like Neupogen® and Neulasta® may appear large. However, as mentioned above, the revenues from the few such highly successful drugs, also referred to as "blockbuster" drugs, are needed to recover the losses incurred on unsuccessful drug candidates and the drugs that receive FDA approval but are less commercially successful. Figure 2, reproduced from a 2010 academic paper, illustrates the lack of profitability among most pharmaceutical products. In this paper, Vernon et al show that only the top 20% of pharmaceutical products that reach the market generate returns in excess of average R&D costs. Earlier academic research found similar results and concluded that "a firm must have an occasional

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28 I understand that Neulasta® requires only one injection whereas Neupogen® is injected daily for a number of days. Bob Azelby (Vice- President and General Manager Oncology, Amgen Inc.), Interview, January 30, 2015.

29 See, for example, Ben Comer, "Amgen deploys 1,000 reps on Prolia," Medical Marketing and Media, June 15, 2010. http://www.mmm-online.com/amgen-deploys-1000-reps-on-prolia/article/173984/#

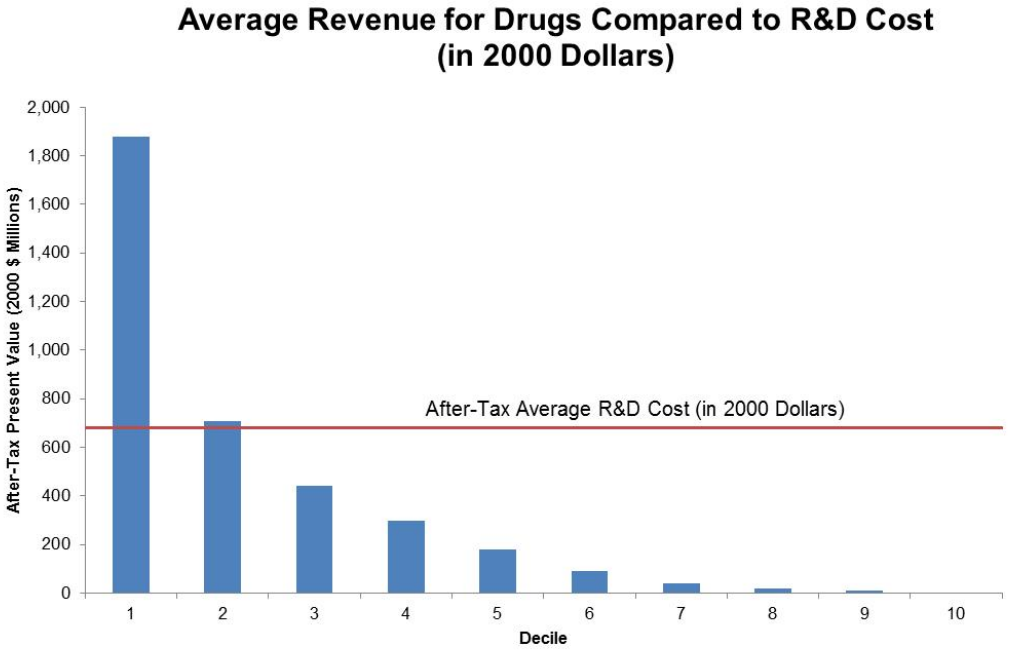
30 Pharmaceutical Research and Manufacturers of America, "Pharmaceutical Industry Profile 2010," Washington, DC: PhRMA, March 2010 at b.

31 Henry Grabowski and John Vernon, "A New Look at the Returns and Risks to Pharmaceutical R&D," *Management Science* 36, no. 7 (1990): 804.

32 Henry Grabowski, "Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition," *Nature Review Drug Discovery,* published online May 12, 2008 at 7.

'blockbuster' compound ... if it is to cover the large fixed costs which characterizes the drug development process."[33] Vernon et al.'s analysis provides a useful illustration of how it can be inappropriate to view the profits from a single blockbuster drug in isolation. Nearly 80% of the drugs in their sample do not recover their own R&D costs, so it is the so-called "blockbuster" drugs that enable pharmaceutical companies to invest in the uncertain R&D needed to bring new products to market and make a profit while doing so.[34] The importance of highly successful drugs in a pharmaceutical company's portfolio is also underscored by the fact that more than 50% of the total value for pharmaceutical companies is derived from the top 10% most successful drugs.[35] To provide a simplified example, if all drugs required the same R&D expenditure, and only one out of five were successful, then successful products would have to earn five times their R&D costs to finance the unsuccessful products.

Figure 2



Source: John Vernon, Joseph Golec, and Joseph DiMasi, "Drug Development Costs When Financial Risk is Measured Using the Fama-French Three-Factor Model," Health Economics Letters 19, no. 9 (2010): 1002-1005.

(36) Amgen considers factors like the expected development time, the expected patent lifespan remaining after projected launch date, and expected set of approved indications when evaluating potential

[33] Henry Grabowski and John Vernon, "A New Look at the Returns and Risks to Pharmaceutical R&D," *Management Science* 36, no. 7 (July 1990); 804-821 at 816.

[34] The values in Figure 2 are for new drugs launched in the 1970s and are generally representative of the relative costs and distribution of revenues for new pharmaceuticals.

[35] Henry Grabowski and Margaret Kyle, "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics* 28 (2007): 491-502 at 496.

research opportunities and making decisions regarding its R&D investments.[36] A reduction in expected patent lifespan, increased uncertainty over expected patent life, or increased uncertainty over the predictability of patent protected revenues would all cause a reduction in the expected return to R&D investment, and would necessarily lead to less innovation.

B.1.4. Amgen's business relies on product revenues and profits to fund R&D

(37) A key aspect of Amgen's business is its reliance on the revenues and profits generated by sales of its successful innovative products to finance the research, development, and commercialization of its current and future innovations. This is not unique to Amgen, as it is widely recognized that R&D expenditures in innovation-intensive industries like pharmaceuticals are highly dependent upon internal financing through retained earnings.[37,38]

(38) Amgen's investment in high-risk R&D complicates its ability to utilize outside funding sources for multiple reasons. First, there are substantial informational asymmetries between Amgen and potential outside investors.[39] The highly advanced and commercially sensitive nature of Amgen's scientific research limits Amgen's ability to share extensive information on its ongoing research outside of the company, even to potential investors, and especially on a real-time basis.[40] Second, the specialized knowledge required to evaluate biotechnology investments limits the ability of outside financing sources (e.g., banks, venture capitalists, institutional investors) to properly evaluate Amgen's R&D opportunities, making them more reluctant to provide financing.[41] For these reasons, innovative pharmaceutical companies like Amgen rely on ongoing product revenues to fund R&D.

(39) Resorting to external funding sources for Amgen's R&D activities would constrain and potentially conflict with Amgen's successful management of its innovative scientific research. The development of pharmaceuticals is highly unpredictable, especially in its early stages. Critical milestones may be achieved at a rapid pace, or may take several years before they materialize. The drug development and approval timelines are subject to FDA and foreign regulatory control. These inherent sources of uncertainty often conflict with the interests of external investors, who wish to understand their likely returns and recoup their investment in the short-to-medium term. As an alternative, Amgen has relied on product-generated revenues and profits to finance its ongoing R&D needs. The use of product-

[36] Gwen Cummings (Executive Director of Finance for R&D, Amgen Inc.), Interview, February 4, 2015.

[37] Kenneth Froot and Jeremy Stein, "Exchange Rates and Foreign Direct Investment: An Imperfect Capital Markets Approach," The Quarterly Journal of Economics 106, no. 4 (1991): 1191; Charles Himmelberg and Bryce Petersen, "R&D And Internal Finance: A Panel Study of Small Firms In High-Tech Industries," The Review of Economics and Statistics 76, no. 1 (1994): 38; Sean Cleary, Paul Povel, and Michael Raith, "The U-Shaped Investment Curve: Theory and Evidence," Journal of Financial and Quantitative Analysis 42, no. 1 (2007): 1-40.

[38] As a *Science* article highlights: "In a market system of pharmaceutical innovation, industry revenues support continued R&D, and patents support revenues.... Because drug companies are making substantial investments with no certainty about outcomes, they rely on patent-protected revenues to recoup their R&D expenditures." Matthew Higgins and Stuart Graham, "Balancing Innovation and Access: Patent Challenges Tip the Scales," *Science* 326 (2009): 370-1 at 370.

[39] Gwen Cummings (Executive Director of Finance for R&D, Amgen Inc.), Interview, February 4, 2015.

[40] James Brown, Steven Fazzari, and Bruce Petersen, "Financing Innovation and Growth: Cash Flow, External Equity, and the 1990s R&D Boom," *The Journal of Finance* 64, no. 1 (2009): 151-185. Gwen Cummings (Executive Director of Finance for R&D, Amgen Inc.), Interview, February 4, 2015.

[41] Alternative external sources of capital, such as debt or equity, are more expensive than internal financing due to informational asymmetries. These informational asymmetries lead creditors and shareholders to perceive the risks associated with the development of a new drug as higher compared to the pharmaceutical companies themselves. Therefore, external sources of financing require higher returns on their investments relative to the pharmaceutical companies. Congressional Budget Office, "Research and Development in the Pharmaceutical Industry," October 2006 at 12.

generated revenues and profits to fund R&D provides Amgen's management the ability to take greater and more timely innovation risks than would be acceptable to external investors. As a consequence, Amgen is able to pursue more innovative research targets with the potential to achieve large societal benefits and the associated financial rewards for the company, compared to less ambitious but more certain projects.

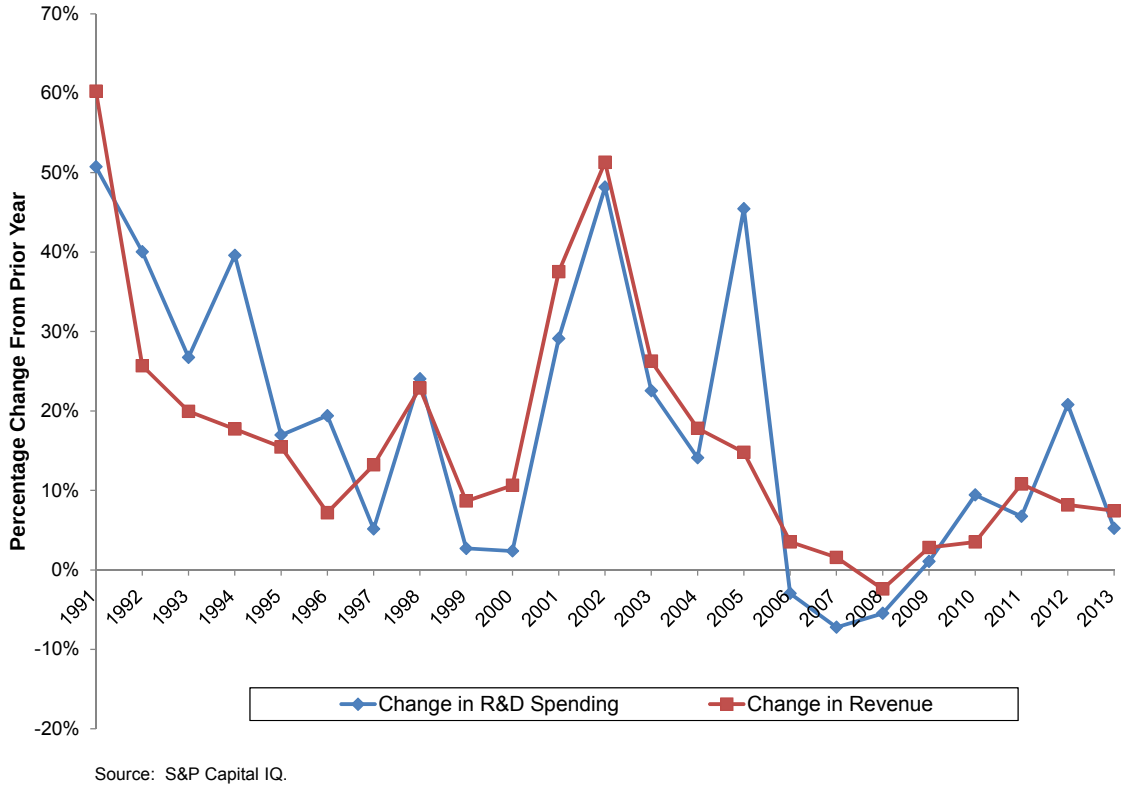
(40) R&D investment is one of the primary areas where Amgen would be able to reduce expenses if faced with a substantial decrease in revenue, and my conversations with Amgen executives confirm that Amgen's R&D investment and budgets are particularly sensitive to its actual and expected revenue.[42] In particular, the area that would likely be hardest hit is investment in "discovery" research aimed at identifying new treatments and approaches that have not yet entered clinical trials. As can be seen in Figure 3, annual changes in Amgen's revenue have been closely related to annual changes in its R&D investment since 1991. Over this time period the average annual change in revenues was 17%, while the average annual change in R&D expenditures was 18%. The correlation between changes in revenues and changes in R&D expenditures is 0.80.[43]

[42] Gwen Cummings (Executive Director of Finance for R&D, Amgen Inc.), Interview, January 30, 2015.

[43] The correlation between two variables is a statistical measure of the degree to which two time series vary together as opposed to independently. If two data series move in perfect lockstep, they have a correlation of 1.0. If they move completely independently of each other, their correlation is 0.0. If they move opposite of each other, but in lockstep upon each movement, they have a correlation of -1.0.

Figure 3

Amgen's Year-on-Year Growth in Revenue and R&D Spending



Source: S&P Capital IQ.

(41) An example of the impact of unexpected changes in Amgen's revenues and profitability on Amgen's R&D expenditures occurred in the middle of the last decade. Health concerns regarding Aranesp, one of Amgen's biggest selling and most profitable products at the time, lead to changes in the FDA approved labels for Aranesp and changes in coverage rules.[44] Between 2006 and 2008 Amgen's Aranesp revenues declined from $4.2 billion to $3.1 billion,[45] and Amgen's expenditures in R&D declined from $3.4 billion to $3.0 billion.[46] In response to this event, Amgen initiated a corporate restructuring that included reducing headcount, including R&D personnel, by 2,200-2,400.[47]

(42) Currently, Amgen is conducting clinical studies on 43 different molecular entities.[48] For some of these new drug candidates, multiple studies are taking place at the same time.[49] In total, Amgen is

[44] http://www.amgen.com/media/media_pr_detail.jsp?year=2007&releaseID=1040963
[45] Amgen 2008 10K, p. 73.
[46] Amgen 2008 10K, p. 68.
[47] http://www.amgen.com/media/media_pr_detail.jsp?year=2007&releaseID=1040963; Gwen Cummings (Executive Director of Finance for R&D, Amgen Inc.), Interview, February 4, 2015,
[48] Amgen 2013 10K at 13.
[49] Amgen, 2013 10K at 13.

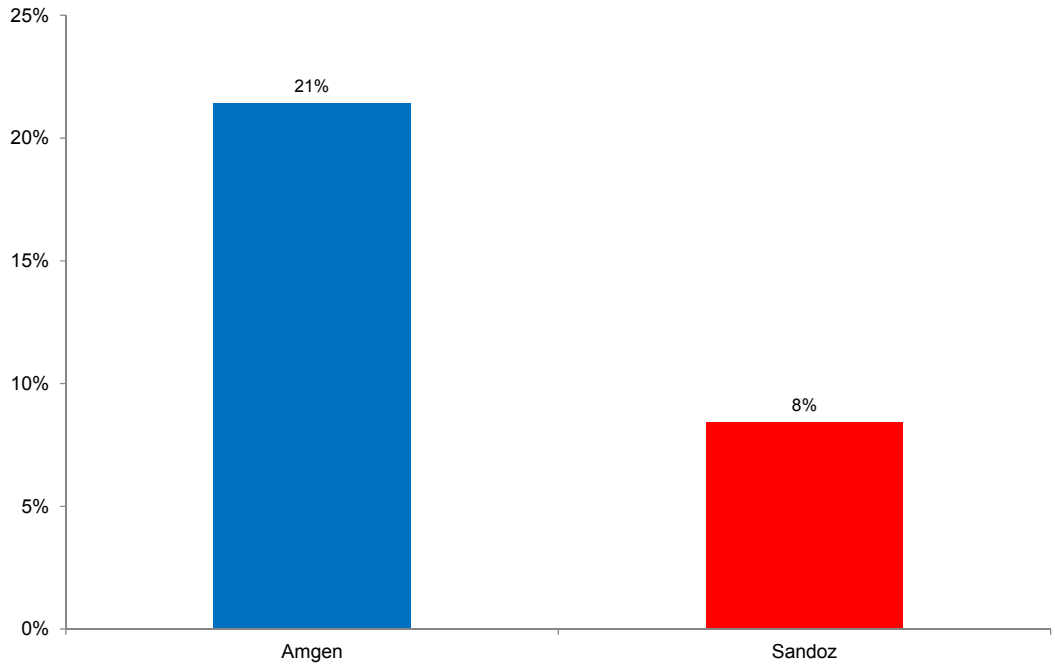
conducting 14 phase III studies, plus an additional 20 phase I and 9 phase II studies.[50] These studies are expensive, time consuming, and highly uncertain. While these investments in R&D and sales and marketing may help Amgen replenish its future revenues, they entail still more financial commitments in the face of potentially declining current revenues.

(43) By contrast, as a biosimilar entrant, Sandoz seeks to capitalize not only on the R&D investment of innovative firms, but also on the post-approval educational and marketing activities innovative firms complete to develop a market for their products. In other words, Sandoz seeks to capitalize on both the scientific innovation of innovative drug developers, such as Amgen, and also the scientific and medical education and physician training Amgen and other innovators provide to develop and expand the markets for their innovative drug products. As a result of its choice of strategy, Sandoz invests far less than Amgen in R&D. As shown in Figure 4 below, in 2014 Amgen devoted 21 percent of its revenues to R&D spending, while Sandoz only spent 8 percent of its revenues on R&D.

[50] Amgen, 2013 10K at 13.

Figure 4

Amgen and Sandoz R&D Expense as a Percentage of Revenue
2014



Source: S&P Capital IQ.

B.2. Unlawfully premature sales of Zarxio would harm Amgen's business

(44) The fact that Sandoz has not disclosed its application or manufacturing processes as called for by the BPCIA for Amgen to review for potential infringement frustrates Amgen's ability to determine whether Sandoz will infringe on Amgen's patents, many of which have years to run. The '427 patent in this case expires in December of 2016, and Amgen has many other patents that could apply to the purification or production of a filgrastim product and could also have many years left to run.

(45) Amgen developed the biological therapeutic product Neupogen®. While I have no medical expertise, I understand that Neupogen®'s active ingredient is a version of human G-CSF also known by its nonproprietary name filgrastim. Amgen obtained FDA approval to make, sell, and promote Neupogen® for five indications:[51] (1) cancer patients receiving myelosuppressive chemotherapy; (2) patients with acute myeloid leukemia receiving induction or consolidation chemotherapy; (3) cancer

[51] A drug receives a set of approved "label indications," or a list of specific conditions and patient populations in which it can be legally marketed as a treatment by the manufacturer, as part of the FDA approval process. "Indications for Drugs (Uses), Approved vs. Non-approved," MedicineNet.com, December 1, 2014, http://www.medicinenet.com/script/main/art.asp?articlekey=20732.

patients receiving bone marrow transplants; (4) patients undergoing peripheral blood progenitor cell collection and therapy; and (5) patients with severe chronic neutropenia.[52]

(46) Amgen also developed a second filgrastim product, Neulasta®, which has been molecularly modified so as to prolong the time period during which Neulasta® remains in circulation, thus allowing Neulasta® to be dosed less frequently than Neupogen®.[53] Amgen has FDA approval to make, sell, and promote its pegfilgrastim product, Neulasta®, for use in treating cancer patients receiving myelosuppressive chemotherapy.[54]

(47) Neupogen® and Neulasta® are highly successful and profitable products. Amgen's SEC filings report that in 2013, its sales of Neupogen® and Neulasta® were $5.8 billion, of which roughly 81% occurred in the United States.[55] Overall U.S. sales of Neupogen® and Neulasta® were $1.2 billion and $3.5 billion respectively.[56] Neupogen® and Neulasta® are Amgen's best-selling products, accounting for 32% of total product sales in 2013.[57] While Amgen does not publically report the profitability of these products, I understand that the contribution margins on Neupogen® and Neulasta® are significant.[58] Amgen, across all of its product lines, has cost of sales equal to approximately 20% of its sales, which is consistent with my understanding of the contribution margins.[59]

(48) On July 24, 2014, Sandoz announced that it filed a Biologics License Application (BLA) with the FDA to market and sell a filgrastim product in the United States under the trade name Zarxio.[60] This announcement followed Sandoz's launch in Europe of the same filgrastim product (under the trade name Zarzio), which Sandoz characterized as "biogeneric" and "biosimilar" to Amgen's Neupogen®, and which has exceeded Neupogen®, its reference product, in European sales.[61] On January 7, 2015, Sandoz announced that its biosimilar filgrastim had been recommended for approval by the FDA Oncologic Drugs Advisory Committee.[62]

(49) I understand that Amgen alleges that Sandoz has not complied with the mandates of the BPCIA, which I understand require, among other things, firms that introduce products that are biosimilar to existing products to provide information to the incumbent to determine whether the entrant might infringe upon the patent rights of the incumbent. Thus while Amgen believes that Zarxio infringes upon at least the '427 patent, Sandoz's failure to comply with the BPCIA has resulted in uncertainty

52 FDA label for Neupogen® (filgrastim), http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103353s5147lbl.pdf

53 I understand that Neulasta® is administered once per chemotherapy cycle whereas Neupogen® is administered daily and that Neulasta lasts in the blood up to 15-times as long as Neupogen. M.D. Green et al., "A radnomized double-blind multicenter phase III study of fixed-dose single administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy," Ann. Oncol. (2003) 14(1): 29-35 and Bob Azelby (Vice- President and General Manager Oncology, Amgen Inc.), Interview, January 30, 2015.

54 FDA label for Neulasta® (pegfilgrastim), http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/pediatricadvisorycommittee/ucm235408.pdf

55 Amgen 2013 10K, p. 42.

56 Amgen 2013 10K, p. 42.

57 Amgen 2013 10K, p. 41.

58 Bob Azelby (Vice- President and General Manager Oncology, Amgen Inc.), Interview, January 30, 2015.

59 Amgen 2013 10K, p. F-2.

60 Sandoz press release, July 24, 2014, http://www.sandoz.com/media_center/press_releases_news/global_news/2014_07_24_FDA_accepts_Sandoz_application_for_biosimilar_filgrastim.shtml

61 Sandoz press release, July 22, 2013, http://www.sandoz.com/media_center/press_releases_news/global_news/zarzio_reg_overtakes_,neupogen_reg_and_granocyte_reg_to_become_most_prescribed_daily_g-csf_in_europe_.shtml

62 "Novartis Biosimilar of Amgen's Neupogen Wins U.S. Panel Backing," Washington Post, January 7. 2015.

regarding the extent of Sandoz's potential infringement. This patent uncertainty prevents Amgen from effectively asserting its intellectual property rights, and magnifies the harm to Amgen from Zarxio's entry. This harm flows from at least three sources. First, unlawfully premature Zarxio sales would directly harm Amgen's revenues and profits from lost sales of Neupogen® and Neulasta®. Second, unlawfully premature Zarxio sales would cause Amgen to reduce its sales, marketing and educational support of innovative new products it has recently introduced, reducing their success and the revenues and profits from those products. Third, unlawfully premature Zarxio sales would result in the erosion of the prices Amgen receives from its sales of Neupogen® and Neulasta®, further reducing the revenues and profits of those products.

(50) If Sandoz were not enjoined from making unlawfully premature sales of Zarxio during the Restricted Period, such sales would reduce Amgen's revenues and profits from sales of its filgrastim products, Neupogen® and Neulasta®. Regardless of Sandoz's pricing strategy, Zarxio's unlawfully premature sales would cut into Amgen's share, reducing the number of units of Neupogen® and Neulasta® that Amgen would sell. Indeed, recent reports project that Amgen will lose substantial share of Neupogen® sales, and find that "[a] low-end estimate has Neupogen® competitors taking at least half the market in five years, 80% should other biosimilars join Sandoz's filgrastim and Granix."[63] Bernstein analyst Ronny Gal stated that "I'm guessing that in the US in five years, Sandoz will be at least half the market."[64] The magnitude of these share loss projections are in part due to the fact that the FDA may approve Zarxio for all five Neupogen® indications, while Teva's Granix product is only approved for one indication, treatment of severe neutropenia in patients receiving chemotherapy.[65] To illustrate the magnitude of potential losses involved, consider if Amgen were to lose half of its U.S. sales of Neupogen® due to unlawfully premature (and potentially infringing) Zarxio sales, this would translate into lost profits of roughly $480 million annually, assuming an 80% contribution margin. Even if Amgen lost only 25% of its U.S. filgrastim sales, its lost profits would be roughly $240 million annually. While Zarxio is not biosimilar to Neulasta®, Amgen believes that, since it has observed substitution between Neupogen® and Neulasta®, some portion of its Neulasta® sales could also be lost to Zarxio, depending on upon how Sandoz prices and markets Zarxio, as well as the contract terms Sandoz might set.[66] If Zarxio's unlawfully premature entry resulted in only a 10% reduction in Neulasta® sales, Amgen would lose over $280 million in addition. In addition to suffering share losses, Amgen would likely have to reduce its own prices in response to Zarxio's unlawfully premature sales. Given the importance of Neupogen® and Neulasta® to Amgen's overall product revenues, such revenue reductions would pose a substantial business risk for Amgen.

(51) In addition, Sandoz's unlawfully premature sales of Zarxio are likely to cause-for an indeterminate number of years beyond the Restricted Period-a significant increase in Amgen's operating costs and expenses above those Amgen would otherwise incur over that period. Because Sandoz's unlawfully premature sales would reduce demand for Neupogen® and Neulasta®, Amgen would experience a lower utilization of its production capacity than it would otherwise enjoy and would lose the associated

63 David Vaczek, "Sandoz gets ready to make the biosimilar case with oncologists," January 20, 2015, Medical Marketing & Media, http://www.mmm-online.com/sandoz-gets-ready-to-make-the-biosimilar-case-with-oncologists/article/393451/

64 David Vaczek, "Sandoz gets ready to make the biosimilar case with oncologists," January 20, 2015, Medical Marketing & Media, http://www.mmm-online.com/sandoz-gets-ready-to-make-the-biosimilar-case-with-oncologists/article/393451/

65 David Vaczek, "Sandoz gets ready to make the biosimilar case with oncologists," January 20, 2015, Medical Marketing & Media, http://www.mmm-online.com/sandoz-gets-ready-to-make-the-biosimilar-case-with-oncologists/article/393451/

66 Bob Azelby (Vice- President and General Manager Oncology, Amgen Inc.), Interview, February 4, 2015.

economies of scale.[67] Amgen would also incur increased marketing, educational, and selling expenses to mitigate the impacts of Sandoz's unlawfully premature sales on Amgen's share, net selling price, and reputation among healthcare providers, payors, distributors, and other market participants. Thus, in addition to the reduced revenues discussed above, the increased costs and expenses resulting from Sandoz's unlawfully premature sales during the Restricted Period would cause a further reduction in Amgen's profits for an indeterminate number of years beyond the Restricted Period.

(52) In response to a loss in revenue, Amgen's management would likely seek to reduce the company's expenses. R&D investment is one of the primary areas where Amgen would be able to reduce expenses if faced with a substantial decrease in revenue, and my conversations with Amgen executives confirm that Amgen's R&D investment and budgets are particularly sensitive to its actual and expected revenue.[68]

(53) Moreover, revenue losses caused by unlawfully premature sales of Zarxio would adversely impact Amgen's sales and profits from other products. The main underlying cause of this spillover to other products is that there is a fixed capacity of sales people, as these personnel need lengthy training before they can properly educate practitioners on the proper use of Amgen's products. Specifically, Amgen has recently introduced two innovations that are in the early stages of their product lifecycles. One is a new first-line indication for Vectibix, a product that treats colorectal cancer, the second leading cause of cancer deaths in the U.S.[69] The second is an on-body injector for Neulasta®, which can be implanted on chemotherapy patients at the time of their chemotherapy, thus removing the need for patients to return to oncology clinics the day after chemotherapy.[70] Additionally, I understand that Amgen has been developing a product called T-VEC, which is intended to treat metastatic melanoma, which it plans to launch later this year.[71] T-VEC is an immunotherapy designed to selectively replicate in tumors (but not normal tissue) and to initiate an immune response to target cancer cells that have metastasized.[72] Amgen believes that this promising treatment for a difficult to treat cancer will be its most complex product launch, due in part to the significant training and education that practitioners would need to effectively need to administer this product.[73]

(54) The sales, marketing, training and educational support of these products is handled by the same salesforce that supports Amgen's Neupogen® and Neulasta® products, and Amgen believes that in the presence of unlawfully premature Zarxio sales, it would likely need to divert sales, marketing and educational support from these products to Neupogen® and Neulasta® to mitigate the risk of share loss and additional erosion in price.[74] For example, I understand that it requires intensive training for enable nurses and other practitioners to correctly install the Neulasta® on-body injector, and that this training is performed by the same sales force that would need to address customer reactions to the premature entry Zarxio. Indeed, market observers expect that Amgen will expend additional

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67 These per-unit cost increases do not include any additional costs that Amgen may incur in restructuring its business in response to the revenue loss, including redeployment and training of the sales force or changes to its manufacturing facilities.

68 Gwen Cummings (Executive Director of Finance for R&D, Amgen Inc.), Interview, January 30, 2015.

69 http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1934128

70 Bob Azelby (Vice- President and General Manager Oncology, Amgen Inc.), Interview, January 30, 2015.

71 Bob Azelby (Vice- President and General Manager Oncology, Amgen Inc.), Interview, February 4, 2015.

72 http://wwwext.amgen.com/media/media_pr_detail.jsp?year=2014&releaseID=1995881

73 Bob Azelby (Vice- President and General Manager Oncology, Amgen Inc.), Interview, February 4, 2015.

74 Bob Azelby (Vice- President and General Manager Oncology, Amgen Inc.), Interview, January 30, 2015.

marketing resources to defend its Neupogen® and Neulasta® products from unlawfully premature Zarxio sales.[75] This diversion of sales, marketing and educational support from its innovative new products to its existing products would likely reduce the success and profits of these new products. Amgen believes that the sales, marketing and educational support for products at the beginning of their lifecycle is crucial to the success, revenues and profits of these products.[76] Therefore, any reduction in success and profits of the new products would likely be long-lasting. Moreover, to the extent that the diversion of support from these new products to Neupogen® and Neulasta® would result in the ineffective use of these new products, or the failure of providers to adopt these products, public health could be harmed.

(55) In addition to the adverse impact on Amgen's revenues, unlawfully premature sales of Zarxio during the Restricted Period would likely make Amgen less attractive to potential investors if investors perceive that Sandoz's unlawfully premature and potentially infringing sales foreshadow new and enduring threats to Amgen's business, Amgen could be forced to alter its financial structure and the research and business priorities the current financial structure enables.[77]

(56) If Amgen were unable to enjoin unlawfully premature sales of Zarxio, and thus be unable to enforce its patent rights with the protections called for in the BPCIA, the risk perception among investors for Amgen's business would likely increase. Analysts and investors would likely reduce their expectations for future revenues and profits of Amgen, resulting in an increased cost of capital just as Amgen's ability to generate revenues and profits from sales of its patented products diminishes.[78] Increasing capital costs make it more expensive for Amgen to conduct its ongoing business, including its underlying R&D activities, and would increase the expected return required to make any given R&D investment profitable. As a result, Amgen would have a diminished ability to pursue R&D opportunities and would be less likely to recoup its investment in those it did pursue. In addition, other biosimilar manufacturers may be inspired to challenge Amgen's other patent-protected innovations or attempt to evade Amgen's patent protection, thus increasing Amgen's litigation costs and further decreasing the investment capital available to operate its business and fund ongoing R&D.

B.3. Summary

(57) If Sandoz were not enjoined from making unlawfully premature sales of Zarxio or infringing sales if it were determined that Zarxio infringed on Amgen's patents, Sandoz's unlawfully premature sales would cause significant short- and long-run reductions in Amgen's revenues, profits, and R&D expenditures, potentially undermining Amgen's ability to sustain its continued innovation and commercialization of new therapeutic products and injuring Amgen's reputation in investment communities. The reduction in revenue and profits caused by Sandoz's unlawfully premature sales would likely cause a significant reduction in Amgen's expenditures on R&D, adversely impacting Amgen's development of future treatments and reducing its ability to sustain its business model. Further, unlawfully premature Zarxio sales would not only impact sales of Neupogen® and Neulasta®,

[75] David Vaczek, "Sandoz gets ready to make the biosimilar case with oncologists," January 20, 2015, Medical Marketing & Media, http://www.mmm-online.com/sandoz-gets-ready-to-make-the-biosimilar-case-with-oncologists/article/393451/

[76] Bob Azelby (Vice- President and General Manager Oncology, Amgen Inc.), Interview, January 30, 2015.

[77] Mary Lehmann (Vice President Finance and Treasury, Amgen Inc.), Interview, February 3, 2015.

[78] Henry Grabowski, "Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition," *Nature Review Drug Discovery,* published online May 12, 2008 at 4.

but would also have spillover effects on other innovative products Amgen has recently introduced. Without dependable enforcement of Amgen's patents against infringing competitors, Amgen (and other innovative firms) would have lower incentives to develop new treatments, resulting in an overall reduction in social welfare.

C. Analysis of competitive effects from entry

(58) I begin this section by describing important characteristics of the market for filgrastim products that impact the competition between an incumbent supplier and a new supplier in the market. I also review examples of entry for other pharmaceuticals that may provide insight into the competitive dynamics in this case. Finally, I examine the impact of unlawfully premature sales of Zarxio on Amgen under a variety of combinations of alternative entry strategies by Sandoz, potential responses by Amgen, and assumptions about customers' reactions to those choices.

(59) In my opinion, these analyses demonstrate that:

- Filgrastim products are used primarily in two types of settings, hospitals and clinics, each of which offers different and sometimes conflicting pricing incentives for competitors and purchasers. It cannot be confidently predicted which pricing incentives would dominate Sandoz's marketing and sales strategy for Zarxio or Amgen's responses to competition from Zarxio.

- Unusual government reimbursement regulations provide substantial competitive advantages to Sandoz (a new entrant) and constrain Amgen's ability to compete effectively to defend its sales.

C.1. Market characteristics impacting competition for filgrastim products

C.1.1. Overview

(60) Certain characteristics of the market for filgrastim products differ in profound and sometimes surprising ways from the competitive dynamics in other product markets. In some situations, these characteristics provide unexpected competitive incentives to new entrants that would affect the impact of Sandoz's unlawfully premature Zarxio sales.

(61) For most products, the entry of new firms selling competing products typically enhances consumer welfare through increased choice and/or lower prices. There are several important distinctions, however, between such "conventional" market dynamics and the market for filgrastim products. These distinctions make predictions based on such "conventional" market dynamics inapplicable to the market for filgrastim products.

(62) One important distinction is that many of the individuals or entities that select and directly purchase filgrastim products are different from the entities that are responsible for paying for their use. In certain important situations, healthcare providers who select and directly purchase the filgrastim products they administer to patients are then reimbursed for the products they purchase and administer by a third-party payor (e.g., Medicare or a private health insurer). This fact can significantly affect the incentives and choices of these purchaser/providers when deciding among competing products.

(63) Another important distinction is that the measure used to determine the amount that a third-party payor will reimburse the provider for the purchase and administration of a filgrastim product may differ based on the setting in which the patient receives the filgrastim product. I discuss below the different

methods for calculating reimbursement amounts based on treatment settings (or "segments"). Further complicating the market dynamics is that the treatment setting in which a patient receives filgrastim products may change over the course of a patient's treatment.

(64) Because Zarxio is a biosimilar product and so-called large molecule drug, one might be tempted to use the experience of small-molecule generic drugs to predict how Zarxio's unlawfully premature sales may affect competition for filgrastim. However, there are many substantial and important differences between filgrastim products and small molecule generics that make such a comparison misleading and inapplicable. In addition, my understanding is that Zarxio's U.S. launch would be the first biosimilar product to be available in the United States. Without substantial historical experience with biosimilar products, there is substantial uncertainty about how competition among an incumbent supplier and a new supplier for biosimilar products will evolve through time. Analyzing the factors that will affect the competitive dynamics is the focus of the remainder of this section.

C.1.2. Market characteristics affecting competition

C.1.2.1. Filgrastim use across treatment settings or segments

(65) The payer for filgrastim products is either private or public and the sites can generally be categorized into three segments: oncology clinics, hospitals, and pharmacy purchasers.[79]

(66) I understand that providers who administer filgrastim on an outpatient basis are reimbursed by Medicare Part B and many private insurers based on the drug's historical Average Selling Price or ASP.[80] I also understand that, under the ASP based system of reimbursement, the provider reimbursement for a given drug in any given quarter is based on a fixed mark-up percentage over that drug's net selling prices over the previous four quarters with a one quarter lag (e.g., ASP plus 6% for Medicare Part B reimbursements).[81] Under Medicare, an important exception occurs when a new product is first introduced to the market. In such cases, because the new product has not previously been sold in the market, there is no historical average selling price on which to base its reimbursement. Consequently, for new product entrants, Medicare will initially reimburse providers who use the new entrant's product based on the new product's list price or Wholesale Acquisition Cost, or "WAC," plus a fixed percentage markup (e.g., typically WAC plus 6% for Medicare reimbursements).[82] Thus, providers will be reimbursed by Medicare for a new drug at WAC plus 6%

[79] Many hospitals operate their own clinics for patients who do not need to remain overnight (known as "outpatient" treatment) in addition to treating patients that remain in the hospital overnight ("inpatient").

[80] The ASP is based on the net selling prices Amgen charged across segments, i.e., to clinics, private hospitals (including drugs sold for inpatient use), and pharmacies. My understanding is that the reimbursement methodologies employed by private insurers, managed care organizations, and HMOs to outpatient providers, both clinics and hospitals, either utilize an ASP-based methodology similar to Medicare or are based on a drug's Wholesale Acquisition Cost or WAC, which is effectively the drug's list price.

[81] Many private payors who use an ASP-based reimbursement methodology reimburse at ASP plus a fixed percent that is higher than 6%. The figure may also be impacted by the status of the U.S. budget. I understand that due to the budget sequester, Medicare reimbursements are currently ASP+4.3%.

[82] WAC can be thought of as the product's list price.

until Medicare has at least two full quarters of prior selling experience on which to base an ASP calculation.[83] Thereafter, the new product will typically be reimbursed by Medicare at ASP plus 6%.

(67) For a new, biosimilar product like Zarxio, this calculation is slightly different because the ASP is calculated off the innovator's price not the entrants. The reimbursement is initially based on the biosimilar product's WAC, as above, but the markup is set to equal 6% of the ASP for the innovator reference drug to which the new drug is biosimilar. So Sandoz's Zarxio would be reimbursed at the Zarxio WAC, plus 6% of the Neupogen® ASP.

(68) For inpatient treatments, hospitals are reimbursed by Medicare Part A according to a fixed schedule of fees for a bundle of services and associated treatments (including drugs) called a Diagnosis Related Group or "DRG." Under the DRG reimbursement methodology, hospitals are not reimbursed separately for individual services and drugs.[84] Rather, a hospital generally receives the same reimbursement for patients with the same DRG. Inpatient hospital reimbursements from private payors are similar in concept to the DRG-based reimbursements paid by Medicare, though there are differences in how the payments are determined.

(69) As described in more detail below, the differences in reimbursement methodologies across segments affect how Sandoz would set its prices for Zarxio if it were not enjoined and Amgen would set prices for its filgrastim products in response. Providers in certain segments, such as inpatient hospitals that are reimbursed under a DRG-based methodology, are likely more focused on the relative acquisition costs of Zarxio, Neupogen®, and Neulasta®. Providers in segments where reimbursements are determined under ASP or WAC-based methodology are likely more likely to be focused on the drugs' relative cost recoveries (i.e., the difference between their acquisition cost for the drug and the reimbursement payment they receive), particularly the cost recoveries for their largest payors, and not only their relative acquisition costs.[85]

C.1.2.2. Unlawfully premature sales of Zarxio would reduce Neupogen® and Neulasta® sales.

(70) Even though overall demand may be fairly inelastic (as the product addresses serious and potentially fatal health risks), there is substitution between Neupogen® and Neulasta®, and Sandoz's unlawfully premature sales of Zarxio during the Restricted Period would likely erode Amgen's sales of Neupogen® and and to a lesser extent Neulasta®. Specifically:

- Amgen's own experience suggests that a relatively small change in the relative net acquisition costs of Neupogen® and Neulasta® results in providers switching between the two products. In October 2010, smaller clinics had been moving away from Neulasta® due to reimbursement concerns, i.e., doctor margins were driving substitution. When Amgen switched to unitary pricing, doctors moved back to the product.[86]

[83] In other words, Medicare uses the WAC in place of ASP for up to the first three quarters of the new entrant's commercial launch. Using the WAC means that Medicare's reimbursements do not take into account any discounts or rebates the new entrant provides to its customers during this initial period.

[84] http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/downloads/AcutePaymtSysfctsht.pdf

[85] Bob Azelby (Vice President and General Manager Oncology, Amgen Inc.), Interview, January 30, 2015.

[86] Bob Azelby (Vice President and General Manager Oncology, Amgen Inc.), Interview, January 30, 2015.

- I understand that Teva's Granix acquired roughly 14% of filgrastim sales in the first fourteen months after launch.[87] However, Sandoz has competitive advantages relative to Teva's Granix product, which shares only a single indication with Neupogen®. Sandoz's product is biosimilar and Sandoz has also signaled its plans to seek an interchangeable label. A Bernstein analyst has projected that Sandoz will take at least half the market within five years.[88] In Europe, Zarzio has exceeded the sales of Neupogen®.[89]

C.2. Implications of reimbursement programs and policies on competition

(71) Healthcare providers' choices between filgrastim products depend on therapeutic characteristics such as safety and efficacy, as well as considerations such as convenience and ease of administration. Providers, however, also have an economic incentive to maximize their profit. Depending on the reimbursement methodology applied, which may differ depending on the treatment setting, providers can generally maximize their profits by making purchasing decisions that minimize their acquisition costs for filgrastim products and/or maximize their cost recovery for filgrastim products. Because the primary reimbursement methodologies differ across the segments where filgrastim products are used, so do the competitive dynamics facing healthcare providers and, therefore, Sandoz and Amgen.

(72) If Sandoz makes unlawfully premature sales of Zarxio in the United States during the Restricted Period, Sandoz can choose among at least three primary strategies for Zarxio:

- Target the cost-sensitive hospital segment (i.e., inpatient hospital use)
- Target the cost recovery-sensitive clinic segment (i.e., outpatient clinic use)
- Compete with Amgen to win sales across both segments

(73) At this time, it is not clear what strategy Sandoz will decide to follow or what actions Amgen will take in response. I understand that there have been indications Sandoz will target the cost recovery-sensitive clinic segment,[90] but there are also predictions by analysts that Sandoz will come out with a 30 to 35 percent discount off of list price.[91] Sandoz has stated that Zarxio will be priced comparably to Neupogen®. For example, Mark McCamish, the head of Global Biopharmaceutical and Oncology Injectables Development at Sandoz, has been quoted as stating that Sandoz "can't say that the price will be less because in some situation the price will be at parity."[92] Another source states that, when asked whether the price of Sandoz's product would be lower than Neupogen®, the "company

87 Bob Azelby (Vice President and General Manager Oncology, Amgen Inc.), Interview, January 30, 2015.
88 David Vaczek, "Sandoz gets ready to make the biosimilar case with oncologists," January 20, 2015, Medical Marketing & Media, http://www.mmm-online.com/sandoz-gets-ready-to-make-the-biosimilar-case-with-oncologists/article/393451/
89 David Vaczek, "Sandoz gets ready to make the biosimilar case with oncologists," January 20, 2015, Medical Marketing & Media, http://www.mmm-online.com/sandoz-gets-ready-to-make-the-biosimilar-case-with-oncologists/article/393451/
90 Bob Azelby (Vice President and General Manager Oncology, Amgen Inc.), Interview, January 30, 2015.
91 David Vaczek, "Sandoz gets ready to make the biosimilar case with oncologists," January 20, 2015, Medical Marketing & Media, http://www.mmm-online.com/sandoz-gets-ready-to-make-the-biosimilar-case-with-oncologists/article/393451/
92 Shannon Firth, "FDA Advisory Committee Endorses Neupogen Biosimilar," Public Health & Policy, January 8, 2015.

indicated that [Zarxio] could be priced at parity with Neupogen" but that other mechanisms such as rebates would be in play.[93]

(74) It is clear, however, that unlawfully premature sales of Zarxio would enable Sandoz to gain market share at Amgen's expense, lead to price erosion for filgrastim products, and put Amgen at a competitive and recurring disadvantage and Sandoz at a competitive advantage after the Restricted Period relative to their positions had Sandoz complied with the requirements of the BPCIA.

(75) Hospitals use filgrastim to treat patients on an inpatient and outpatient basis. In the inpatient setting, hospitals tend to be cost-sensitive, and to maximize their profit under fixed, DRG-based reimbursements used for inpatient treatments, hospital purchasers typically focus on obtaining the lowest prices for drugs regarded to be therapeutically similar. If Zarxio were viewed by payors and providers as a therapeutic alternative for either Neupogen® or Neulasta®, Sandoz would have an incentive to price Zarxio lower than Neupogen® or the equivalent price of Neulasta® to target cost-sensitive inpatient hospital usage. In other words, competition between Sandoz and Amgen would primarily focus on which drug costs the hospital the least for the treatment provided during the patient's hospital stay. In response, Amgen may be forced to lower its prices to hospitals to retain the business.

(76) If Sandoz decided to target clinics when launching unlawfully premature Zarxio sales, the ASP-based reimbursement methodology would have the greatest impact on Sandoz's pricing strategy. Clinical filgrastim usage is focused largely on treating and preventing the onset of chemotherapy induced neutropenia, and Zarxio would be a potential substitute for both Neupogen® and Neulasta®. Because of the provider's cost recovery incentives under ASP-based reimbursements, Sandoz would compete with Neupogen® and Neulasta® by setting its prices and discounts such that the cost recovery for Zarxio (i.e., the difference between reimbursement to the clinics and the clinics' acquisition costs) is higher than, or at least equal to, that of Neupogen® and Neulasta®.

(77) A third strategy Sandoz might follow is to make unlawfully premature sales in both the hospital and clinic segments. In choosing this strategy, Sandoz would have to find the balance between the somewhat conflicting incentives of hospitals' desire for low prices on one hand and clinics' desire for higher cost recovery on the other hand. Because the methodology for calculating the ASP-based reimbursements incorporates prices in both segments, lower prices in the hospital segment would reduce Zarxio's ASP-based reimbursements and make Sandoz less competitive among clinics. Sandoz would have to determine the optimal pricing balance across the segments to compete with Amgen in both.

(78) In doing so, Sandoz would likely set its hospital net price for Zarxio below Amgen's current net prices and set Zarxio prices and discounts for clinics in such a way as to generate a larger cost recovery "profit" for clinic providers than they can obtain by purchasing and administering Neupogen® and Neulasta®. Regardless of the exact prices that Sandoz decides to charge, such a strategy would likely lead to substantial revenue reductions for Amgen through both price erosion and share loss. As in the previous examples, Amgen's primary response to Sandoz's unlawfully premature sales would be to

[93] Anees Malik and Hristina Ivanova, "Sandoz's Biosimilar Filgrastim Scores Positive Recommendation from FDA Advisory Committee," Decision Resources, January 22, 2015.

reduce prices in one or both segments, which again leads to a downward price and reimbursement spiral as a result of the ASP calculation and substantial recurring harms.

D. Tests for injunction

(79) In deciding whether to grant an injunction, I understand the Court will consider and balance the following issues:

i. The economic effects of the patent uncertainty created by Sandoz's failure to comply with the requirements of the BPCIA;

ii. Whether Sandoz's unlawfully premature Zarxio sales would cause irreparable harm to Amgen (i.e., whether the manufacture, importation into the U.S., sale, offer to sell, and/or use of Zarxio in the United States prior to the time that Sandoz could have entered in compliance with the BPCIA and prior to the expiration of any applicable Amgen patents would cause irreparable harm to Amgen);

iii. Whether monetary damages would be adequate to compensate Amgen for the harms that Sandoz's unlawfully premature sales are likely to cause;

iv. Whether an injunction is warranted given the burdens such an injunction would place on Amgen and Sandoz, respectively; and

v. Whether the public interest would be disserved if Sandoz were enjoined.

I first address the fact that the patent uncertainty created by Sandoz's failure to abide by the requirements of the BPCIA itself creates irreparable harm to Amgen. I then address the question of whether Sandoz' unlawfully premature entry causes irreparable harm to Amgen, and discuss the economic factors underlying each of these issues in tum in the sections below.

D.1. The patent uncertainty created by Sandoz's failure to comply with the requirements of the BPCIA provides grounds for granting an injunction

(80) Sandoz's refusal to comply with the requirements of the BPCIA has three effects, each of which provides grounds for granting an injunction. First, it has made it more difficult for Amgen to determine whether Sandoz is infringing Amgen's patents. This refusal to comply with requirements in the BPCIA that protect patent rights creates patent uncertainty that threatens to undermine the value and effectiveness of Amgen's patents, and is inconsistent with the efficient operation of the patent system and the BPCIA. In particular, one aspect of determining whether preliminary injunctions should be issued is the likelihood of success on the merits. However, Sandoz's refusal to comply with requirements in the BPCIA has made it difficult for Amgen to determine which patents are infringed or how. This fact leads me to conclude that, from an economic perspective, an injunction should be issued. That is, Sandoz should not be rewarded for any difficulties in demonstrating likelihood of success in this or any subsequent patent litigation created by its lack of transparency. Allowing Sandoz to evade the patent protection requirements in the BPCIA and launch a product that may well have been found to be infringing had Sandoz followed the requirements would be contrary to the public interest. Amgen has many patents to processes used in the manufacture of recombinant

proteins, including patents directed to techniques that can be used in manufacturing filgrastim products, and Amgen's ability to enforce its patents and obtain the rewards contemplated by the patent system and the BPCIA should be supported with an injunction preventing Sandoz from marketing products which it has acted deliberately to evade potential infringement claims against prior to launch. Once launched, irreparable harm to Amgen would occur even if the products were later proven to be infringing and enjoined.

(81) Second, if Sandoz had complied with the requirements of the BPCIA and Amgen had determined that Sandoz's manufacture of Zarxio infringed Amgen's existing patents, I understand that compliance with the proceedures mandated by the BPCIA would have required as many as 410 days before Zarxio entry could occur.

(82) Finally, the fact that Zarxio could be the first biosimilar product to be introduced under the BPCIA creates a potential further societal harm should Sandoz's interpretation of the BPCIA become accepted. This harm would flow from the increased patent uncertainty that other firms would have over their patent protected biologic products, and the incentives provided to generic entrants to introduce biosimilar products that could infringe upon the patents of incumbents, and to attempt to conceal any such infringement. This would create a reduction in the incentives to invest in R&D and innovate throughout the industry, thus harming society. Further, as matter of public policy, if Sandoz's interpretation of the BPCIA were to be accepted, it is likely that similar litigation in the future would face the same issue as in this litigation: absent transparency regarding possible infringement, assessing the likely harms, and whether they are irreparable, becomes very difficult.

D.2. Irreparable harm to Amgen

(83) In my opinion, if Sandoz not is enjoined from disregarding the requirements of the BPCIA and, if appropriate, from making infringing Zarxio sales in the United States, Amgen would suffer a number of recurring harms. First, as a direct result of Sandoz's unlawfully premature sales, Amgen would suffer revenue reductions, share losses, and increased costs, leading to a substantial reduction in Amgen's profits. As discussed above, these lost profits could likely be in the hundreds of millions of dollars. The lost profits caused by Sandoz's unlawfully premature sales would recur beyond the Restricted Period, particularly to the extent that Sandoz's failure to comply with the BPCIA allows it to infringe on Amgen's patents. Because these direct, recurring effects of Sandoz's unlawfully premature sales would persist into the indefinite future, there is no foreseeable date in the future when the full extent of harms to Amgen can be estimated with reasonable certainty. Second, Amgen's lost profits would cause substantial and recurring harm to Amgen's ability to invest in the R&D and commercialization needed to support its current pipeline of innovative new products and to discover and develop future products. Third, Sandoz's unlawfully premature sales would harm Amgen by reducing the success, revenues and profits of other innovative new products. In my opinion, the profit losses would be disruptive to Amgen's cycle of innovation and commercialization of new products central to Amgen's business. Fourth, as a direct result of Zarxio's unlawfully premature sales, Amgen would suffer a disruption of its customer relationships resulting from the uncertainty over the effectiveness of Amgen's patent protection, as well as other recurring harms to Amgen's business.

(84) In this section, I discuss the direct, immediate, and recurring harms to Amgen due to Sandoz's unlawfully premature Zarxio sales, as follows:

- Amgen's lost profits, due to share losses and revenue reductions, would be substantial.
- Amgen's lost profits would begin immediately and recur into the indefinite future well after the Restricted Period.
- These lost profits would be disruptive to Amgen's cycle of R&D innovation.
- Amgen would suffer other intangible harms that are difficult to quantify monetarily.

D.2.1. Amgen's profit losses from unlawfully premature sales would be substantial

(85) Unlawfully premature sales of Zarxio would compete with both of Amgen's existing filgrastim products, Neupogen® and Neulasta®. Amgen faces the strong likelihood of losing significant revenue through a combination of reduced market share and/or lower prices, as described in Section C. While there is uncertainty about the precise impact of Zarxio's unlawfully premature sales on Amgen, it is clear that Amgen's likely profit losses are substantial. Some of this uncertainty derives from the fact that many factors that would determine the impact on Amgen are unknown, such as Sandoz's future marketing and pricing strategy, Amgen's future price and marketing reactions, the fraction of customer demand that might shift to Zarxio, the effect of eventual post-patent entry of new competitors and the complex evolution and interaction of all those factors through time.

(86) The magnitude of losses that Sandoz's unlawfully premature sales would cause to Amgen's business over time cannot be determined with reasonable certainty in advance. Nonetheless, it is clear that Sandoz's unlawfully premature sales would cause Amgen to incur substantial lost profits, although there is uncertainty about the full magnitude of those lost profits. Lost profits of the magnitude and duration likely to occur would impose uncertainty and disruption to Amgen's business model and planning, including a reduced ability to invest in R&D as described below.

D.2.2. Amgen's profit losses would persist and recur even after the Restricted Period

(87) Zarxio's unlawfully premature sales would result in persistent and recurring revenue reductions and lost profits for Amgen well after the Restricted Period. First, by making unlawfully premature Zarxio sales during the Restricted Period, Sandoz would obtain a substantial head-start advantage that would allow Sandoz to gain and maintain more market share than it would otherwise achieve by beginning Zarxio sales after the Restricted Period, and this market share advantage would persist into the indefinite future. Conversely, as a direct result of Zarxio's unlawfully premature sales, Amgen's market share after Sandoz begins making unlawfully premature sales of Zarxio would be lower than it otherwise would have been for both Neupogen® and Neulasta®. Second, the profits Amgen would lose due to Sandoz's unlawfully premature sales would have a lasting and recurring impact on its R&D investment and its ability to maintain the cycle of R&D and innovation that allows Amgen to develop and commercialize its next generation of products.

D.2.2.1. Recurring loss due to persistence of share losses

(88) If Sandoz is not enjoined from making disregarding its obligations under the BPCIA and, if appropriate, further enjoined from making infringing Zarxio sales prior to the expiration of Amgen's patents, Sandoz's unlawfully premature sales would cause Amgen's filgrastim market share to be lower than it would have been had Sandoz waited until after the Restricted Period to sell Zarxio. The decrease in Amgen's filgrastim share would persist for an indefinite period of time, but in any case well after the Restricted Period. Furthermore, Sandoz's unlawfully premature entry would likely divert the sales, marketing, and educational efforts of Amgen from the support of newly introduced products to supporting the sales of Neupogen® and Neulasta®, diminishing the success of these products, and further harming Amgen. I understand that Amgen has a variety of new products being introduced, such as the Neulasta® on-body injector that could be highly successful products. However, Amgen's oncology business has limited staff to conduct the sales, marketing and educational support for its products, and such sales, marketing and educational support are important for the success of its products, especially for new product launches. This diversion of support would harm Amgen by reducing the success and future profitability of these products.

(89) In my opinion, by starting unlawfully premature Zarxio sales during the Restricted Period, Sandoz would obtain a substantial head-start advantage relative to what Sandoz otherwise would achieve if it waited until after the Restricted Period. In part because of the exposure to physicians and other key decision makers and the ability to build physician experience with Zarxio during the Restricted Period as a result of its unlawfully premature sales, Sandoz would gain and maintain a higher share of the market sooner than it would otherwise achieve and it would maintain this advantage after Amgen's patents expire. Sandoz's market share gains would accrue from Amgen during the Restricted Period, persist relative to Amgen in the post-Restricted Period, and accrue from other filgrastim manufacturers that wait to enter until after they comply with the BPCIA.

D.2.3. Other intangible harms to Amgen

(90) Zarxio's unlawfully premature sales would also lead to several other less tangible but recurring harms to Amgen that are difficult to quantify and compensate by monetary damages. I discuss some of these harms below.

(91) If Amgen were unable to enforce the patent protections of the BPCIA or to enjoin unlawfully premature sales of Zarxio, the risk perception among investors for Amgen's business would likely increase. Uncertainty over patent protected revenue and cash flow would affect the market valuation of innovative drug companies.[94] This reduction in market value in turn increases the cost of capital for Amgen, reducing its ability to continue to invest in additional R&D and raising its costs to finance current operations. Increasing capital costs would also increase the expected return required to make any given R&D investment successful. As a result, if Sandoz were not enjoined from making unlawfully premature sales of Zarxio, Amgen would likely undertake fewer such opportunities and be less likely to recover its investment on those it does undertake.

[94] Henry Grabowski, "Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition," *Nature Review Drug Discovery*, published online May 12, 2008 at 4.

(92) In addition, other generic or biosimilar product manufacturers may be inspired to challenge the enforcement of Amgen's patent-protected innovations and disregard the requirements of the BPCIA, thus increasing Amgen's litigation costs and further decreasing the investment capital available to operate its business and fund ongoing R&D. Moreover, the impact of an increase in Amgen's cost of capital and potential future litigation expenses would be difficult to estimate with reasonable confidence and would likely recur into the indefinite future.

(93) Amgen's reputation among doctors, patients, and payors could also be harmed by Sandoz's unlawfully premature sales. If Sandoz were to enter the market now, and later to be enjoined because of enforcement of a patent the applicability of which Amgen only later learns, the resulting removal of Sandoz's product from the market would cause customer confusion that Sandoz could portray as, and that could therefore be seen as, Amgen's fault. Amgen faces the risk of lasting harm to its goodwill caused by its enforcement of rights granted to it under the BPCIA and the U.S. patent system.

D.3. Inadequacy of monetary damages

(94) Monetary damages would be inadequate to compensate Amgen for the harms caused by unlawfully premature (and potentially infringing) sales of Zarxio for at least five reasons: (i) harms to Amgen from patent uncertainty (e.g., concerns that Amgen's patents will be less enforceable and hence less valuable if Sandoz were permitted to disregard the requirements of the BPCIA aimed at protecting patent rights; as well as uncertainty as to what patents are being infringed by Sandoz) are inherently difficult to quantify and hence compensate through monetary damages; (ii) other harms to Amgen that are monetary in nature are uncertain and difficult to reliably estimate, and there would be inevitable dispute over alternative measures of the magnitude of those harms; (iii) Amgen's monetary losses caused by Sandoz's unlawfully premature sales would continue to recur into the indefinite future, persisting after the Restricted Period and possibly for as long as Amgen continues to sell filgrastim products; (iv) the resulting revenue losses would have monetary and non-monetary repercussions, such as lost R&D investment opportunities, that in tum cause far-reaching harm that would persist into the distant future; (v) other intangible harms such as the disruption of Amgen's business, disruption to Amgen's customer and payor relationships, and the diminished ability to maintain and recruit key personnel, are inherently recurring and non-monetary, making it difficult to establish a monetary equivalent.

(95) Sandoz's unlawfully premature sales of Zarxio would fundamentally and irrevocably alter the nature of the market for filgrastim products by adding the first biosimilar competitor to the market. The revenue and profit losses Amgen would suffer are difficult to predict reliably ex ante, but they are likely to be substantial and recur well after the Restricted Period. Since the harms caused by Sandoz's unlawful premature entry would continue to recur for an indefinite time period well beyond the Restricted Period, the retrospective calculation of Amgen's lost profits would either have to be postponed far into the future, or multiple interim adjudications would be required to compensate Amgen as and when the harm caused by Sandoz's unlawful premature entry accrues.

(96) Zarxio's unlawfully premature sales would diminish Amgen's ability to invest in the R&D necessary for Amgen to continue to successfully develop innovative drugs. Given the inherent uncertainty in the

research on which Amgen focuses, the harm to Amgen's business from Zarxio's unlawfully premature sales will be difficult to predict and quantify, and monetary damages cannot restore to Amgen the fruits of its lost innovation. For example, Amgen was forced to delay clinical trials for denosumab after the revenue decline Amgen absorbed in 2007. The value of obtaining earlier FDA approval of such a drug would be very difficult to establish with reasonable certainty. Similarly, if Amgen were to delay or cancel a discovery R&D project and, as a result, another company were to obtain a patent that otherwise could have been Amgen's, the losses to Amgen would be potentially enormous, would recur over a long time period, and be difficult to quantify with any reasonable certainty. Monetary damages would not be adequate compensation for the loss of a potentially game-changing opportunity. In short, monetary damages are inadequate to compensate Amgen for the harm unlawfully premature sales of Zarxio would cause to Amgen's future innovation and core business.

(97) Amgen would also suffer intangible harms such as harm to its reputation, loss of customer relationships, diminished ability to maintain and recruit key personnel, and increases in its cost of capital. Monetary damages would be inadequate to compensate for these harms as they too are recurring in nature and inherently non-monetary, making it difficult to establish a monetary equivalent.

D.4. Balance of burdens

(98) The burden Amgen would bear if Sandoz were not enjoined from an unlawfully premature launch of Zarxio in the United States is far larger than the burden Sandoz would bear if Sandoz were enjoined. The different burdens faced by Amgen and Sandoz are properly analyzed in light of the different business models of the two companies. Amgen would incur greater hardships owing to the threat that unlawfully premature (and potentially infringing) entry poses to Amgen's business. In contrast, Sandoz's business routinely accommodates the calculated risks associated with adverse litigation outcomes. A failure to enjoin Sandoz's unlawfully premature sales of Zarxio would also subject Amgen to substantially larger financial losses than Sandoz would face in losing the potential for incremental sales. In addition, Amgen would suffer greater hardships in the form of disruption to its customer relationships and risk to its reputation with investors than Sandoz stands to experience from a delay in forming its customer relationships until after the Restricted Period.

(99) Each of these factors is discussed below. First, however, it is important to note that Sandoz largely brings the burdens of an injunction on itself. Sandoz could have complied with the BPCIA and, as appropriate, could wait until Amgen's patents expire to launch Zarxio. In fact, one of the steps of the BPCIA information exchange calls for the biosimilar applicant to identify those patents for which it will wait for expiry before commercially marketing its product.

D.4.1. Burdens on Amgen from the disruption of Amgen's business model are greater than the corresponding burdens imposed on Sandoz by an injunction

(100) Amgen's business depends upon its ability to sustain innovative R&D efforts by reinvesting profits from its patent-protected drugs. Amgen invests heavily in R&D to discover and commercialize innovative products for previously unmet medical needs, and this research is expensive and highly uncertain. Amgen expects and depends upon the security and predictability of its patent rights, both to provide a reliable source of internally generated funds to sustain R&D and to ensure that future

returns will be sufficiently secure to justify the enormous investment necessary to discover and commercialize new innovations.

(101) As described above, the harms imposed on Amgen by Sandoz's unlawfully premature Zarxio sales include the disruption of Amgen's core business in several important ways. Amgen's lost profits from Zarxio's unlawfully premature sales would hinder Amgen's ability to sustain the level of research and development investment it otherwise would make. In addition, the loss of dependable enforcement of patent rights associated with a decision to allow Sandoz to compete against Amgen's patented products by ignoring the patent protections contained in the BPCIA would undermine investor confidence in Amgen's fundamental business, which depends upon the security of its patent rights, and increase its cost of capital.

(102) In contrast to Amgen, manufacturing and selling copies of patented products is a conscious part of Sandoz's business strategy. An injunction against unlawfully premature Zarxio sales would merely postpone Sandoz's sales to after Sandoz's obligations under the BPCIA are met, assuming Zarxio was determined to not infringe on Amgen's patents. The burden of an injunction against unlawfully premature sales of Zarxio is wholly avoidable for Sandoz by simply complying with the requirements of the BPCIA.

(103) The risks associated with Sandoz's business strategy are of its own choosing and, consequently, so are the burdens associated with this strategy. In operating its business, Amgen's has chosen other risks, notably those associated with developing and commercializing innovation treatments. In contrast, the consequences of Sandoz's patent challenges and infringing sales burden Amgen with risks that are not of Amgen's choosing.

D.4.2. Financial burdens on Sandoz from an injunction are considerably smaller than the corresponding burdens on Amgen from allowing Sandoz to make unlawfully premature sales

(104) The revenue reductions that Amgen would suffer if Sandoz makes unlawfully premature Zarxio sales would be considerably larger than the revenues that Sandoz might obtain through those sales, making the financial burden on Amgen larger if Sandoz is not enjoined than the financial burden on Sandoz if Sandoz were enjoined.[95] Any sale that Sandoz takes away from Amgen as a result of an unlawfully premature sale by Sandoz would reduce Amgen's revenues and increase Sandoz's revenues. To the extent that Sandoz's prices would be lower than the equivalent Amgen prices, Amgen's reduction in revenues would be larger than Sandoz's gains. In other words, for each unit that Sandoz obtains from Amgen, Sandoz would generate less revenue than the corresponding reduction in Amgen's revenue. In aggregate, therefore, Sandoz's unlawfully premature sales of Zarxio would generate less total revenue than Amgen's lost sales of Neupogen® and Neulasta®.[96] Of

[95] In considering the balance of burdens, another comparison would be Amgen's lost profits compared to Sandoz's profit gains. This comparison is not possible without information on Sandoz's profits from Zarxio sales. However, it seems unlikely that Sandoz would be able to produce Zarxio more efficiently and, therefore, at higher profit margins than Amgen can product Neupogen® and Neulasta®. Assuming Sandoz's profit margins are lower than Amgen's, the relative comparison would tip further in Amgen's favor.

[96] There are two potential exceptions for which Sandoz's sales could generate sufficient revenue to cover Amgen's losses. First, if demand for filgrastim products were elastic, Sandoz's price reduction could theoretically expand the total filgrastim sales and provide Sandoz with sufficient sales to cover the difference. This appears unlikely given that the overall demand for filgrastim

course, to the extent that Sandoz generates higher revenues from these sales, due to following a particular pricing strategy, there will be no benefit to society from lower prices.

(105) In my opinion, Amgen is likely to suffer revenue losses as a result of price erosion, during the Restricted Period and continuing indefinitely thereafter, on sales that Amgen continues to make. Sandoz receives no revenue on its side of the ledger corresponding to the revenue reductions suffered as a result of price erosion, and hence Sandoz suffers no corresponding burden should it be enjoined.

D.5. Public interest considerations

(106) In determining whether the public interest would be disserved if Amgen is granted an injunction to prevent Sandoz from making unlawfully premature Zarxio sales in the United States during the Restricted Period, Amgen contends that allowing Zarxio to be prematurely sold and marketed in the United States would result in substantial negative repercussions for innovation and innovative firms. Specifically, undermining the certainty and security of legitimate patent protection and the patent protections contained in the BPCIA carries with it the risk of seriously reducing innovation incentives essential to the development of new products, particularly new pharmaceuticals, and that the value created by such new products dwarfs the relatively minor and temporary cost savings (to the extent that any cost savings would be realized by payors and consumers) that might flow from the premature competition that Zarxio would bring.[97]

(107) In my opinion, deciding between potential cost savings from premature entry on one hand and the harm to innovation incentives that such sales would cause on the other hand is the key economic question for the Court to resolve when considering the impact on the public interest. For the reasons set forward below, it is my opinion that the harms to the innovation incentives and the adverse reverberations that would result from unlawfully premature Zarxio sales far outweigh the social benefits of potential cost savings that may result from unlawfully premature Zarxio sales. In my opinion, an injunction against unlawfully premature Zarxio sales prior to compliance with the requirements of the BPCIA and, if appropriate, patent expiry would not disserve the public interest. Rather, it would preserve the incentives needed to develop the innovations that lead to enhanced patient welfare and reduced total medical costs. To the extent the public has an interest in gaining the benefits of a patented invention at lower prices, that interest is most wisely served by awaiting whatever price declines occur once Sandoz complies with the requirements of the BPCIA.

products appears to be inelastic. Second, Sandoz could launch infringing Zarxio sales at a higher price than Neupogen® or the equivalent Neulasta® price. This could occur if Sandoz were to set its WAC, discounts, and net selling price to exploit the incentives from the ASP-based reimbursement system such that (1) prices paid by to providers increase over what these providers currently pay for Neupogen® and/or Neulasta® and (2) reimbursements from insurers that reimburse providers using ASP also increase.

97 In general, a Court might also consider whether or not public health would be enhanced by denying an injunction and allowing the sales of an infringing or potentially infringing product. Public health would not be enhanced by the sale of Zarxio because Zarxio does not serve any unmet medical need, and the introduction of Zarxio would not result in any significant increase in the number of neutropenia patients served. On the contrary, public health may be harmed if Amgen's R&D investments that would be delayed as a result of Zarxio's infringing sales would have yielded new, innovative treatments not otherwise available.

(108) Non-enforcement of legitimate patent rights potentially undermines the incentives for innovation, which would disserve the public interest, and Sandoz's refusal to comply with the BPCIA increases the chances that Amgen will be unable to successfully assert its patent rights. In contrast, an injunction against unlawfully premature sales would preserve the incentive to develop the innovations that gives rise to the possibility of lower prices in the first place. In other words, without Amgen's invention of Neupogen® and Neulasta®, there would be no reference product against which Sandoz could argue that its unlawfully premature sales would "save" costs. In addition, it is far from certain that competition between Sandoz and Amgen during the Restricted Period would lead to substantially lower prices, reduce treatment costs, or generate savings for payors or patients.

(109) Overall, this analysis leads to the following public interest paradox. Competition from Sandoz's unlawfully premature sales alone does not assure the public that it would realize substantially lower prices. If competition from Sandoz's unlawfully premature sales does lead to lower prices on filgrastim products, Sandoz would benefit, healthcare providers and payors may (or may not) temporarily benefit, Amgen would suffer enormous recurring harms, and innovation incentives would be adversely affected for existing and potential innovators to the detriment of the public interest. Any benefits to providers and payors will accrue in any event once Amgen's patents expire, and prior to that time would be more than offset by the losses in innovation incentives that are certain to result if Sandoz is allowed to make unlawfully premature sales. As described in more detail below, it is my opinion that enjoining Sandoz from launching Zarxio in the United States prior to Sandoz's complying with the BPCIA and, if appropriate, prior to the expiration of Amgen's patents would not disserve the public interest.

D.5.1. Public policy implications of patent right enforcement

(110) The enforcement of intellectual property rights balances two opposing interests. First, there are public interest benefits and welfare gains from stimulating innovation. Granting exclusive intellectual property rights to inventors to commercialize their patented inventions rewards innovation and ensures that innovators are provided with incentives to engage in research and development. These investments in R&D can advance the public interest by creating new products, improving existing products, or developing more efficient technologies for producing existing products. Protecting intellectual property rights ensures that new and useful information is disseminated publicly, which then encourages further innovation, without fear that the value derived from an invention will be improperly usurped by others. Second, competition offers many benefits including increased production efficiency and lower prices for purchasers. In the United States, there are a variety of public policies that have been designed to protect and promote competition, and appropriately so, including the BPCIA itself. While the BPCIA allows for entrants to take advantage of an expedited approval process, it also requires those entrants to provide information to the reference drug owner to assist in determining whether the entrants' products infringe the reference drug owner's patents.

(111) The patent provisions of the BPCIA serve to protect an important public interest in innovation. This is distinct from and complementary to the protections afforded to innovators by the 12 years of data exclusivity also granted by the BPCIA. The patent provisions protect innovation by giving force to the exclusionary rights granted by a patent. As the BPCIA recognizes, the reference product sponsor may have patents from a variety of sources. Some of those patents may arise from the same risk-

based investment that generated the data that supported FDA licensure of the reference product, such as patents on the molecule itself. Some patents may come from follow-on research into and improvements on the use of that molecule in therapeutic treatments, such as patents on therapeutic indications other than the one for which the product was first approved. Some patents may come from innovation by the reference product sponsor in unrelated areas of science that nevertheless could apply to the proposed biosimilar, such as patents that address the manufacture of a range of biologic or chemical molecules or that improve the purity, safety, or efficiency of those manufacturing processes. Recognizing the importance of patent protection, there is no requirement in the BPCIA that the reference product sponsor itself practice patents to enforce them against the proposed biosimilar. The reference product sponsor need not even have performed the inventive work leading to the patents to be enforced; the BPCIA provides that the reference product sponsor may list patents exclusively licensed to the reference product sponsor as well as those actually owned by the reference product sponsor. In other words, I understand that the reference product sponsor may list and therefore assert patents granted on the invention of a third party but that the reference product sponsor regards as sufficiently valuable to have secured an exclusive license. In this manner, the BPCIA more broadly serves to protect and thereby support the innovation incentives that patents create, beyond the specific patent-protected inventions that stem from the research and development on which the reference product received approval for its first therapeutic indication.

(112) Once an innovation has occurred, a narrow and time-inconsistent view of the public interest suggests that the public interest may then be served by reneging on the promised patent protection and encouraging competition at the expense of intellectual property rights. This view, however, is short-sighted. If the government or the courts sometimes disregard patents and allow competition, inventors would be reluctant to invest in research and development in the first place. As a result, striking the right balance requires a policy that foregoes competition for a predictable period of time, even if competition would yield short-run cost savings. While there is a temptation to renege on intellectual property protection once a new product has been invented, it is critical that government refrain from doing so. Otherwise, it would send a strong message to innovators that patent protection is uncertain.

(113) Allowing unlawfully premature sales of Zarxio during the Restricted Period would threaten the innovation incentives described above. Creating patent uncertainty and potentially allowing the expropriation of Amgen's legitimate profits would shift the balance away from innovation, with potentially dramatic and negative consequences. Firms like Sandoz, whose primary business strategy is to copy the products developed and patented by other firms, would have an increased incentive to capitalize on the research and development efforts of innovative firms, resulting in lower innovation incentives and ultimately in fewer breakthrough drugs.

D.5.2. The public interest benefits from innovation far exceed the benefits from short-term cost savings

(114) The invention and development of Neupogen® and Neulasta® has generated many medical benefits. First, the use of Amgen's filgrastim products has reduced the incidence of febrile neutropenia, a life-threatening condition for which doctors had limited if any options for treatment prior to Amgen's

introduction of Neupogen® in 1991.[98] Reduced incidence of febrile neutropenia has reduced the number of hospitalizations, for which the costs are estimated to range from $12,000 to $38,000 on average per incident.[99] Second, Neupogen®'s development and introduction reduced the risk and relative severity of chemotherapy-induced neutropenia, allowing oncologists greater flexibility in prescribing more aggressive chemotherapy and improving survival rates for some conditions by as much as 40%.[100] Similarly, Neupogen® has provided treatment options to patients with chronic neutropenia and other indications for which there were limited treatment options available prior to Neupogen®. These treatment options have resulted in increased quality of life.[101]

(115) The economic value generated by filgrastim's innovation is immense. As an illustration, consider the likely savings in hospitalization costs alone from the reduced incidences of febrile neutropenia. A study found that neutropenia treatments have reduced the incidence of febrile neutropenia from 39.5% to 22.4%—a reduction of 17%.[102] Assuming that there are 250,000 chemotherapy patients treated with filgrastim in the U.S., a 17% reduction in febrile neutropenia incidence suggests that over 42,000 febrile neutropenia incidents were avoided due to filgrastim treatment. Using the cost estimates of $12,000 to $38,000 per hospitalization, 42,000 fewer febrile neutropenia hospitalizations would result in medical cost savings of approximately $0.5 to $1.2 billion annually, illustrating the magnitude of the value generated. Such estimates of cost savings, however, do not take into account the increased treatment options, increased quality of life, and reduced mortality which are likely to be even more valuable than the reduced hospitalization costs.

(116) The avoided hospitalization cost illustrates a fraction of the economic value created by the innovation of Neupogen® and Neulasta®. A comprehensive and established framework in economics for analyzing the total economic value of innovation is to view the introduction of a new product as a price reduction from an infinitely high price to the market price.[103] The economic value of Amgen's innovation is measured as the total patient benefit created by a reduction in the price of Neupogen® from a price at which no patient could or would purchase the drug to a price at which patients can and do acquire the drug. The total net consumer benefit from a product, which economists call consumer surplus, can be calculated as the total monetary value from the product's consumption, represented by the area under the product's market demand curve, and subtracting from it the total amount paid

98 See generally, George Morstyn and T. Michael Dexter, eds., Filgrastim (r-metHuG-CSF) in Clinical Practice (1994).

99 Vincent Caggiano et al., "Incidence, Cost, and Mortality of Neutropenia Hospitalization Associated with Chemotherapy," *Cancer* 103, no. 9 (2005): 1916-1924 at 1917.

100 A study exploring the effect of G-CSFs in children with leukemia demonstrated that "those who were treated with filgrastim to reduce adverse effects of chemotherapy had remission and overall survival rates that were superior to those without treatment." Elisabeth G. Blanchard and Seth J. Corey, "Filgrastim Therapy: A Bone of Contention," *Blood* 109, no. 8 (2007): 3125-3126. Another study found that treatments with G-CSF permit escalation of chemotherapy dose and shortened intervals between chemotherapy treatments for breast cancer patients, resulting in significant effects on survival. Robert Livingston, "Dose Intensity and High Dose Therapy: Two Different Concepts," *Cancer* 74 (1994): 1177-1183. See also, Nicole M. Kuderer, et al, "Impact of Primary Prophylaxis with Granulocyte Colony-Stimulating Factor on Febrile Neutropenia and Mortality in Adult Cancer Patients Receiving Chemotherapy: a Systematic Review," *Journal of Clinical Oncology* 25, no. 21 (2007): 3158-3167.

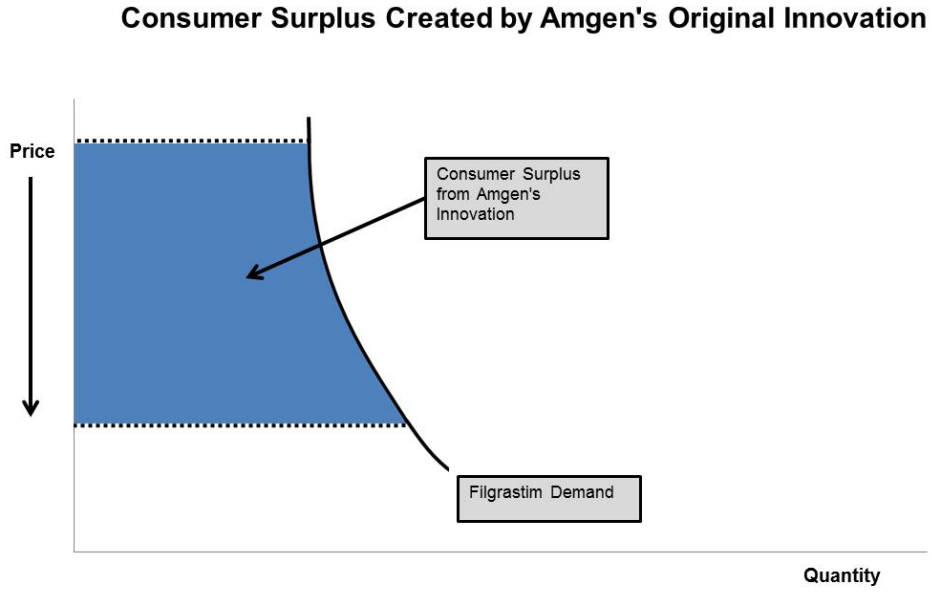
101 Eric A. Jones et al, "Quality of Life of Patients With Severe Chronic Neutropenia Receiving Long- Term Treatment With Granulocyte Colony-Stimulating Factor," *The Journal of the American Medical Association* 270, no. 9 (1993): 1133.

102 Nicole M. Kuderer et al, "Impact of Primary Prophylaxis with Granulocyte Colony-Stimulating Factor on Febrile Neutropenia and Mortality in Adult Cancer Patients Receiving Chemotherapy: a Systematic Review," *Journal of Clinical Oncology* 25, no. 21 (2007): at 3163.

103 See, for example, John Hicks, "The Valuation of Social Income." *Economica* 7 (1940): 105-24, and Franklin Fisher and Karl Shell, *The Economic Theory of Price Indices* (New York: Academic Press, 1972).

by consumers to acquire the product.[104] The consumer surplus is illustrated in Figure 5 by the area shaded in blue.

Figure 5



Source: Hypothetical illustration.

(117) An estimate of the total consumer surplus created would require detailed knowledge of the demand curve of all consumers, and such information is not available. However, there is information that confirms that this consumer surplus is very large. For some patients, filgrastim is literally a life-saving drug. Consumption of a life-saving drug would generate large surpluses, particularly when the patient is a young person with many years of productive life ahead. These units of filgrastim are represented on the left side of Figure 5, where the consumer surplus generated by consumption of those units is so high that it cannot be depicted on the graph. In addition, we have information about the shape and slope of the demand curve on the right-hand side of the curve as well. Estimates of the price elasticity of demand for specialty oncology drugs, including filgrastim, have been made by health economist Dana Goldman.[105] Goldman et al. estimate that such drugs have a market elasticity of about -0.1. This provides information on the shape of the demand curve on the right-hand side of the figure. In particular, the highly inelastic demand for oncology drugs suggests that the value of these drugs, as measured by the price patients would be willing to pay for them, increases relatively rapidly as one moves leftward up the curve from the point on the right side where the demand curve intersects the

[104] See, for example, John Hicks, "The Generalised Theory of Consumer's Surplus," *The Review of Economic Studies* 13, no. 2 (1945-1946): 68-74, and Robert Willig, "Consumer's Surplus Without Apology," *The American Economic Review* 66, no. 4 (1976): 589-597.

[105] See, for example, Dana Goldman et al., "Benefit Design and Specialty Drug Use," *Health Affairs* 25, no. 5 (2006): 1319-1331. They estimate the elasticity by examining a range of implicit prices generated by differences in insurance copay percentages. The average drug copay percentage in this study is approximately 22%.

current price.[106] Inelastic demand is to be expected from a product like filgrastim that consumers value very highly. Patients are unlikely to alter their consumption of filgrastim much in response to changes in its price. Taken together, the high value of filgrastim to at least some consumers, combined with the measured inelasticity of demand for the marginal or lowest value consumers, suggests that the total surplus created by Amgen's filgrastim innovation is enormous. As discussed below, economic research (including my own) suggests that consumers obtain most of that value.

D.5.2.1. Consumers capture the majority of benefits from innovative products like Neupogen® and Neulasta®

(118) The aggregate social benefit of a biological innovation is divided between patients and the innovator. Patients derive benefits from an innovative biological drug because the price they pay for the drug is lower than the price they, in principle, would be willing to pay for it. The price a patient would be willing to pay for a drug can be particularly high for drugs that save or prolong life, or prevent the development of serious medical conditions, such as neutropenia. The innovator earns profits because the price at which it sells its innovative drug typically exceeds the drug's cost of production. Economists refer to this profit as producer surplus. The sum of the consumer and producer surplus is the aggregate social benefit (or total surplus) from a new product.

(119) My own academic research suggests that the vast majority of the social benefit of pharmaceutical innovations is enjoyed by patients. My work with Anupam Jena (2006) calculates that the development and sale of HIV anti-retroviral drugs in the late 1980s generated social benefits of approximately $1.39 trillion.[107] We estimate that patients captured approximately $1.33 trillion, more than 95% of the benefits, while innovators captured approximately $63 billion, less than 5%, of the social benefits.[108] Similarly, in another paper, my co-authors and I found that innovation in cancer treatments have yielded $1.9 trillion in social value of which only 5%to 19% was captured by the healthcare providers and pharmaceutical companies.[109] Other research also shows that the vast majority of the social benefits from innovations in other industries also flow to consumers rather than the companies that developed the innovations. For example, Nordhaus (2004) estimates that consumers captured approximately 98% of the total social benefits from innovations in the non-farm business sector from 1948 through 2001.[110]

(120) As discussed previously, statements by Sandoz suggest that it plans to price Zarxio at "parity" with Neupogen®, and thus would not bring price competition to the market. However, even if I were to assume that Sandoz's unlawfully premature sales of Zarxio were made at prices below Amgen's current selling prices, and that consumers and payors therefore achieved cost savings as a result of

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106 More precisely, the elasticity measures not the slope of the curve, but rather the percentage change in quantity that would result from a given (small) percentage change in price. The elasticity is related to the inverse of the slope of the curve, so a lower elasticity number (in absolute value) corresponds to a steeper curve.

107 The figures reported in our paper are expressed in year 2000 dollars and discounted to 1980. These figures are based on figures commonly used in the economic literature about the value of a year of extended life ($100,000), data on years that the HIV anti-retroviral drugs can extend life, and the number and time profile of U.S. HIV diagnoses, including more than 1.5 million infected U.S. citizens.

108 Tomas Philipson and Anupam Jena. "Who Benefits from New Medical Technologies? Estimates of Consumer and Producer Surpluses for HIV/AIDS Drugs." *Forum for Health Economics and Policy* 9, no. 2 (2006), Article 3.

109 Darius N. Lakdawalla, Eric C. Sun, Anupam B. Jena, Carolina M. Reyes, Dana P. Goldman, and Tomas J. Philipson, "An economic evaluation of the war on cancer," *Journal of Health Economics* 29, no. 3 (2010), 333-346.

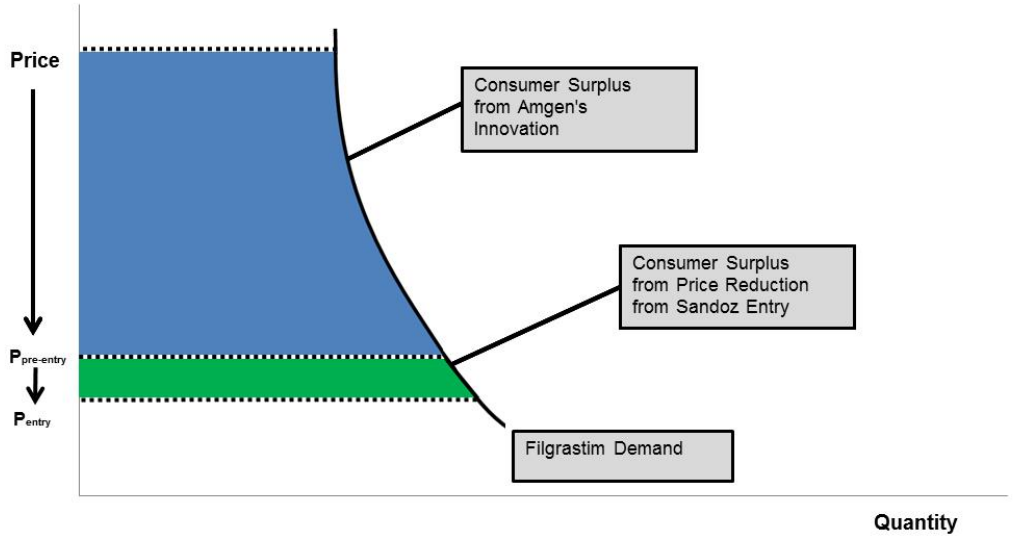
110 William Nordhaus, "Schumpeterian Profits in the American Economy: Theory and Measurement," NBER Working Paper Series, Working Paper 10433 at 22.

Sandoz's premature sales, these sales would at most provide only limited incremental consumer surplus. As Sandoz's product is being pursued as biosimilar, it does not provide additional therapeutic benefits to patients beyond those created by Amgen's development of Neupogen®. The primary consumer welfare benefit of Zarxio, therefore, is the potential of lower prices as a way to add economic value, although, as I discussed earlier, there is evidence that Sandoz may not, in fact, offer lower prices.

(121) In contrast to the very large value created by Amgen's invention and successful promotion of Neupogen® and Neulasta®, the introduction of Zarxio would make at most a very modest contribution to welfare. Figure 5 illustrates the relatively small size of any additional consumer surplus that could be generated when Sandoz introduces Zarxio in green. In contrast to the large consumer surpluses generated by the original innovation, the additional surplus created by lower prices from Zarxio's introduction would be limited by both the size of the price reduction and the fact that the gains from all the welfare benefits associated with consuming the innovation would already be available and attributable to the original innovation. Only the pecuniary gains of incremental financial savings would remain to be generated for consumers. In addition, whatever marginal financial savings Sandoz would generate for consumers or payors from infringing sales would simply accelerate by a brief period those gains that will occur in any case.

Figure 5

Incremental Consumer Surplus that Might be Created by Price Reductions from Infringing Zarxio Sales Would be Small Relative to the Consumer Surplus Created by Amgen's Innovation



Source: Hypothetical illustration.

(122) The observation that patients are the largest beneficiaries of biological product innovations has at least two important public policy implications. First, to the extent that the introduction of new biological products is reduced by patent infringement and erosion of patent protection implicit in allowing infringing product sales, patients stand to lose the most from that reduction. In assessing the social costs of a given reduction in innovation, primary attention should be paid to the impact it has on patients' benefits. Second, since the incentives to innovate are related to the profits from innovation and these profits are only a fraction of the innovation's contribution to social benefit, protecting whatever rewards currently exist is important to preserve the rate of innovation in biological products. To the extent Sandoz's unlawfully premature Zarxio sales would affect innovation by Amgen and potentially others, the detrimental effects on innovation would fall overwhelmingly on the patients who would benefit most from biological innovation. Moreover, to the extent that Sandoz's unlawfully premature entry reduces the ability of Amgen to successful introduce innovative new products like T-VEC, or reduces the effectiveness of practitioners' use of these innovative but complex products requiring extensive training for proper use to treat life-threatening illnesses, due the diversion of education and training resources to support Neupogen® and Neulasta®, overall public health would suffer.

D.5.3. Would Sandoz's unlawfully premature sales likely result in lower prices and health care costs?

(123) It is far from certain that competition between Sandoz and Amgen during the Restricted Period would lead to substantially lower prices for filgrastim products. Indeed, as previously discussed, public statements indicate that Sandoz plans to price Zarxio at "parity" with Neupogen®. The interaction of the factors related to competition for and pricing of filgrastim products may lead to competitive outcomes that are different than those predicted by competition as described in introductory economics textbooks. In particular, the introduction of a new competitor may not lead to significantly lower prices because, counterintuitively, the rules governing the reimbursement of filgrastim products can lead to competitive forces that sustain higher prices in certain settings. This outcome results largely from the ASP-based methodology used to reimburse providers in the clinic segment.

(124) Whatever price reductions Sandoz may offer to take sales from Amgen, the fact remains that the revenues those sales generate are largely a reallocation of revenues from Amgen to Sandoz. In my opinion, such a reallocation of revenue would not serve the public interest, particularly since the economic incentives it would foster would encourage infringement and discourage the R&D expenditures that drive medical research and innovation.

(125) To the extent that Zarxio's launch does result in lower prices and, therefore, cost savings for payors, this comes at the expense of substantial revenue losses for Amgen. In fact, the larger the price declines and, therefore, the cost savings, the larger the harm to Amgen. As discussed earlier, Amgen's revenue losses would result in a direct reduction in its R&D expenditures, particularly in nascent discovery research. These R&D reductions may cause permanent and long-term harm to Amgen's business by limiting the potential for future drug development. In addition, a reduction in future drug development would also run counter to the public interest in the long run by reducing the probability of new and innovative treatments for other medical conditions.

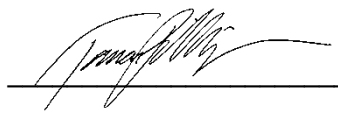
(126) In my opinion, the public interest would also be disserved if Sandoz or other companies with a similar strategy are encouraged or emboldened by the denial of an injunction to infringe innovators' patents or to conceal infringement. Wasteful legal expenditures throughout the pharmaceutical industry may increase if such encouragement leads to more litigation. Amgen and other innovative research companies would be discouraged from making investments, reducing the amount of new R&D, which would reduce the number of new drug treatments available in the future. On those R&D efforts that they do undertake, innovators would appropriately demand a higher return, knowing that the risk associated with those investments has increased due to reduced security of patents. This, again, could put upward pressure on health costs in the long run and would, in my opinion, disserve the public interest.

(127) This case is likely to be closely watched by investors and pharmaceutical companies because it is among the first examples of a biosimilar drug in the United States. Moreover, it is between the leading biotech company in the world (i.e., Amgen) and a leading generic drug manufacturer (i.e., Sandoz). As a result, investors are likely to pay particular attention to the outcome when considering investments in companies with significant patent-protected biological drugs. Moreover, pharmaceutical manufacturers, both biosimilar manufacturers and innovative drug developers, may look to the outcome of this case to understand the likelihood of being able to enforce biological and related patents and the likely remedies a court may impose.

D.5.3.1. Would enforcement of the BPCIA harm public health?

(128) Sandoz may argue that competition would lead to additional consumption of filgrastim products and, therefore, improve the state of public health in the United States. For that argument to be true, there would have to be patients that would benefit from filgrastim treatment who currently do not receive treatment due to its cost. In my opinion, the only significant public health implication of an injunction against unlawfully premature sales of Zarxio lies in the impact the grant or denial of such an injunction will have on the incentives for and the future levels of continuing R&D investment in new therapeutic treatments by Amgen in particular and by all innovative firms in general. To the extent that this reduction in R&D would result in delays in new and innovative treatments, the public health would be harmed if Sandoz is not enjoined.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.



Tomas J. Philipson, PhD

February 5, 2015

Date

Appendix A. Curriculum vitae

April, 2014

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EMPLOYMENT

DANIEL LEVIN PROFESSOR OF PUBLIC POLICY, **UNIVERSITY OF CHICAGO,** IRVING B. HARRIS GRADUATE SCHOOL OF PUBLIC POLICY STUDIES.(1998-PRESENT)

ASSOCIATE FACULTY MEMBER, **UNIVERSITY OF CHICAGO**, DEPARTMENT OF ECONOMICS, (1998-PRESENT)

SENIOR LECTURER, THE LAW SCHOOL, **UNIVERSITY OF CHICAGO**, (1998-2006).

VISITING ASSISTANT PROFESSOR**, YALE UNIVERSITY,** DEPARTMENT OF ECONOMICS, (1994)

ASSISTANT & ASSOCIATE PROFESSOR, **UNIVERSITY OF CHICAGO,** DEPARTMENT OF ECONOMICS, (1990-98)

POST-DOCTORAL FELLOW**, UNIVERSITY OF CHICAGO,** DEPARTMENT OF ECONOMICS, (1989)

PUBLIC SERVICE

SENIOR ECONOMIC ADVISOR TO THE COMMISSIONER, **THE FOOD AND DRUG ADMINISTRATION, (2003-04)**

SENIOR ECONOMIC ADVISOR TO THE ADMINISTRATOR, **CENTERS FOR MEDICARE AND MEDICAID SERVICES, (2004)**

SENIOR HEALTH CARE ADVISOR, **CAMPAIGN OF SENATOR JOHN MCCAIN FOR PRESIDENT OF THE UNITED STATES (2008)**

COMMISSION MEMBER, **NATIONAL KEY INDICATOR COMMISSION (**APPOINTED BY SPEAKER OF US HOUSE OF REPRESENTATIVES DEC 2010)

PROFESSIONAL AFFILIATIONS

Forbes Magazine, Op-ed Contributor, Tomas Philipson-The Health Care Economy.

John M. Olin Program in Law & Economics, The Law School, University of Chicago, (1999-present)

George J. Stigler Center, GSB, University of Chicago, Faculty Associate (1995-present)

The Center for Health and Social Sciences, The University of Chicago, Steering Committee, (2004-present).

The Milken Institute, Senior Fellow, (2004-present)

National Bureau of Economic Research (NBER), Faculty Research Fellow (1996-99), Research Associate (1999-present)

Schaeffer Center for Health Policy and Economics, Fellow, University of Southern California, (2009-present)

Chairman, Project FDA, Manhattan Institute (2008-present)

American Enterprise Institute, Visiting Scholar, (2007-present)

Senior Fellow, the Heartland Institute, (2007-present)

Adjunct Staff, RAND Corporation, (2005-present)

The World Bank, Research Fellow, (2003).

Center for Poverty Research, University of Chicago, Faculty Associate (1996-present)

Robert Wood Johnson Clinical Scholars Program, Core Faculty (1995-2002)

Population Research Center-NORC, University of Chicago (1993-present)

Scientific Advisory Board, Alliance for Potato Research and Education, (2011-)

PROFESSIONAL SERVICE

European Journal of Health Economics, Editorial Board, (2009-2011)

Health Economics, Editorial Board (2005-2013)

Forums in Health Economics and Health Policy, Berkeley Electronic Press, Founding Co-Editor (2004-present)

Economic Inquiry, Editorial Board (1996-2001)

University-wide Council on Research, The University of Chicago,(1999-2002).

University Technology Transfer Office (UCTech), The University of Chicago, Faculty Advisory Committee, 2004-2010

Working Group, Making Markets for Vaccines, Center for Global Development, Washington DC, (2003-2004)

Executive Committee, Scientific Committee, 2006 Meetings, American Society for Health Economics (ASHE).

Executive Committee, Scientific Committee, 2007 Meetings, International Health Economics Association (IHEA), Copenhagen, Denmark.

Executive Committee, Scientific Committee, 2008 Meetings, American Society for Health Economics (ASHE).

Executive Committee, Scientific Committee, 2009 Meetings, International Health Economics Association (IHEA), Beijing, China.

Advisor, Kennedy Commission, NICE, The UK Health Service, 2009.

Advisory Committee on Personalized Medicine, PCAST, the President of the United States, 2007.

Award Committee, The Kenneth J. Arrow Award, International Health Economics Association, 2007-2012.

Center for Medicine in The Public Interest, Advisory Board, (2006-2010).

National AIDS Prevention Center, UCSF, Scientific Advisory Board (1995-98)

EDUCATION

The Wharton School and University of Pennsylvania, MA and PhD., Economics (1989)

- Recipient of the William Carey Prize for Outstanding Dissertation.

Claremont Graduate School, M.A., Mathematics (1985)

- 4.0 GPA

Uppsala University, B.Sc. Mathematics (1984)

- Expedited Graduation.

AWARDS

Finalist, *Annual Research Award*, National Institute for Health Care Management Foundation, 2010.

The Garfield Award, Research America, 2007

[Awarded for most influential health economics paper in a given year]

Prêmio Haralambos Simeonidisand, Brazilian Economic Association, 2006

[Awarded for best paper in any field of economics in a given year]

The Kenneth J. Arrow Award, International Health Economics Association, 2006.

[Awarded for best paper in the field of health economics in a given year]

The Kenneth J. Arrow Award, International Health Economics Association, 2000.

[Awarded for best paper in the field of health economics in a given year]

Group Recognition Award, Office of the Commissioner, The Food And Drug Administration, 2004.

The Milken Institute Award for Distinguished Economic Research, The Milken Institute, 2003

[Awarded to best paper in any field of economics in a given year]

Alfred P. Sloan Foundation. Research Fellow. (1996-98).

John M. Olin Foundation. Faculty Fellow. (1996-97).

Earhart Foundation. (1990, 1992-94).

Royal Swedish Academy of Sciences. (1988-89).

Marcus Wallenberg Foundation. (1985-86).

Mathematics Clinic, Claremont Graduate School. (1985).

Swedish-American Society. (1985).

Kallenberg Foundation. (1984-85).

University of Uppsala, Sweden. International Fellowship. (1984).

Engwall Foundation, Sweden. (1982-87).

RESEARCH GRANTS

Center for Health and the Social Sciences

"The War on Cancer",2009
"Me-too Innovation and Pharmaceutical Markets", 2005.
"Estimating the Welfare Effects of Alternative Liability Regimes", 2006.
"The Impact of Personalized Medicine on the Pharmaceutical Industry", 2007.

RAND Corporation, "Estimating the Welfare Effects of Alternative Liability Regimes", 2007.

National Institutes of Health ,"The Economics of Terminal Care", 2007.

US Department of Agriculture, "Economics and Obesity", 2003.

The World Bank, "African Health Care Delivery", 2002-03.

National Institutes of Health (NIA P30 AG-12657-06) "The Growth in Obesity and Technological Change." (2000).

National Institutes of Health (NIA AG16494). "Old-Age Longevity and The Market for Long-Term Care." (1999-2002).

John M. Olin Foundation. "Population, Longevity, and Human Capital." Joint with Gary Becker, Edward Glaeser, and Kevin Murphy. (2000).

National Institutes of Health (NIA AG14897). "Old-Age Longevity and Insurance." (1997-98).

National Science Foundation (SBR-9709635). "Data Markets." (1997-2000).

George J. Stigler Center for The Study of The Economy and The State. (1993-2007).

John M. Olin Foundation. "The Formation of Preferences." Joint with Gary Becker, Casey Mulligan, and Kevin Murphy. (1996-2000).

National Science Foundation (SBR-9409917). "Trade Under Incomplete Information: An Empirical Examination for the Case of HIV." (1994-97).

National Institutes of Health (AHCPR HS 08066-02). "The Demand for Immunity and the Effects of Public Health." (1993-97).

Rockefeller Foundation. (1994).

Center for Disease Control. Joint with Karen Goldstein and Robert Daum. (1993-94).

PUBLICATIONS

ECONOMIC ASPECTS OF LONGEVITY

Books

Philipson, T., A. Jena, and E. Sun, (2010), Longevity, and Inequality, American Enterprise Institute Press.

Papers:

Becker, G., T. Philipson, and R. Soares, (2005), "The Quantity and Quality of Life and The Evolution of World Inequality", American Economic Review, March, v 95, No 1, pp 277-291

Philipson, T., and Rodrigo R. Soares. "The Quantity of Life and the Welfare Cost of AIDS in Sub-Saharan Africa", G. López-Casasnovas, B. Rivera, and L. Currais, Editors, Health and Economic Growth: Findings and Policy Implications, MIT Press, Cambridge, 2005.

Geoffard, P-Y., and T. Philipson. "Pricing and R&D when Consumption Affects Longevity", The RAND Journal of Economics, v 33, No 1, Spring (2002), 85-95

Lakdawalla, D., and T., Philipson. "The Rise in Old Age Longevity and the Market for Long Term Care," American Economic Review, v 92, No 1 , March (2002), pp 295-306.

Philipson, T. and R. Soares. (2002) "World Inequality and the Rise in Longevity", B. Pleskovic and N. Stern, Editors, Annual World Bank Conference on Development Economics 2001/2002, Oxford University Press, New York, 2002, p.245-259.

Cawley, J., and T. Philipson. "An Empirical Examination of Information Barriers to Trade in Longevity-Based Insurance." American Economic Review 89.4, September, (1999): 827-48.

Dow, W., T. Philipson, and X. Sala-I-Martin. "Longevity Complementarities Under Competing Risks." American Economic Review 89.5, December, (1999): 1357-1372.

Philipson, T., and G. Becker. "Old-Age Longevity and Mortality Contingent Claims." Journal of Political Economy 106.3 (1998): 550-574.

Working papers:

Egan, M.,R. Koijen, C. Mulligan, and T. Philipson (2013) "Adjusting Measures of Economic Output for Health : Is the Business Cycle Countercyclical?" , NBER-WP.

Jena, A., Mulligan, C., T., Philipson, and E. Sun, (2008) "The Value of Life in General Equilibrium", NBER Working Paper

Becker, G., K. Murphy, and T. Philipson (2007) "The Value of Life Near Its End and Terminal Care", NBER Working Paper No.13333,

Mullin, C., and T. Philipson (1997). "The Future of Old-Age Longevity: Competitive Pricing of Mortality Contingent Claims." NBERWorking Paper # 6042

DATA MARKETS

Books:

Philipson, T. 2000, Data Markets; The Production of Health Statistics. The University of Chicago Press, pre-publication contract, 2000.

Papers:

Malani, A., and T. Philipson, (2010), "Is Medical R&D Different? The Output-Development Link and its Implications", NBER Working Paper.

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ECONOMIC EPIDEMIOLOGY AND PUBLIC HEALTH

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Johnson & Johnson (Gibson Dunn), Medtronic (McDermott Will)
McKesson (Morrison & Foerster), Lorillard (Shook Hardy & Bacon)
Guidant (Skadden Arps) Schering-Plough (Wachtell Lipton)

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CONSULTANT AND NON-ACADEMIC APPOINTMENTS

Founding Partner, Precision Health Economics LLC.

Board Member, PACE Council, Eli Lilly, 2012-

Associate, *Goldman Sachs*, New York (1987).

Honorary Board of Directors, *The Round Table Group (http://www.roundtablegroup.com)*, Chicago (1997-).

Appendix B. Materials considered

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, vs. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, Defendants.	Case No. 3:14-cv-04741-RS **DECLARATION OF VERNON M. WINTERS IN SUPPORT OF AMGEN'S MOTION FOR PRELIMINARY INJUNCTION**

I, Vernon M. Winters, declare and state as follows:

1. I am an attorney licensed to practice before this Court and a partner of the law firm Sidley Austin LLP, attorneys of record for plaintiffs Amgen Inc. and Amgen Manufacturing, Limited (together, "Amgen") in the above-captioned matter. I have personal knowledge of the facts set forth in this Declaration, and if called upon as a witness, I could and would testify competently as to these facts.

2. Attached hereto as **Exhibit 1** is a true and correct copy of: Shannon Firth, "FDA Advisory Committee Endorses Neupogen Biosimilar,"

3. Attached hereto as **Exhibit 2** is a true and correct copy of the September 2014 update to the Center for Drug Evaluation and Research (CDER) Billable Biologic Product List. Neupogen® and Neulasta® appear on page 2.

4. Attached hereto as **Exhibit 3** are true and correct copies of printouts from the Food and Drug Administration website, http://www.fda.gov. The first printout shows the "Drug Details" for Neupogen® as part of the Drugs@FDA section of the FDA website. It can be accessed from www.fda.gov by clicking the "Drugs" tab on the homepage, clicking the "Drug Information (Drugs@FDA)" link, and then by entering "Neupogen" into the search field. The second printout shows the "Label and Approval History" for Neupogen®. It can be accessed by clicking the "Approval History, Letters, Reviews, and Related Documents" link from the previous "Drug Details" webpage. The third printout shows the "Drugs@FDA Glossary of Terms." It can be accessed by clicking the "Glossary" link on either of the two previous web pages or by navigating to http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm.

5. Attached hereto as **Exhibit 4** is a true and correct copy of: Derrick Gingery, "ODAC Asks Sandoz if Biosimilar Price is Right," *The Pink Sheet Daily* (Jan. 7, 2015).

6. Attached hereto as **Exhibit 5** is a true and correct copy of: Sue Sutter, "Biosimilar Pricing: Sandoz Vows Not To Make *Omnitrope* 'Mistake' With Filgrastim," *The Pink Sheet* (Dec. 22, 2014).

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I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct and that the foregoing was executed on February 5, 2015, in San Francisco, California.

/s/ Vernon M. Winters

Vernon M. Winters

EXHIBIT 1

PUBLIC HEALTH & POLICY 01.08.2015 0 COMMENTS

FDA Advisory Committee Endorses Neupogen Biosimilar

— Outlook good for biosimilars under abbreviated pathway.

by Shannon Firth
Contributing Writer

SILVER SPRING -- An FDA advisory panel's endorsement of a copycat biologic meant to boost white blood cell counts could clear a path for future biosimilars.

Persuaded by extensive data from sponsors and the FDA's own analysis, the Oncologic Drugs Advisory Committee (ODAC) unanimously recommended approving EP2006, a proposed biosimilar to Neupogen (filgrastim), on Wednesday.

The pioneering EP2006, a recombinant granulocyte colony-stimulating factor currently sold as Neupogen (Amgen) is used to increase white blood cell counts after treatments that lead to neutropenia. It is the first drug to

be reviewed under a new pathway established under the Biologics Price Competition and Innovation Act of 2009.

The development process for biosimilars differs from the standard new drug application, explained Janet Woodcock, MD, director of the Center for Drug Evaluation and Research (CEDR) in her opening remarks. Instead of focusing on safety and efficacy, the applicant aims to show a finding of biosimilarity.

In advance of the meeting, the FDA's technical staff published briefing documents in support of the new drug, based on "a demonstration of 'no clinically meaningful differences' between the proposed product and the reference product in terms of safety, purity, and potency."

The already licensed Neupogen is indicated for use in "reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML2 [acute myeloid leukemia]," as well as "to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia." Other approved indications include promoting myeloid recovery following autologous bone marrow transplant and for mobilizing hematopoietic stem cells in preparation for autologous peripheral blood transplants, noted the briefing documents.

Sandoz-Novartis is seeking marketing approval for the same indications.

In addition to 5 animal studies used to measure pharmacodynamic toxicity and local tolerance, the applicant presented one pivotal and 4 supporting studies to demonstrate similar pharmacodynamic and pharmacokinetic attributes. Sandoz-Novartis also provided an analysis of EP2006's, proposed name Zarxio's, structure, function and pharmaceutical properties, highlighting its identical primary structure and "highly similar formulation," excepting a difference in a buffering agent and in pH.

While the committee did not dispute that EP2006 was "highly similar" to

While the committee did not dispute that EP2006 was "highly similar" to US-licensed Neupogen, details of one study gave some members pause.

An evenly randomized, double-blinded, non-inferiority study compared EP2006 to US-licensed Neupogen in 218 breast cancer patients. All of the patients received TAC chemotherapy (Taxotere, Adriamycin and Cyclophosphamide) followed by 5 mcg/kg of EP2006 or US -licensed Neupogen for up to 14 days.

The primary endpoint of the study was the mean duration of severe neutropenia, indicated by a white blood cell count of less than 500 (.5 Gi/L) in the first cycle of chemotherapy. Sandoz found a mean difference in which Neupogen met the endpoint .04 days faster than EP2006 at a confidence interval of 90 percent. This difference was acceptable, according to the study's non-inferiority margin of 1 day. However some panel members took issue with the margin and with certain discrepancies in the data.

Scott Waldman, MD, PHD, a professor of the department of pharmacology and experimental therapeutics at the Sidney Kimmel Medical College at Thomas Jefferson University in Philadelphia, said he was perplexed by differences between Sandoz's analysis of the results and those of FDA's technical staff.

"It still is of concern that there are three times the number of patients who didn't recover their neutrophil counts versus the other in one data set," he said.

Edvardas Kaminskas MD, deputy director of the division of hematology products at the FDA pointed out that the divergence between the data sets happened in the curve after patients had past what he termed "the danger zone" of severe neutropenia and neutropenia.

Ginna Laport, MD professor of Medicine at the Stanford University Medical

Center and a bone marrow transplant specialist, agreed with Waldman that the data sets needed to be reconciled; however, "at the end of the day we care that our patients recover their **neutrophils** in a clinically meaningful rapid way and there's no question that both groups did that."

After tallying the final votes for licensure based on "the totality of the evidence" Deborah Armstrong, MD, the committee chair and professor of Oncology and director of Breast and Ovarian Surveillance Service at Johns Hopkins University School of Medicine said in spite of the data set concerns, "the panel agrees that these are very similar compounds in terms of what we were asking these drugs to do." All 14 voting members agreed that EP2006 should be licensed as a biosimilar for "each of the five indications for which Neupogen is currently licensed."

Pricing

One objective of the new pathway is to promote competition and address critical access needs. To that end, James Liebmann, MD, an assistant professor of Medicine at the University of Massachusetts in Worcester, asked the sponsor whether the new drug would be priced less than Neupogen.

Mark McCamish, MD, PhD, head of Global Biopharmaceutical and Oncology Injectables Development at Sandoz, said "We can't say that the price will be less because in some situation the price will be at parity." The cost, however, would be less for consumers, payers and the health care economy, he said.

The FDA is not required to follow the advice of its advisory committees, but it often does.

EXHIBIT 2

CDER Therapeutic Biologic Products

This list is intended to include all the Center for Drug Evaluation and Research (CDER) user fee billable therapeutic biological products and potencies approved under Section 351 of the Public Health Service Act. The Orange Book includes a section entitled "Drug Products with Approval under Section 505 of the Act Administered by CBER." Included on that list are several products that have been transferred to CDER which would be considered billable also.

Product fees are assessed for each potency in which the approved (non-revoked, non-suspended) product is manufactured in final dosage form. In certain circumstances, products which have been discontinued from marketing but are still licensed are not assessed product fees. Those products are identified on the CDER Discontinued Biologic Product List section.

The potency information contained in this list is based on information in our database. Companies are responsible for alerting CDER to any discrepancies regarding potency information. For product approvals after October 1, 2005, the Biologics License Application Submission Tracking Number (BLA STN) approval date reflects the approval date of the product. For product approvals prior to October 1, 2005, the BLA STN approval date reflects the approval date of the original BLA.

The list is updated semi-annually. (Latest Update – SEPTEMBER 2014)

:********** CDER Billable Biologic Product List **********

Applicant/License No: AbbVie Inc. / License 1889

Trade Name: **Humira**

Proper Name: Adalimumab

BLA STN:	Approval Date:	Potency:
125057/0	12/31/2002	40 mg/0.8 mL

Applicant/License No: Alexion Pharmaceuticals, Inc. / License 1743

Trade Name: **Soliris**

Proper Name: Eculizumab

BLA STN:	Approval Date:	Potency:
125166/0	3/16/2007	10 mg/mL

Applicant/License No: Allergan, Inc. / License 1145

Trade Name: **Botox**

Proper Name: Onabotulinum Toxin Type A

BLA STN:	Approval Date:	Potency:
103000/0	12/9/1991	100 u/vial
BLA STN:	Approval Date:	Potency:
103000/5101	4/14/2005	50 u/vial
BLA STN:	Approval Date:	Potency:
103000/5122	11/10/2005	200 u/vial

Trade Name: **Botox Cosmetic**

Proper Name: Onabotulinum Toxin Type A

BLA STN:	Approval Date:	Potency:
103000/5000	4/12/2002	100 u/vial
BLA STN:	Approval Date:	Potency:
103000/5101	4/14/2005	50 u/vial

********** CDER Billable Biologic Product List **********

Applicant/License No: Amgen, Inc. / License 1080

Trade Name: **Aranesp**
Proper Name: Darbepoetin alfa (polysorbate solution)

BLA STN:	Approval Date:	Potency:
103951/0	9/17/2001	25 mcg/0.42 mL syringe
		25 mcg/mL vial
		40 mcg/0.4 mL syringe
		40 mcg/mL vial
		60 mcg/0.3 mL syringe
		60 mcg/mL vial
		100 mcg/0.5 mL syringe
		100 mcg/mL vial
		150 mcg/0.3 mL syringe
		150 mcg/0.75 mL vial
		200 mcg/0.4 mL syringe
		200 mcg/mL vial
		300 mcg/0.6 mL syringe
		300 mcg/mL vial
		500 mcg/mL vial

Trade Name: **Epogen**
Proper Name: Epoetin alfa

BLA STN:	Approval Date:	Potency:
103234/0	6/1/1989	2000 u/mL
		3000 u/mL
		4000 u/mL
		10000 u/mL
		10000 u/mL md
		20000 u/mL md
		40000 u/mL

Trade Name: **Neulasta**
Proper Name: Pegfilgrastim

BLA STN:	Approval Date:	Potency:
125031/0	1/31/2002	6 mg/0.6 mL

Trade Name: **Neupogen**
Proper Name: Filgrastim

BLA STN:	Approval Date:	Potency:
103353/0	2/20/1991	300 mcg/0.5 mL
		300 mcg/mL
		480 mcg/0.8 mL
		480 mcg/1.6 mL

Trade Name: **Nplate**
Proper Name: Romiplostim

BLA STN:	Approval Date:	Potency:
125268/0	8/22/2008	250 mcg/vial
		500 mcg/vial

:********** CDER Billable Biologic Product List **********

Trade Name: **Prolia**
Proper Name: Denosumab

BLA STN:	Approval Date:	Potency:
125320/0	6/1/2010	60 mg/mL

Trade Name: **Vectibix**
Proper Name: Panitumumab

BLA STN:	Approval Date:	Potency:
125147/0	9/27/2006	20 mg/mL

Trade Name: **Xgeva**
Proper Name: Denosumab

BLA STN:	Approval Date:	Potency:
125320/7	11/18/2010	120 mg/1.7mL (70mg/mL)

Applicant/License No: Amylin Pharmaceuticals, LLC / License 1854

Trade Name: **Myalept**
Proper Name: Metreleptin

BLA STN:	Approval Date:	Potency:
125390/0	2/24/2014	11.3 mg/vial

Applicant/License No: Auxilium Pharmaceuticals, Inc. / License 1816

Trade Name: **Xiaflex**
Proper Name: Collagenase Clostridium Histolyticum

BLA STN:	Approval Date:	Potency:
125338/0	2/2/2010	0.9 mg/vial

Applicant/License No: Bayer Healthcare Pharmaceuticals Inc. / License 1778

Trade Name: **Betaseron**
Proper Name: Interferon beta-1b

BLA STN:	Approval Date:	Potency:
103471/0	7/23/1993	0.3 mg/vial

Applicant/License No: Biogen Idec, Inc. / License 1697

Trade Name: **Avonex**
Proper Name: Interferon beta-1 a

BLA STN:	Approval Date:	Potency:
103628/0	5/17/1996	30 mcg/0.5 mL syringe 30 mcg/vial

Trade Name: **Plegridy**
Proper Name: Peginterferon beta-1a

BLA STN:	Approval Date:	Potency:
125499/0	8/15/2014	63 mcg/0.5mL syringe + 94 mcg/0.5mL syringe (starter pack) 125 mcg/0.5mL syringe

:********** CDER Billable Biologic Product List **********

Trade Name: **Tysabri**
Proper Name: Natalizumab

BLA STN:	Approval Date:	Potency:
125104/0	11/23/2004	300 mg/15 mL

Applicant/License No: Biomarin Pharmaceutical, Inc. / License 1649

Trade Name: **Aldurazyme**
Proper Name: Laronidase

BLA STN:	Approval Date:	Potency:
125058/0	4/30/2003	2.9 mg/5 mL

Trade Name: **Naglazyme**
Proper Name: Galsulfase

BLA STN:	Approval Date:	Potency:
125117/0	5/31/2005	5 mg/5 mL

Trade Name: **Vimizim**
Proper Name: Elosulfase alfa

BLA STN:	Approval Date:	Potency:
125460/0	2/14/2014	5 mg/5 mL

Applicant/License No: Bristol-Myers Squibb / License 1713

Trade Name: **Nulojix**
Proper Name: Belatacept

BLA STN:	Approval Date:	Potency:
125288/0	6/15/2011	250 mg/vial

Trade Name: **Orencia**
Proper Name: Abatacept

BLA STN:	Approval Date:	Potency:
125118/0	12/23/2005	250 mg/vial
BLA STN:	Approval Date:	Potency:
125118/122	7/29/2011	125 mg/mL

Trade Name: **Yervoy**
Proper Name: Ipilimumab

BLA STN:	Approval Date:	Potency:
125377	3/25/2011	5 mg/mL

Applicant/License No: BTG International Inc. / License 1861

Trade Name: **Voraxaze**
Proper Name: Glucarpidase

BLA STN:	Approval Date:	Potency:
125327	1/17/2012	1000 u/vial

********** CDER Billable Biologic Product List **********

Applicant/License No: Dyax Corp. / License 1789

Trade Name:	Proper Name:	BLA STN:	Approval Date:	Potency:
Kalbitor	Ecallantide	125277/0	12/1/2009	10 mg/mL

Applicant/License No: EKR Therapeutics, Inc. / License 1814

Trade Name:	Proper Name:	BLA STN:	Approval Date:	Potency:
Retavase	Reteplase	103786/0	5/6/1998	18.1 mg/vial

Applicant/License No: Eli Lilly and Company / License 1891

Trade Name:	Proper Name:	BLA STN:	Approval Date:	Potency:
CYRAMZA	Ramucirumab	125477/0	4/21/2014	500 mg/50mL (10mg/mL)
Trulicity	Dulaglutide	125469/0	9/18/2014	0.75 mg/0.5mL 1.5 mg/0.5mL

Applicant/License No: EMD Serono Inc. / License 1773

Trade Name:	Proper Name:	BLA STN:	Approval Date:	Potency:
Rebif	Interferon beta-1a	103780/0	3/7/2002	8.8 mcg/0.2 mL 22 mcg/0.5 mL 44 mcg/0.5 mL

Applicant/License No: EUSA Pharma (USA) Inc. / License 1829

Trade Name:	Proper Name:	BLA STN:	Approval Date:	Potency:
Erwinaze	asparaginase Erwinia chrysanthemi	125359	11/18/2011	10000 IU/vial
ProstaScint	Capromab Pendetide	103608/0	10/28/1996	0.5 mg/mL

:********** CDER Billable Biologic Product List **********

Applicant/License No: Genentech, Inc. / License 1048

Trade Name: **Actemra**
Proper Name: Tocilizumab

BLA STN:	Approval Date:	Potency:
125276/0	1/8/2010	80 mg/4 mL (20 mg/mL)
BLA STN:	Approval Date:	Potency:
125472/0	10/21/2013	162 mg/0.9 mL

Trade Name: **Activase, Cathflo Activase**
Proper Name: Alteplase

BLA STN:	Approval Date:	Potency:
103172/0	11/13/1987	2 mg/vial 50 mg/vial 100 mg/vial

Trade Name: **Avastin**
Proper Name: Bevacizumab

BLA STN:	Approval Date:	Potency:
125085/0	2/26/2004	25 mg/mL

Trade Name: **GAZYVA**
Proper Name: Obinutuzumab

BLA STN:	Approval Date:	Potency:
125486/0	11/1/2013	1000 mg/40 mL (25 mg/mL)

Trade Name: **Herceptin**
Proper Name: Trastuzumab

BLA STN:	Approval Date:	Potency:
103792/0	9/25/1998	440 mg/vial

Trade Name: **Kadcyla**
Proper Name: ado-trastuzumab emtansine

BLA STN:	Approval Date:	Potency:
125427/0	2/22/2013	100 mg/vial 160 mg/vial

Trade Name: **Lucentis**
Proper Name: Ranibizumab

BLA STN:	Approval Date:	Potency:
125156/0	6/30/2006	0.5 mg/0.05 mL
BLA STN:	Approval Date:	Potency:
125156/0076	8/10/2012	0.3 mg/0.05 mL

Trade Name: **Perjeta**
Proper Name: Pertuzumab

BLA STN:	Approval Date:	Potency:
125409/0	6/8/2012	420 mg/14 mL (30 mg/mL)

Trade Name: **Pulmozyme**
Proper Name: Dornase alfa

BLA STN:	Approval Date:	Potency:
103532/0	12/30/1993	1 mg/mL

********** CDER Billable Biologic Product List **********

Trade Name: **Rituxan**
Proper Name: Rituximab

BLA STN:	Approval Date:	Potency:
103705/0	11/26/1997	100 mg/10 mL (10 mg/mL)

Trade Name: **TNKase**
Proper Name: Tenecteplase

BLA STN:	Approval Date:	Potency:
103909/0	6/2/2000	50 mg/vial

Trade Name: **Xolair**
Proper Name: Omalizumab

BLA STN:	Approval Date:	Potency:
103976/0	6/20/2003	75 mg/vial 150 mg/vial

Applicant/License No: Genzyme Corp. / License 1596

Trade Name: **Campath**
Proper Name: Alemtuzumab

BLA STN:	Approval Date:	Potency:
103948/0	5/7/2001	30 mg/mL

Trade Name: **Fabrazyme**
Proper Name: Agalsidase beta

BLA STN:	Approval Date:	Potency:
103979/0	4/24/2003	5 mg/vial 35 mg/vial

Trade Name: **Lumizyme**
Proper Name: Alglucosidase alfa

BLA STN:	Approval Date:	Potency:
125291/0	5/24/2010	50 mg/vial

Trade Name: **Myozyme**
Proper Name: Alglucosidase alfa

BLA STN:	Approval Date:	Potency:
125141/0	4/28/2006	50 mg/vial

Applicant/License No: Glaxo Group Limited d/b/a/ GlaxoSmithKline / License 1809

Trade Name: **Arzerra**
Proper Name: Ofatumumab

BLA STN:	Approval Date:	Potency:
125326/0	10/26/2009	100 mg/5 mL (20 mg/mL)

Applicant/License No: GlaxoSmithKline LLC / License 1727

Trade Name: **Tanzeum**
Proper Name: Albiglutide

BLA STN:	Approval Date:	Potency:
125431/0	4/15/2014	30 mg/pen

:********** CDER Billable Biologic Product List **********

Trade Name: **Tanzeum**
Proper Name: Albiglutide

125431/0	4/15/2014	50 mg/pen

Applicant/License No: Hoffmann-La Roche, Inc. / License 0136

Trade Name: **Pegasys**
Proper Name: Peginterferon alfa-2a

BLA STN:	Approval Date:	Potency:
103964/0	10/16/2002	180 mcg/0.5 mL syringe 180 mcg/mL
103964/5204	9/29/2011	135 mcg/0.5 mL syringe

Trade Name: **Pegasys/ Copegus Combination Pack**
Proper Name: Peginterferon alfa-2a, co-packaged with Ribavirin

BLA STN:	Approval Date:	Potency:
125083/0	6/4/2004	180 mcg/0.5 mL + 1000 mg (140 x 200 mg tablets) 180 mcg/0.5 mL + 1200 mg (168 x 200 mg tablets) 180 mcg/0.5 mL + 800 mg (112 x 200 mg tablets)

Applicant/License No: Human Genome Sciences, Inc / License 1820

Trade Name: **Benlysta**
Proper Name: Belimumab

BLA STN:	Approval Date:	Potency:
125370	3/9/2011	120 mg/vial 400 mg/vial

Trade Name: **Raxibacumab**
Proper Name: Raxibacumab

BLA STN:	Approval Date:	Potency:
125349/0	12/14/2012	1700 mg/34 mL (50 mg/mL)

Applicant/License No: ImClone Systems, Inc. / License 1695

Trade Name: **Erbitux**
Proper Name: Cetuximab

BLA STN:	Approval Date:	Potency:
125084/0	2/12/2004	100 mg/50 mL (2mg/mL)

Applicant/License No: Immunex Corp. / License 1132

Trade Name: **Enbrel**
Proper Name: Etanercept

BLA STN:	Approval Date:	Potency:
103795/0	11/2/1998	25 mg/vial

:********** CDER Billable Biologic Product List **********

Trade Name: **Enbrel**
Proper Name: Etanercept

BLA STN:	Approval Date:	Potency:
103795/5184	9/27/2004	50 mg/mL syringe

Applicant/License No: Ipsen Biopharm Limited / License 1787

Trade Name: **Dysport**
Proper Name: Abobotulinum Toxin Type A

BLA STN:	Approval Date:	Potency:
125274/0	4/29/2009	300 U/vial 500 U/vial

Applicant/License No: Janssen Biologics B.V. / License 1865

Trade Name: **ReoPro**
Proper Name: Abciximab

BLA STN:	Approval Date:	Potency:
103575/0	12/22/1994	2 mg/mL

Applicant/License No: Janssen Biotech, Inc. / License 1864

Trade Name: **Remicade**
Proper Name: Infliximab

BLA STN:	Approval Date:	Potency:
103772/0	8/24/1998	100 mg/vial

Trade Name: **Simponi**
Proper Name: Golimumab

BLA STN:	Approval Date:	Potency:
125289/0	4/24/2009	50 mg/0.5 mL

Trade Name: **Simponi Aria**
Proper Name: Golimumab

BLA STN:	Approval Date:	Potency:
125433/0	7/18/2013	50 mg/4mL

Trade Name: **Stelara**
Proper Name: Ustekinumab

BLA STN:	Approval Date:	Potency:
125261/0	9/25/2009	90 mg/mL

Trade Name: **SYLVANT**
Proper Name: Siltuximab

BLA STN:	Approval Date:	Potency:
125496/0	4/23/2014	100 mg/vial 400 mg/vial

********** CDER Billable Biologic Product List **********

Applicant/License No: MedImmune, LLC / License 1799

Trade Name: **Synagis (Liquid)**
Proper Name: Palivizumab

BLA STN:	Approval Date:	Potency:
103770/0	6/19/1998	50 mg/0.5 mL
		100 mg/mL

Applicant/License No: Merck Sharp & Dohme Corp. / License 0002

Trade Name: **Keytruda**
Proper Name: Pembrolizumab

BLA STN:	Approval Date:	Potency:
125514/0	9/4/2014	50 mg/vial

Applicant/License No: Merz Pharmaceuticals / License 1830

Trade Name: **Xeomin**
Proper Name: IncobotulinumtoxinA

BLA STN:	Approval Date:	Potency:
125360/0	7/30/2010	50 u/vial
		100 u/vial

Applicant/License No: Novartis Pharmaceuticals Corp. / License 1244

Trade Name: **Extavia**
Proper Name: Interferon Beta-1b

BLA STN:	Approval Date:	Potency:
125290/0	8/14/2009	0.3 mg/vial

Trade Name: **Ilaris**
Proper Name: Canakinumab

BLA STN:	Approval Date:	Potency:
125319/0	6/17/2009	180 mg/vial

Trade Name: **Simulect**
Proper Name: Basiliximab

BLA STN:	Approval Date:	Potency:
103764/0	5/12/1998	10 mg/vial
		20 mg/vial

Applicant/License No: Prometheus Laboratories Inc. / License 1848

Trade Name: **Proleukin**
Proper Name: Aldesleukin

BLA STN:	Approval Date:	Potency:
103293/0	5/5/1992	22 MIU/vial

:********** CDER Billable Biologic Product List **********

Applicant/License No: Regeneron Pharmaceuticals, Inc. / License 1760

Trade Name: **Arcalyst**
Proper Name: Rilonacept

BLA STN:	Approval Date:	Potency:
125249/0	2/27/2008	220 mg/vial

Trade Name: **Eylea**
Proper Name: Aflibercept

BLA STN:	Approval Date:	Potency:
125387	11/18/2011	2 mg/0.05 mL (40 mg/mL)

Applicant/License No: Sanofi-Aventis U.S. LLC / License 1752

Trade Name: **Elitek**
Proper Name: Rasburicase

BLA STN:	Approval Date:	Potency:
103946/0	7/12/2002	1.5 mg/vial
BLA STN:	Approval Date:	Potency:
103946/5020	1/6/2006	7.5 mg/vial

Trade Name: **Leukine**
Proper Name: Sargramostim

BLA STN:	Approval Date:	Potency:
103362/0	3/5/1991	250 mcg/vial 500 mcg/mL

Trade Name: **Zaltrap**
Proper Name: ziv-aflibercept

BLA STN:	Approval Date:	Potency:
125418/0	8/3/2012	25 mg/mL

Applicant/License No: Savient Pharmaceuticals, Inc. / License 1801

Trade Name: **Krystexxa**
Proper Name: Pegloticase

BLA STN:	Approval Date:	Potency:
125293/0	9/14/2010	8 mg/mL

Applicant/License No: Schering Corp. / License 0994

Trade Name: **Intron A**
Proper Name: Interferon alfa-2b

BLA STN:	Approval Date:	Potency:
103132/0	6/4/1986	10 MIU/vial (powder) 18 MIU/vial (powder) 22.8 MIU/3.8 mL (3 MIU/0.5mL) (md vials) 32 MIU/3.2 mL (5 MIU/0.5mL) (md vials) 50 MIU/vial (powder)

:********** CDER Billable Biologic Product List **********

Trade Name: **PegIntron**
Proper Name: Peginterferon alfa-2b

BLA STN:	Approval Date:	Potency:
103949/0	1/19/2001	67.5 mcg/pen (powder) 74 mcg/vial (powder) 108 mcg/pen (powder) 118.4 mcg/vial (powder) 162 mcg/pen (powder) 177.6 mcg/vial (powder) 202.5 mcg/pen (powder) 222 mcg/vial (powder)

Trade Name: **Sylatron**
Proper Name: Peginterferon alfa-2b

BLA STN:	Approval Date:	Potency:
103949/5153	3/29/2011	296 mcg/vial 444 mcg/vial 888 mcg/vial

Applicant/License No: Seattle Genetics, Inc. / License 1853

Trade Name: **Adcetris**
Proper Name: Brentuximab vedotin

BLA STN:	Approval Date:	Potency:
125388/0	8/19/2011	50 mg/vial

Applicant/License No: Shire Human Genetic Therapies, Inc. / License 1593

Trade Name: **Elaprase**
Proper Name: Idursulfase

BLA STN:	Approval Date:	Potency:
125151/0	7/24/2006	6 mg/3 mL

Applicant/License No: Sicor Biotech, UAB / License 1803

Trade Name: **Granix**
Proper Name: tbo-filgrastim

BLA STN:	Approval Date:	Potency:
125294/0	8/29/2012	600 mcg/mL

Applicant/License No: Sigma Tau Pharmaceuticals Inc. / License 1850

Trade Name: **Oncaspar**
Proper Name: Pegaspargase

BLA STN:	Approval Date:	Potency:
103411/0	2/1/1994	750 IU/mL

:********** CDER Billable Biologic Product List **********

Applicant/License No: Smith & Nephew, Inc. / License 2004

Trade Name: **Regranex**
Proper Name: Becaplermin

BLA STN:	Approval Date:	Potency:
103691/0	12/16/1997	100 mcg/gram

Trade Name: **Santyl**
Proper Name: Collagenase

BLA STN:	Approval Date:	Potency:
101995/0	6/4/1965	250 u/gram

Applicant/License No: Solstice NeuroSciences, LLC / License 1718

Trade Name: **MYOBLOC**
Proper Name: RimabotulinumToxinB

BLA STN:	Approval Date:	Potency:
103846/0	12/8/2000	5000 IU/mL

Applicant/License No: Spectrum Pharmaceuticals, Inc. / License 1832

Trade Name: **Zevalin**
Proper Name: Ibritumomab tiuxetan

BLA STN:	Approval Date:	Potency:
125019/0	2/19/2002	3.2 mg/2 mL

Applicant/License No: Swedish Orphan Biovitrum AB (publ) / License 1828

Trade Name: **Kepivance**
Proper Name: Palifermin

BLA STN:	Approval Date:	Potency:
125103/0	12/15/2004	6.25 mg/vial

Trade Name: **Kineret**
Proper Name: Anakinra

BLA STN:	Approval Date:	Potency:
103950/0	11/14/2001	100 mg/0.67 mL

Applicant/License No: Takeda Pharmaceuticals U.S.A.,Inc. / License 1898

Trade Name: **Entyvio**
Proper Name: Vedolizumab

BLA STN:	Approval Date:	Potency:
125476/0	5/20/2014	300 mg/vial

Applicant/License No: ThromboGenics Inc. / License 1866

Trade Name: **Jetrea**
Proper Name: Ocriplasmin

BLA STN:	Approval Date:	Potency:
125422/0	10/17/2012	0.5 mg/0.2 mL (2.5 mg/mL)

:********** CDER Billable Biologic Product List **********

Applicant/License No: UCB, Inc. / License 1736

Trade Name: **Cimzia**

Proper Name: Certolizumab pegol

BLA STN:	Approval Date:	Potency:
125160/0	4/22/2008	200 mg/vial
BLA STN:	Approval Date:	Potency:
125160/080	5/13/2009	200 mg/mL

Applicant/License No: Vidara Therapeutics Research Limited / License 1905

Trade Name: **Actimmune**

Proper Name: Interferon gamma-1b

BLA STN:	Approval Date:	Potency:
103836/0	2/25/1999	100 mcg/0.5 mL

Applicant/License No: Wyeth Pharmaceuticals, Inc. / License 0003

Trade Name: **Neumega**

Proper Name: Oprelvekin

BLA STN:	Approval Date:	Potency:
103694/0	11/25/1997	5 mg/vial

CDER Discontinued Biologic Product List

Applicant/License No: Amgen, Inc. / License 1080

Trade Name: **Aranesp**

Proper Name: Darbepoetin alfa (albumin solution)

BLA STN:	Approval Date:	Discontinued Date:	Potency:
103951/0	9/17/2001	9/27/2012	25 mcg/0.42 mL syringe
		9/27/2012	25 mcg/mL vial
		9/27/2012	40 mcg/0.4 mL syringe
		9/27/2012	40 mcg/mL vial
		9/27/2012	60 mcg/0.3 mL syringe
		9/27/2012	60 mcg/mL vial
		9/27/2012	100 mcg/0.5 mL syringe
		9/27/2012	100 mcg/mL vial
		9/27/2012	150 mcg/0.3 mL syringe
		9/27/2012	150 mcg/0.75 mL vial
		9/27/2012	200 mcg/0.4 mL syringe
		9/27/2012	200 mcg/mL vial
		9/27/2012	300 mcg/0.6 mL syringe
		9/27/2012	300 mcg/mL vial
		9/27/2012	500 mcg/mL vial

Applicant/License No: Astellas Pharmaceuticals US, Inc. / License 1748

Trade Name: **Amevive**

Proper Name: Alefacept

BLA STN:	Approval Date:	Discontinued Date:	Potency:
125036/0	1/30/2003	9/24/2008	7.5 mg/vial
		9/28/2012	15 mg/vial

Applicant/License No: Boehringer Ingelheim Pharma KG / License 1251

Trade Name: **Verluma**

Proper Name: Nofetumomab

BLA STN:	Approval Date:	Discontinued Date:	Potency:
103769/0	10/13/1998	8/13/2013	10 mg/mL

Applicant/License No: Centocor Ortho Biotech Products LP / License 1824

Trade Name: **Orthoclone OKT3**

Proper Name: Muromonab-CD3

BLA STN:	Approval Date:	Discontinued Date:	Potency:
103463/0	9/14/1992	1/11/2012	1 mg/mL

Applicant/License No: Eisai, Incorporated / License 1862

Trade Name: **Ontak**

Proper Name: Denileukin diftitox

BLA STN:	Approval Date:	Discontinued Date:	Potency:
103767/0	2/5/1999	1/30/2014	150 mcg/mL

CDER Discontinued Biologic Product List

Applicant/License No: Eli Lilly & Company / License 1611

Trade Name: **Xigris**

Proper Name: Drotrecogin alfa (Activated)

BLA STN:	Approval Date:	Discontinued Date:	Potency:
125029/0	11/21/2001	10/26/2011	5 mg/vial
		10/10/2011	20 mg/vial

Applicant/License No: Genentech, Inc. / License 1048

Trade Name: **Raptiva**

Proper Name: Efalizumab

BLA STN:	Approval Date:	Discontinued Date:	Potency:
125075/0	10/27/2003	9/1/2009	125 mg/vial

Applicant/License No: Genzyme Corp. / License 1596

Trade Name: **Campath**

Proper Name: Alemtuzumab

BLA STN:	Approval Date:	Discontinued Date:	Potency:
103948/0	5/7/2001	7/6/2011	10 mg/vial

Applicant/License No: GlaxoSmithKline LLC / License 1727

Trade Name: **Bexxar Therapeutic Regime**

Proper Name: Tositumomab and Iodine I-131 Tositumomab

BLA STN:	Approval Date:	Discontinued Date:	Potency:
125011/0	6/27/2003	3/10/2014	0.1 mg/mL I-131 Tositumomab
		3/10/2014	1.1 mg/mL I-131 Tositumomab
		3/10/2014	14 mg/mL Tositumomab

Applicant/License No: Hemispherx Biopharma, Inc. / License 1703

Trade Name: **Alferon N Injection**

Proper Name: Interferon alfa-n3 (Human Leukocyte Derived)

BLA STN:	Approval Date:	Discontinued Date:	Potency:
103158/0	10/10/1989	6/27/2013	5 MIU/vial

Applicant/License No: Hoffmann-La Roche, Inc. / License 0136

Trade Name: **Mircera**

Proper Name: Methoxypolyethylene glycol epoetin beta

BLA STN:	Approval Date:	Discontinued Date:	Potency:
125164/0	11/14/2007	9/24/2008	50 mcg/0.3 mL
		9/24/2008	50 mcg/mL
		9/24/2008	75 mcg/0.3 mL
		9/24/2008	100 mcg/0.3 mL
		9/24/2008	100 mcg/mL
		9/24/2008	150 mcg/0.3 mL
		9/24/2008	200 mcg/0.3 mL

********** CDER Discontinued Biologic Product List **********

Trade Name: **Mircera**
Proper Name: Methoxypolyethylene glycol epoetin beta

BLA	STN:	Approval Date:	Discontinued Date:	Potency:
125164/0		11/14/2007	9/24/2008	200 mcg/mL
			9/24/2008	250 mcg/0.3 mL
			9/24/2008	300 mcg/mL
			9/24/2008	400 mcg/0.6 mL
			9/24/2008	400 mcg/mL
			9/24/2008	600 mcg/0.6 mL
			9/24/2008	600 mcg/mL
			9/24/2008	800 mcg/0.6 mL
			9/24/2008	1000 mcg/mL

Trade Name: **Roferon A**
Proper Name: Interferon alfa-2a

BLA	STN:	Approval Date:	Discontinued Date:	Potency:
103145/0		6/4/1986	6/1/2009	3 MIU/0.5 mL syringe
			6/1/2009	6 MIU/0.5 mL syringe
			6/1/2009	9 MIU/0.5 mL syringe

Trade Name: **Zenapax**
Proper Name: Daclizumab

BLA	STN:	Approval Date:	Discontinued Date:	Potency:
103749/0		12/10/1997	7/7/2011	25 mg/5 mL

Applicant/License No: Kadmon Pharmaceuticals, LLC / License 1867

Trade Name: **Infergen**
Proper Name: Interferon alfacon-1

BLA	STN:	Approval Date:	Discontinued Date:	Potency:
103663/0		10/6/1997	7/25/2013	30 mcg/mL

Applicant/License No: MedImmune, LLC / License 1799

Trade Name: **Synagis**
Proper Name: Palivizumab

BLA	STN:	Approval Date:	Discontinued Date:	Potency:
103770/0		6/19/1998	2/28/2007	50 mg/vial (powder)
			2/28/2007	100 mg/vial (powder)

Applicant/License No: Palatin Technologies, Inc. / License 1588

Trade Name: **NeutroSpec Technetium (99m Tc)**
Proper Name: Fanolesomab

BLA	STN:	Approval Date:	Discontinued Date:	Potency:
103928/0		7/2/2004	9/22/2008	0.25 mg/vial

********** CDER Discontinued Biologic Product List **********

Applicant/License No: Recordati Rare Diseases, Inc / License 1899

Trade Name: **Elspar**

Proper Name: Asparaginase

BLA STN:	Approval Date:	Discontinued Date:	Potency:
101063/0	1/10/1978	4/9/2014	10000 IU/vial

Applicant/License No: Schering Corp. / License 0994

Trade Name: **Intron A**

Proper Name: Interferon alfa-2b

BLA STN:	Approval Date:	Discontinued Date:	Potency:
103132/0	6/4/1986	9/23/2013	10 MIU/mL (solution)
		9/23/2013	22.5 MIU/1.5 mL md pen
		9/23/2013	37.5 MIU/1.5 mL md pen
		9/23/2013	75 MIU/1.5 mL md pen

Trade Name: **PegIntron/ReBETOL Combo Pack**

Proper Name: Peginterferon alfa-2b and Ribavirin

BLA STN:	Approval Date:	Discontinued Date:	Potency:
125196/0	6/13/2008	6/25/2009	4 (120 mcg/0.5mL) Redipen & 140 (200 mg) capsules Ribavirin
		6/25/2009	4 (150 mcg/0.5mL) Redipen & 168 (200 mg) capsules Ribavirin
		6/25/2009	4 (150 mcg/0.5mL) Redipen & 196 (200 mg) capsules Ribavirin
		6/25/2009	4 (50 mcg/0.5mL) Redipen & 112 (200 mg) capsules Ribavirin
		6/25/2009	4 (80 mcg/0.5mL) Redipen & 112 (200 mg) capsules Ribavirin

EXHIBIT 3

Drugs@FDA
FDA Approved Drug Products

Drug Details

Drug Name(s)	**NEUPOGEN**
FDA Application No.	**(BLA) 103353**
Active Ingredient(s)	**FILGRASTIM**
Company	**AMGEN**
Original Approval or Tentative Approval Date	**February 20, 1991**

- **There are no Therapeutic Equivalents**
- **Approval History, Letters, Reviews, and Related Documents**
- **Label Information**

Products on Application (BLA) #103353
Click on a column header to re-sort the table:

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	RLD	TE Code
NEUPOGEN	FILGRASTIM	300MCG/1ML	VIAL	Prescription	No	None
NEUPOGEN	FILGRASTIM	480MCG/1.6ML	VIAL	Prescription	No	None
NEUPOGEN	FILGRASTIM	300MGC/0.5ML	SYRINGE	Prescription	No	None
NEUPOGEN	FILGRASTIM	480MCG/0.8ML	SYRINGE	Prescription	No	None

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Division of Online Communications
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10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

Label and Approval History

Drug Name(s) NEUPOGEN
FDA Application No. (BLA) 103353
Active Ingredient(s) FILGRASTIM
Company AMGEN

Go to Approval History

Label Information

What information does a label include?[10]
Note: Not all labels are available in electronic format from FDA.

View the label approved on 09/13/2013 (PDF)[11] for NEUPOGEN, BLA no. 103353

- **To see older, previously-approved labels, go to the "Approval History" section of this page. Older labels are for historical information only and should not be used for clinical purposes.**

Approval History
BLA 103353

Note: Not all reviews are available in electronic format from FDA.
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			Letter (PDF)[17]	
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02/20/1991	0000	Approval	Review (PDF)[27]	Label is not available on this site.

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- **There are no Therapeutic Equivalents**

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Drugs

Drugs@FDA Glossary of Terms

Abbreviated New Drug Application (ANDA)
An Abbreviated New Drug Application (ANDA) contains data that, when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Generic drug applications are called "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent (i.e., performs in the same manner as the innovator drug). Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

Abbreviated New Drug Application (ANDA) Number
This six-digit number is assigned by FDA staff to each application for approval to market a generic drug in the United States.

Active Ingredient
An active ingredient is any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.

Approval History
The approval history is a chronological list of all FDA actions involving one drug product having a particular FDA Application number (NDA). There are over 50 kinds of approval actions including changes in the labeling, a new route of administration, and a new patient population for a drug product.

Application
See New Drug Application (NDA), Abbreviated New Drug Application ANDA), or Biologic License Application (BLA)

Approval Letter
An official communication from FDA to a new drug application (NDA) sponsor that allows the commercial marketing of the product.

Application Number
See FDA Application Number

Biologic License Application (BLA)
Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The Act requires a firm who manufactures a biologic for sale in interstate commerce to hold a license for the product. A biologics license application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical affects of the biologic product. If the information provided meets FDA requirements, the application is approved and a license is issued allowing the firm to market the product.

Biological Product
Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.
In general, the term "drugs" includes **therapeutic biological products**.

Brand Name Drug
A brand name drug is a drug marketed under a proprietary, trademark-protected name.

Chemical Type
The Chemical Type represents the newness of a drug formulation or a new indication for an existing drug formulation. For example, Chemical Type 1 is assigned to an active ingredient that has never before been marketed in the United States in any form. (**list of Chemical Types and their meanings**[1])

Company
The company (also called applicant or sponsor) submits an application to FDA for approval to market a drug product in the United States.

Discontinued Drug Product
Products listed in Drugs@FDA as "discontinued" are approved products that have never been marketed, have been discontinued from marketing, are for military use, are for export only, or have had their approvals withdrawn for reasons other than safety or efficacy after being discontinued from marketing.

Dosage Form
A dosage form is the physical form in which a drug is produced and dispensed, such as a tablet, a capsule, or an injectable.

Drug
A drug is defined as:

- A substance recognized by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)

Drug Product
The finished dosage form that contains a drug substance, generally, but not necessarily in association with other active or inactive ingredients.

FDA Action Date
The action date tells when an FDA regulatory action, such as an original or supplemental approval, took place.

FDA Application Number
This number, also known as the NDA (New Drug Application) number, is assigned by FDA staff to each application for approval to market a new drug in the United States. One drug can have more than one application number if it has different dosage forms or routes of administration

Generic Drug
A generic drug is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. Before approving a generic drug product, FDA requires many rigorous tests and procedures to assure that the generic drug can be substituted for the brand name drug. The FDA bases evaluations of substitutability, or "**therapeutic equivalence**," of generic drugs on scientific evaluations. By law, a generic drug product must contain the identical amounts of the same active ingredient(s) as the brand name product. Drug products evaluated as "therapeutically equivalent" can be expected to have equal effect and no difference when substituted for the brand name product.

Label

The FDA approved label is the official description of a drug product which includes indication (what the drug is used for); who should take it; adverse events (side effects); instructions for uses in pregnancy, children, and other populations; and safety information for the patient. Labels are often found inside drug product packaging.

Marketing Status
Marketing status indicates how a drug product is sold in the United States. Drug products in Drugs@FDA are identified as:

- Prescription
- Over-the-counter
- Discontinued
- None - drug products that have been tentatively approved

Medication Guide
A medication guide contains information for patients on how to safely use a drug product.

NDA (see New Drug Application)

New Drug Application (NDA)
When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA a new drug application (NDA). The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed in the United States. For internal tracking purposes, all NDA's are assigned an NDA number.

New Drug Application (NDA) Number
This six digit number is assigned by FDA staff to each application for approval to market a new drug in the United States. A drug can have more than one application number if it has different dosage forms or routes of administration. In Drugs@FDA, you can find the NDA number under the column named "FDA Application."

NME (see New Molecular Entity)

New Molecular Entity (NME)
A New Molecular Entity is an active ingredient that has never before been marketed in the United States in any form.

Over-the-Counter Drugs (OTC)
FDA defines OTC drugs as safe and effective for use by the general public without a doctor's prescription.

Patient Package Insert (PPI)
A patient package insert contains information for patients' understanding of how to safely use a drug product.

Pharmaceutical Equivalents
FDA considers drug products to be pharmaceutical equivalents if they meet these three criteria:

- they contain the same active ingredient(s)
- they are of the same dosage form and route of administration
- they are identical in strength or concentration

Pharmaceutically equivalent drug products may differ in characteristics such as

- shape
- release mechanism
- labeling (to some extent)
- scoring
- excipients (including colors, flavors, preservatives)

Prescription Drug Product
A prescription drug product requires a doctor's authorization to purchase.

Product Number
A product number is assigned to each drug product associated with an NDA (New Drug Application). If a drug product is available in multiple strengths, there are multiple product numbers.

Reference Listed Drug (see RLD)

Review
A review is the basis of FDA's decision to approve an application. It is a comprehensive analysis of clinical trial data and other information prepared by FDA drug application reviewers. A review is divided into sections on medical analysis, chemistry, clinical pharmacology, biopharmaceutics, pharmacology, statistics, and microbiology.

Review Classification

The NDA and BLA classification system provides a way of describing drug applications upon initial receipt and throughout the review process and prioritizing their review. (List of Review Classifications and their meanings[2])

RLD (Reference Listed Drug)
A Reference Listed Drug (RLD) is an approved drug product to which new generic versions are compared to show that they are bioequivalent. A drug company seeking approval to market a generic equivalent must refer to the Reference Listed Drug in its Abbreviated New Drug Application (ANDA). By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart.

Route
A route of administration is a way of administering a drug to a site in a patient. A comprehensive list of specific routes of administration appears in the CDER Data Standards Manual[3].

Strength
The strength of a drug product tells how much of the active ingredient is present in each dosage.

Supplement
A supplement is an application to allow a company to make changes in a product that already has an approved new drug application (NDA). CDER must approve all important NDA changes (in packaging or ingredients, for instance) to ensure the conditions originally set for the product are still met.

Supplement Number
A supplement number is associated with an existing FDA New Drug Application (NDA) number. Companies are allowed to make changes to drugs or their labels after they have been approved. To change a label, market a new dosage or strength of a drug, or change the way it manufactures a drug, a company must submit a supplemental new drug application (sNDA). Each sNDA is assigned a number which is usually, but not always, sequential, starting with 001.

Supplement Type
Companies are allowed to make changes to drugs or their labels after they have been approved. To change a label, market a new dosage or strength of a drug, or change the way it manufactures a drug, a company must submit a supplemental new drug application (sNDA). The supplement type refers to the kind of change that was approved by FDA. This includes changes in manufacturing, patient population, and formulation.

Tentative Approval
If a generic drug product is ready for approval before the expiration of any patents or exclusivities accorded to the **reference listed drug** product, FDA issues a tentative approval letter to the applicant. The tentative approval letter details the circumstances associated with the tentative approval. FDA delays final approval of the generic drug product until all patent or exclusivity issues have been resolved. A tentative approval does not allow the applicant to market the generic drug product.

Therapeutic Biological Product
A therapeutic biological product is a protein derived from living material (such as cells or tissues) used to treat or cure disease.

Therapeutic Equivalence (TE)
Drug products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. Drug products are considered to be therapeutically equivalent **only** if they meet these criteria:

- they are **pharmaceutical equivalents** (contain the same **active ingredient(s)**; **dosage form** and **route of administration**; and **strength**.)
- they are assigned by FDA the same **therapeutic equivalence codes** starting with the letter "A ." To receive a letter "A", FDA
- designates a brand name drug or a generic drug to be the **Reference Listed Drug** (RLD).
- assigns therapeutic equivalence codes based on data that a drug sponsor submits in an **ANDA** to scientifically demonstrate that its product is bioequivalent (i.e., performs in the same manner as the Reference Listed Drug).

Therapeutic Equivalence (TE) Codes
The coding system for **therapeutic equivalence** evaluations allows users to determine whether FDA has evaluated a particular approved product as therapeutically equivalent to other **pharmaceutically equivalent** products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter). Sample TE codes: AA, AB, BC (More on TE Codes[4])

- FDA assigns therapeutic equivalence codes to **pharmaceutically equivalent** drug products. A drug product is deemed to be **therapeutically equivalent** ("**A**" rated) only if:
- a drug company's approved application contains adequate scientific evidence establishing through *in vivo* and/or *in vitro* studies the bioequivalence of the product to a selected **reference listed drug**.
- those active ingredients or dosage forms for which no *in vivo* bioequivalence issue is known or suspected.
- Some drug products have more than one TE Code.
- Those products which the FDA does not deem to be therapeutically equivalent are "**B**" rated.

Over-the-counter drugs are not assigned TE codes.

Page Last Updated: 02/02/2012
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EXHIBIT 4

2 of 7 DOCUMENTS

The Pink Sheet Daily

January 7, 2015

SECTION: Vol. 15 No. 10

LENGTH: 922 words

HEADLINE: ODAC Asks **Sandoz** If Biosimilar Price Is Right

BODY:

Among the most striking differences seen between a typical advisory committee meeting and FDA's first for a 351(k) application was a somewhat extensive discussion of pricing.

Specifically, **Sandoz Inc.** was asked whether its filgrastim biosimilar, if approved, would help lower costs.

FDA decisions cannot take price into account, and the agency usually avoids such discussions if they come up during the advisory committee meetings.

Agency officials did not interrupt the discussion of the "elephant in the room that nobody acknowledges," as Oncologic Drugs Advisory Committee member James Liebmann put it during the Jan. 7 meeting. But the answers **Sandoz** gave were not definitive.

Sandoz argued during the meeting at which its biosimilar to **Amgen Inc.** 's *Neupogen* was considered that consumer and payer costs would be lower. But **Sandoz** would not state it would price the product, which has the proposed trade name *Zarxio* , below Neupogen.

Some models have estimated price reductions of 20% to 30% once biosimilars enter the market.

"We can't say that the price would be less because in some situations the price will be at parity because of other relative terms that will come into existence that's there," said Mark McCamish, **Sandoz** global head of biopharmaceuticals and oncology injectables development. "Price is a relatively complex situation."

Committee members voted unanimously to recommend approval of Zarxio for all five Neupogen indications (*see related story*, "**Sandozs** Biosimilar Filgrastim Sails Through FDA Panel" "The Pink Sheet Daily" Jan. 7, 2015).

ODAC agreed with FDA review staff that there were no clinically meaningful differences that would raise concerns ("**Sandozs** Biosimilar Filgrastim Highly Similar To Neupogen FDA Staff Say" "The Pink Sheet Daily" Jan. 5, 2015).

McCamish and other executives of companies looking to enter the biosimilar market have argued price will not be the only issue involved, indicating that rebates could be higher, which would affect the overall cost.

Sandoz in particular said it would not make the same pricing mistake with Zarxio that it made with *Omnitrope* (somatropin [rDNA origin]), a 505(b)(2) follow-on biologic. The company priced it too low, which hindered sales ("Biosimilar Pricing **Sandoz** Vows Not To Make emOmnitropeem Mistake With Filgrastim" "The Pink Sheet" Dec. 22, 2014).

FDA officials did not speak during the pricing discussion at the committee meeting. The agency said in a statement issued after the meeting that it generally doesn't stop discussions "that occur during the natural course of a meeting if a committee member brings something up."

Comments about the potential for cost savings also emerged during the open public hearing session. Representatives of a number of advocacy groups and patients argued in favor of allowing biosimilars on the market because of the potential for cost reductions.

But the extended conversation among committee members may be another signal of the difference in how biosimilar advisory committee meetings may function compared to those for new drugs. Cost may become a more regular discussion topic, even if it does not play a part in the agency's ultimate approval decision.

How advisory committees would handle various aspects of a biosimilar application has been an issue potential sponsors were anticipating as the filgrastim meeting approached ("Biosimilar Sponsors Offer Advisory Committee Primer" "The Pink Sheet" Dec. 22, 2014).

Sandoz Initiates Discussion During Presentation

Sandoz broached the pricing issue when consultant Louis Weiner, chairman of the Georgetown University Medical Center Department of Oncology, suggested during a presentation on the clinical perspective for biosimilar use that the products would lower costs and spur competition.

Liebmann, an assistant professor at the University of Massachusetts Department of Medicine, said he was pleased the issue emerged and noted it has not been acknowledged in previous advisory committee meetings.

He asked **Sandoz** officials directly: "Is the consultant correct? Would this really bring down cost?"

The question drew some laughter from the crowd. McCamish said experience with the product in Europe - where it was approved for marketing in 2009 - showed that costs fell.

"There has been a substantial increase in the use so we are addressing access, and there has been a substantial reduction in cost because of the competition that's there," McCamish said.

But Liebmann pushed for a more direct answer, saying European pricing models are different from the U.S. and may not be relevant.

"The point of my question was that I was hoping that the sponsor would address it," he said. "You could simply say 'Yes we're going to price it less than Neupogen.' And if you're honest that would be delightful."

Price Parity, Lower Cost

McCamish said mechanisms in place such as rebates will help patients save money.

"The cost will be less to the consumer, to the payer, to the health care economy," he said. "It has to be; otherwise it doesn't make sense."

Sandoz's filgrastim 351(k) submission is the first to reach the advisory committee stage. It also was the first to be publicly disclosed as filed ("**Sandoz** emNeupogenem Biosimilar Heads To **ODAC** Cmte May Be Students As Much As Advisors" "The Pink Sheet Daily" Dec. 8, 2014).

Since **Sandoz's** announcement, two other companies have stated they have submitted biosimilar applications ("Apotex Biosimilar Goes To FDA But May Enter Crowded Market" "The Pink Sheet Daily" Dec. 17, 2014).

By Derrick Gingery

LOAD-DATE: January 7, 2015

EXHIBIT 5

2 of 2 DOCUMENTS

The Pink Sheet

December 22, 2014

SECTION: Vol. 14 No. 122

LENGTH: 875 words

HEADLINE: Biosimilar Pricing: Sandoz Vows Not To Make Omnitrope 'Mistake' With Filgrastim

BODY:

As it closes in on approval of its first U.S. biosimilar under the 351(k) pathway, **Novartis AG** 's **Sandoz Inc.** division is vowing not to repeat the pricing mistakes it made with the human growth hormone *Omnitrope* eight years ago.

Sandoz exec Mark McCamish told the FDA/CMS Summit in Washington, D.C., Dec. 11 that U.S. consumers, providers and payers will not be disappointed in the savings they see with biosimilars approved under the Biologics Price Competition and Innovation Act.

"This needs to make a difference. We understand that," said McCamish, global head of biopharmaceutical and oncology injectables development.

Sandoz's biosimilar version of **Amgen Inc.** 's granulocyte colony-stimulating factor *Neupogen* (filgrastim) is in line potentially to be the first product licensed under this pathway. The application has a March 2015 user fee date, with an FDA advisory committee scheduled for Jan. 7 ("Sandoz emNeupogenem Biosimilar Heads To ODAC Cmte May Be Students As Much As Advisors" "The Pink Sheet Daily" Dec. 8, 2014).

Complex Commercial Models

However, McCamish cautioned that price is not a simple issue given the complexity of U.S. commercial models.

"For example, it could be that with a rebate system that our price may be identical to or even higher" than the innovator product, "but the rebate would be much greater, so that ultimately the cost is lower."

McCamish said Sandoz learned its lesson with the launch of Omnitrope (somatropin [rDNA origin]).

Approved in 2006 under the 505(b)(2) pathway, Omnitrope is widely viewed as the first follow-on biologic cleared in the U.S., coming four years before the 351(k) biosimilar pathway was established through the BPCIA. Sandoz's Omnitrope application referenced **Pfizer Inc.** 's *Genotropin* ("FDA Clears Omnitrope Product Is Not The Process But Nor Is It A Pathway" "The Pink Sheet" Jun. 5, 2006).

In launching Omnitrope, Sandoz focused on price and failed to take into account the financial incentives specific to each player in the health care delivery system.

"We made a mistake" with Omnitrope, McCamish said. "Initially, we priced it at a substantial reduction, and through the specialty pharmacies, because they make a profit based on a percentage of the sales price of the drug, we had a lousy experience in selling the product because we priced it too low, and we had to increase the price to sell the product."

In contrast, managed care organizations do not have the same constraints, so they "want the lowest price that's there and that drives the benefit to the patients," McCamish said.

Initial uptake of Omnitrope also was hampered by a delivery device that was criticized as inferior and less convenient than those of branded human growth hormone products ("Omnitropes Low Switch Rate Due To Inferior Delivery Device Express Scripts" "The Pink Sheet" Nov. 26, 2007).

In addition, Sandoz previously has acknowledged it underestimated the level of commercial support it needed to put behind the follow-on product, such as patient-training services and reimbursement assistance ("Price Isnt Enough Sandoz Hones Biosimilars Strategy With Lessons From Omnitrope" "The Pink Sheet" Nov. 22, 2010).

"I don't think you'll be disappointed; otherwise all the work that we've done doesn't come to fruition," McCamish said. "At the same time, price is going to be challenging because it will vary depending upon the stakeholder that's there. We have to know who's incentivized for this. But ultimately, the cost to the supplier, to the patient, will be lower."

By using the BPCIA pathway, Sandoz seeks to capitalize on a Medicare reimbursement formula that not only does not discourage prescribing of biosimilars, but actually may make prescribing such products more financially attractive than their branded counterparts ("Biosimilar Reimbursement Under The Sequester The Lower The Price The Bigger The Spread" "The Pink Sheet Daily" Aug. 8, 2014).

Sumant Ramachandra, senior VP and chief scientific officer of **Hospira Inc.** , echoed McCamish's remarks on U.S. expectations for cost savings.

Based on Hospira's experience with two biosimilars in Europe and one in Australia, "this is not going to be a situation where people will be disappointed," he said.

Hospira is the U.S. commercialization partner on **Celltrion Inc.** 's biosimilar version of **Johnson & Johnson** 's tumor necrosis factor-inhibitor *Remicade* (infliximab). The biosimilar application was submitted under the 351(k) pathway and has a June 2015 user fee date ("emRemicadeem Biosimilar From Celltrion Includes Bridging Extrapolation And Switching Data" "The Pink Sheet Daily" Aug. 11, 2014).

With Competition Comes Greater Use

The benefits to be gained are not just in cost savings, but also in outcomes, Ramachandra said.

In Hospira's experience, introduction of biosimilars has led to more patients gaining access to biologic therapies than before.

"What you're actually seeing is patients who didn't have access to certain drugs suddenly start getting access to the drug. Their medical outcome ends up being better, so the [value] part of the equation ... starts actually accelerating," he said.

"Competition always brings an end benefit. If it's not in year one, it will eventually happen in year two."

By Sue Sutter

LOAD-DATE: December 22, 2014

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

AMGEN INC. and AMGEN MANUFACTURING, LIMITED, Plaintiffs, vs. SANDOZ INC., SANDOZ INTERNATIONAL GMBH, and SANDOZ GMBH, Defendants.	Case No. 3:14-cv-04741-RS **[PROPOSED] ORDER GRANTING AMGEN'S MOTION FOR A PRELIMINARY INJUNCTION**

Having considered the Motion for a Preliminary Injunction filed on February 5, 2015, by Plaintiffs Amgen Inc. ("Amgen") and Amgen Manufacturing, Limited, and the opposition thereto filed by Defendant Sandoz Inc. ("Sandoz"), and the materials submitted in support of and opposition to that motion, as well as all other arguments and the record of this case, and good cause having been shown, the Court orders as follows:

IT IS HEREBY ORDERED THAT Plaintiffs' Motion for a Preliminary Injunction shall be and hereby is GRANTED;

IT IS FURTHER ORDERED THAT: Sandoz and all those acting in concert with it or on its behalf, are enjoined from engaging in the commercial manufacture, use, offer to sell, sale within the United States, or importation into the United States of any biosimilar filgrastim product:

(1) until the Court decides the parties' pending motions for judgment on the pleadings and, if the Court resolves those motions in Amgen's favor, until the acts set forth in Paragraphs 2 to 8 below have been completed;

(2) Sandoz provides Amgen with copy of the Biologics License Application submitted to FDA under 42 U.S.C. § 262(k) for Sandoz's biosimilar filgrastim product and such other information that describes the process or processes used to manufacture it, all of which Sandoz shall provide no later than 20 days after the Court enters on the docket its ruling on the pending motions for judgment on the pleadings;

(3) (A) Amgen provides Sandoz with

(i) a list of patents for which Amgen believes a claim of patent infringement could reasonably be asserted by Amgen, or by a patent owner that has granted an exclusive license to Amgen with respect to filgrastim, if a person not licensed by Amgen engaged in the making, using, offering to sell, selling, or importing into the

United States of the biological product that is the subject of Sandoz's subsection (k) application, and

(ii) an identification of the patents on such list that Amgen would be prepared to license to Sandoz,

all of which Amgen shall provide to Sandoz not later than 60 days after Amgen's receipt from Sandoz of the information called for by Paragraph 2;

(B) Sandoz provides Amgen with

(i) at Sandoz's election, a list of patents to which Sandoz believes a claim of patent infringement could reasonably be asserted by Amgen if a person not licensed by Amgen engaged in the making, using, offering to sell, selling, or importing into the United States of the biological product that is the subject of Sandoz's subsection (k) application; and

(ii) with respect to each patent listed by Amgen under Subparagraph 3(A) or by Sandoz under clause (i) of this Subparagraph 3(B),

(I) a detailed statement that describes, on a claim by claim basis, the factual and legal basis of the opinion of Sandoz that such patent is invalid, unenforceable, or will not be infringed by the commercial marketing of the biological product that is the subject of Sandoz's subsection (k) application, or

(II) a statement that Sandoz does not intend to begin commercial marketing of the biological product before the date that such patent expires; and

(iii) a response regarding each patent identified by Amgen under clause (ii) of Subparagraph 3(A),

all of which Sandoz shall provide to Amgen not later than 60 days after its receipt from Amgen of the information called for by Subparagraph 3(A);

(C) Amgen provides Sandoz with a detailed statement that describes, with respect to each patent described in clause (ii)(I) of Subparagraph 3(B), on a claim by claim basis, the factual and legal basis of Amgen's opinion that such patent will be infringed by the commercial marketing of the biological product that is the subject of Sandoz's subsection (k) application and a response to the statement concerning validity and enforceability provided under clause (ii)(I) of Subparagraph 3(B), all of which Amgen shall provide to Sandoz not later than 60 days after its receipt from Sandoz of the information called for by Subparagraph 3(B);

(4) (A) Amgen and Sandoz engage in good faith negotiations to agree on which, if any, patents listed by Amgen or Sandoz under Subparagraphs 3(A) through 3(C) shall be the subject of an action for patent infringement by Amgen under Paragraph 6, which negotiations shall commence immediately upon Sandoz's receipt from Amgen of the information called for by Subparagraph 3(C);

(B) if within 15 days of commencing negotiations under Subparagraph 4(A), Sandoz and Amgen have failed to agree on a final and complete list of which, if any, patents listed under Paragraph 3, by Sandoz or Amgen, shall be the subject of an action for patent infringement by Amgen under Paragraph 6, then the provisions of Paragraph 5 shall next be completed;

(5) (A) Sandoz will notify Amgen of the number of patents that Sandoz will provide to Amgen under clause (B)(i)(I) of this Paragraph 5;

(B) (i) on a date to be agreed to by Amgen and Sandoz but in no case later than 5 days after Sandoz notifies Amgen under clause (A) of this Paragraph 5, Sandoz and Amgen will simultaneously exchange:

(I) the list of patents that Sandoz believes should be the subject of an action for patent infringement under Paragraph 6; and

(II) the list of patents, in accordance with clause (B)(ii) of this Paragraph 5, that Amgen believes should be the subject of an action for patent infringement under Paragraph 6;

(ii) (I) subject to subclause (II) of this clause (B)(ii) of this Paragraph 5, the number of patents listed by Amgen under clause (B)(i)(II) of this Paragraph 5 may not exceed the number of patents listed by Sandoz under clause (B)(i)(I) of this Paragraph 5; and

(II) if Sandoz does not list any patent under clause (B)(i)(I) of this Paragraph 5, Amgen may list one patent under clause (B)(i)(II) of this Paragraph 5.

(6) Amgen will either

(A) commence a patent infringement action against Sandoz on each patent agreed upon through good faith negotiation under Subparagraph 4(A), within 30 days after the parties reach such agreement, or

(B) commence a patent infringement action against Sandoz with respect to each patent included on the lists exchanged pursuant to clauses (B)(i)(I) and (B)(i)(II) of Paragraph 5, within 30 days after the parties exchange such lists, and

(C) Sandoz, not later than 30 days after a complaint is served on it an action for patent infringement described in this Paragraph 6, will provide FDA with notice and a copy of the complaint.

(7) In the case of a patent that

(A) is issued to, or exclusively licensed by, Amgen after the date that Amgen provided the list to Sandoz under Subparagraph 3(A), and

(B) Amgen reasonably believes that, due to the issuance of such patent, a claim of patent infringement could reasonably be asserted by Amgen if a person not licensed by Amgen engaged in the making, using, offering to sell, selling, or importing into the United States of the biological product that is the subject of Sandoz's subsection (k) application,

not later than 30 days after such issuance or licensing, Amgen provides to Sandoz a supplement to the list provided by Amgen under Subparagraph (3)(A) that includes such patent, and not later than 30 days after such supplement is provided, Sandoz shall provide a statement to Amgen in accordance with Subparagraph 3(B), and such patent shall be subject to Paragraph 8.

(8) (A) Sandoz provides notice to Amgen not later than 180 days before the date of the first commercial marketing of its biosimilar filgrastim product licensed under 42 U.S.C. § 262(k), which notice Sandoz may not give until the later of (A) FDA licensure of that biosimilar filgrastim product, and (B) Amgen's commencement of the patent infringement action pursuant to Paragraph 6;

(B) After receiving the notice under Subparagraph 8(A) and before the date of the first commercial marketing of such biological product, Amgen may seek a preliminary injunction prohibiting Sandoz from engaging in the commercial manufacture or sale of such biological product until the court decides the issue of patent validity, enforcement, and infringement with respect to any patent that is:

(i) included in the list provided by Amgen under Subparagraph 3(A) or in the list provided by Sandoz under Subparagraph 3(B); and

(ii) not included, as applicable, on:

(I) the list of patents described in Paragraph 4; or

(II) the list of patents described in Subparagraph 5(B).

(C) If Amgen seeks a preliminary injunction under Subparagraph 8(B), Amgen and Sandoz shall reasonably cooperate to expedite such further discovery as is needed in connection with the preliminary injunction motion.

IT IS SO ORDERED.

Date: March __, 2015

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Honorable Richard Seeborg

United States District Judge