IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and CITY OF HOPE, Plaintiffs, v. IMMUNEX RHODE ISLAND CORP. and AMGEN INC., Defendant.	C.A. No. 19-602-CFC [redacted] PUBLIC VERSION FILED: July 23, 2019

GENENTECH'S EMERGENCY MOTION TO ENFORCE STATUTORY PROHIBITION ON COMMERCIAL MARKETING

Pursuant to Federal Rules of Civil Procedure 7(b)(1) and 65 and 42 U.S.C. § 262(*l*)(8), Plaintiff Genentech, Inc. respectfully moves to enforce the statutory prohibition on commercial marketing, thereby prohibiting each of defendants Immunex Rhode Island Corp. and Amgen Inc., their affiliates, subsidiaries, and each of their officers, agents, servants and employees and those acting in privity or in concert with them, from commercially marketing within the United States products that are the subject of BLA Nos. 761028/S-003 and 761028/S-004, until such time as Amgen Inc. provides notice of its intent to commercially market such products pursuant to 21 U.S.C. § 262(*l*)(8) and 180 days have elapsed. The legal and factual bases for the relief requested are fully set forth in the accompanying Opening Brief and supporting materials.

DATED: July 10, 2019

MCCARTER & ENGLISH, LLP

/s/ Daniel M. Silver

Michael P. Kelly (# 2295)
Daniel M. Silver (# 4758)
Alexandra M. Joyce (#6423)
Renaissance Centre
405 N. King Street, 8th Floor
Wilmington, Delaware 19801
Tel.: (302) 984-6300
Fax: (302) 984-6399
mkelly@mccarter.com
dsilver@mccarter.com
ajoyce@mccarter.com

Attorneys for Plaintiffs Genentech, Inc. and City of Hope

OF COUNSEL:

Paul B. Gaffney
David I. Berl
Thomas S. Fletcher
Kyle E. Thomason
Teagan J. Gregory
Charles L. McCloud
Kathryn S. Kayali
Jonathan S. Sidhu
Williams & Connolly LLP
725 Twelfth St. NW
Washington, DC 20005
(202) 434-5000

Attorneys for Plaintiff Genentech, Inc.

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AVERMENT OF COUNSEL

The undersigned counsel hereby certifies that counsel for Plaintiffs conferred with counsel for Defendants, including verbally in one or more teleconferences involving Delaware counsel for all parties, regarding the relief sought in the foregoing motion and that counsel were unable to reach agreement on the relief sought.

DATED: July 10, 2019

MCCARTER & ENGLISH, LLP

/s/ Daniel M. Silver

Michael P. Kelly (#2295)
Daniel M. Silver (#4758)
Alexandra M. Joyce (#6423)
Renaissance Centre
405 N. King Street, 8th Floor
Wilmington, Delaware 19801
Tel.: (302) 984-6300
Fax: (302) 984-6399
mkelly@mccarter.com
dsilver@mccarter.com
ajoyce@mccarter.com

Attorneys for Plaintiffs Genentech, Inc. and City of Hope

OF COUNSEL:

Paul B. Gaffney
David I. Berl
Thomas S. Fletcher
Teagan J. Gregory
Jonathan S. Sidhu
Williams & Connolly LLP
725 Twelfth St. NW
Washington, DC 20005
(202) 434-5000

Attorneys for Plaintiff Genentech, Inc.

IN THE UNITED STATES DISTRICT COURT
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GENENTECH, INC. and CITY OF HOPE, Plaintiffs, v. IMMUNEX RHODE ISLAND CORP. and AMGEN INC., Defendant.	)	C.A. No. 19-602-CFC CONSOLIDATED [redacted]

[PROPOSED] ORDER GRANTING
GENENTECH'S EMERGENCY MOTION TO ENFORCE
STATUTORY PROHIBITION ON COMMERCIAL MARKETING

IT IS HEREBY ORDERED this _____ day of _____, 2019, that:

1. Genentech's Emergency Motion to Enforce Statutory Prohibition on Commercial Marketing is GRANTED. Amgen is required pursuant to 42 U.S.C. § 262(*l*)(8)(A) to provide notice prior to commercial marketing of a product "licensed under subsection (k)." Amgen's Mvasi manufactured at the facility and using the processes approved in BLA No. 761028/S-003 is a biological product "licensed under subsection (k)." Amgen's Mvasi distributed with the label approved in BLA No. 761028/S-004 is a biological product "licensed under subsection (k)." Genentech has demonstrated that Amgen has not provided to it the notice required by law with respect to either of these biological products.

2. Accordingly, each of defendants Immunex Rhode Island Corp. and Amgen Inc., their affiliates, subsidiaries, and each of their officers, agents, servants and employees and those acting in privity or in concert with each defendant, is prohibited from commercially marketing within the United States the products that are the subject of BLA Nos. 761028/S-003 and

761028/S-004 until Amgen Inc. provides notice of its intent to commercially market such product pursuant to 21 U.S.C. § 262(*l*)(8) and 180 days have elapsed.

3. Amgen and Immunex shall provide notice of this Order within three (3) days to any affiliates, subsidiaries, and each of their officers, agents, servants and employees and those acting in privity or in concert with Amgen or Immunex that is involved in any effort to market commercially within the United States the products that are the subject of BLA Nos. 761028/S-003 and 761028/S-004.

_____

Honorable Colm F. Connolly

CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that true and correct copies of the foregoing document were caused to be served on July 10, 2019 on the following counsel in the manner indicated:

VIA EMAIL:

Melanie K. Sharp
James L. Higgins
YOUNG CONAWAY STARGATT & TAYLOR, LLP
1000 North King Street
Wilmington, DE 19801
(302) 571-6600
msharp@ycst.com
jhiggins@ycst.com

Amir A. Naini
Siegmund Gutman
Michelle M. Ovanesian
PROSKAUER LLP
2029 Century Park East, Suite 2400
Los Angeles, CA 90067-3010
(310) 284-5641
anaini@proskauer.com
sgutman@proskauer.com
movanesian@proskauer.com

Attorneys for Immunex Rhode Island Corp. and Amgen Inc.

Dated: July 10, 2019

/s/ Daniel M. Silver
Daniel M. Silver (#4758)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and CITY OF HOPE	)	
	)	
Plaintiffs,	)	C. A. No.: 19-602-CFC
	)	
v.	)	[redacted]
	)	
IMMUNEX RHODE ISLAND CORP., and AMGEN INC.	)	
	)	[redacted]
	)	
Defendant.		

PUBLIC VERSION FILED: July 23, 2019

OPENING BRIEF IN SUPPORT OF
EMERGENCY MOTION TO ENFORCE
STATUTORY PROHIBITION ON COMMERCIAL MARKETING

OF COUNSEL:

Paul B. Gaffney
David I. Berl
Thomas S. Fletcher
Kyle E. Thomason
Teagan J. Gregory
Charles L. McCloud
Kathryn S. Kayali

WILLIAMS & CONNOLLY LLP
725 Twelfth St. NW
Washington, DC 20005
(202) 434-5000

Attorneys for Plaintiff Genentech, Inc.

Daralyn J. Durie
Adam R. Brausa
Eric C. Wiener
Eneda Hoxha
DURIE TANGRI
271 Leidesdorff Street
San Francisco, CA 94111

Attorneys for Plaintiffs Genentech, Inc. and City of Hope

MCCARTER & ENGLISH, LLP
Michael P. Kelly (# 2295)
Daniel M. Silver (# 4758)
Renaissance Centre
405 N. King Street, 8th Floor
Wilmington, Delaware 19801
Tel.: (302) 984-6300
Fax: (302) 984-6399
mkelly@mccarter.com
dsilver@mccarter.com

Attorneys for Plaintiffs Genentech, Inc. and City of Hope

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OTHER AUTHORITIES

For the past several months, Amgen repeatedly has denied any concrete plan to launch Mvasi, its biosimilar version of Genentech's Avastin. Appendix ("App.") at A56 (S. Vunnum Tr.) at 59:7-16, 60:2-7, 60:17-23; *id.* at A51-A52 (J. Yant Tr.) at 70:12-23, 77:16-19; *id.* at A64 (June 18, 2019 Hearing Tr.) at 78:22-25 ("[W]e have not made that decision yet . . . . those decisions are ongoing."). At the same time, it has frustrated all discovery into the truth of those denials, including recently cancelling on very short notice depositions of key marketing, regulatory, and launch-planning executives. In a recent filing with the Court, however, Amgen warned that it "could decide to launch . . . Mvasi at any time," Case No. 17-cv-1407-CFC, D.I. 431 at 1 n. 1, and according to a document Amgen produced [redacted] it appears Amgen is [redacted] Mvasi into distribution channels for launch [redacted], App. at A509.

Under the BPCIA Amgen cannot yet start selling this product lawfully, because it has not provided 180 days' notice before "the first commercial marketing of the biological product licensed under subsection (k)." 42 U.S.C. § 262(*l*)(8). A cornerstone of the statute's "carefully calibrated scheme," *Sandoz v. Amgen*, 137 S. Ct. 1664, 1670 (2017) ("*Sandoz II*"), subsection (*l*)(8) ensures that litigants and the court have "the opportunity to litigate the relevant patents *before* the biosimilar is marketed," *id.* at 1672 (emphasis added), and to do so in a manner that avoids "hurried motion practice," *Amgen, Inc. v. Apotex Inc.*, 827 F.3d 1052, 1065 (Fed. Cir. 2016). Compliance is "mandatory" and enforceable. *Id*. at 1065-66; *Amgen, Inc. v. Sandoz, Inc.*, 794 F.3d 1347, 1360 (Fed. Cir. 2015) ("*Sandoz I*"), *rev'd in part*, *Sandoz II*, 137 S.Ct. 1664.

Amgen purports to have provided such notice in October 2017, shortly after FDA's approval of a product made at Amgen Thousand Oaks ("ATO") accompanied by a label[1] that

[1] Drug products licensed by FDA must be accompanied by FDA-approved prescribing information, often referred to as a "label," that instructs physicians and patients on their use. *See* 21 C.F.R. § 201.56.

largely copied the Avastin label. But the product Amgen intends to market is something different, manufactured [redacted] at a different facility (Amgen Rhode Island ("ARI")) that infringes different Genentech patents. These differences required a separate FDA approval, something Amgen—for the reasons set out below—strategically postponed until nearly a year after the FDA's approval of its first application. Amgen also would market the current version of Mvasi under a new label modified, it would appear, for the sole purpose of trying to argue that Amgen was no longer inducing infringement of Genentech's U.S. Patent No. 9,795,672 ("Fyfe")—another change requiring a new application and separate FDA approval, obtained only in June 2019. The (*l*)(8) notice Amgen served in October 2017 plainly did not disclose its plans to market a version of Mvasi for which Amgen had not yet even sought FDA approval at that time.

Genentech accordingly asks the Court to enforce the law and prohibit Amgen from marketing its new version of Mvasi before complying with the BPCIA's (*l*)(8) notice requirement. Consistent with the statute, enforced compliance will clear the path of Amgen's discovery obstructions and ensure that the parties and the Court have adequate time to schedule preliminary injunction proceedings to address the infringement that would result from Amgen's marketing of its new product.

Genentech conferred with Amgen on July 10 and sought confirmation that Amgen would not begin commercial marketing [redacted]. Amgen declined to provide such confirmation, and Genentech therefore is filing a motion for Temporary Restraining Order pending resolution of this motion and any appeal therefrom.

BACKGROUND

A. Amgen's Potemkin Application

1. In November 2016 Amgen filed an abbreviated biologics license application

seeking approval to manufacture Mvasi at ATO pursuant to processes described in that filing and to market Mvasi with a particular label (the "ATO Application"). [redacted].[2]

2. [redacted]. As Amgen's witnesses have explained, [redacted] App. at A57 at 192:19-21. Indeed years before filing the ATO Application Amgen understood that [redacted] App. at A288.

3. Amgen knew that [redacted].'" App. at A289. But Amgen also [redacted]. *See* 42 U.S.C. § 262(i)(2) (defining "biosimilar"); *id.* § 262(k)(2)(A)(i) (required information). Amgen thought it could "[redacted]

[2] [redacted] App. at A97, A98 [redacted]

[3] *See* App. at A58 at 194:8-11 [redacted] *id.* at A57 at 191:5-8 ([redacted] *id.* at 189:19-20 [redacted] *id.* at A53 at 151:24–152:1 ([redacted]

[redacted].[4] As the [redacted] testified:

[redacted]

App. at A54 (J. Yant Tr.) at 163:20-164:1. Then, once approved, Amgen [redacted]

[redacted].

See, e.g., *id.* at A316.

4. [redacted]

[redacted] *Id.* at A342. [redacted]

[redacted] *Id.* [redacted] *Id.* at A342.

[4] *See, e.g.*, App. at A270 [redacted]; *id.* at A283, A286 [redacted]); *id.* at A54 [redacted] *id.* at A255 [redacted]; *id.* at A342 [redacted] *id.* at A316 [redacted])").

5. Amgen's regulatory gambit had consequences for the patent dispute it anticipated with Genentech. After the FDA accepted the ATO Application in January 2017, Amgen purported to begin the BPCIA's "patent dance." It notified Genentech pursuant to 42 U.S.C. § 262(*l*)(2), triggering the exchange of infringement and validity contentions over the product and label described in the ATO Application. Less than a month after the FDA approved that application, Amgen provided Genentech notice pursuant to (*l*)(8) along with "a confidential version of FDA's letter of approval of BLA No 761028 for Mvasi™ (bevacizumab-awwb), which also includes the approved labeling for Mvasi™." App. at A1. The pending 17-1407 action was filed that day.[5]

B. The ARI Application

6. In the meantime, Amgen stuck to its secret regulatory strategy. With approval of the ATO Application in hand, Amgen prepared its ARI Application. Amgen kept the FDA in the dark about its plans, in particular that [redacted]e, *id.* App. at A59 (S. Vunnum Tr.) at 260:1-7, revealing that key fact only when it filed the ARI Application in August 2018, *id.* at A99; *id.* at A101-A104.

7. The ARI Application was a surprise to Genentech as well. The 17-1407 Case was already well underway, having commenced the previous fall after months of "patent dance" exchanges over the ATO Application and receipt of Amgen's October 2017 (*l*)(8) notice. Genentech promptly advised the Court of Amgen's application to license a new version of Mvasi manufactured at ARI and that, pursuant to the BPCIA, Genentech was analyzing it for evidence

[5] As Amgen had already decided to wait years to launch, with a different Mvasi manufactured at ARI, *see* pp. 3-4 & notes 3-4 *supra*, this (*l*)(8) notice was plainly tactical, an excuse to sue preemptively in Los Angeles and avoid further dealings before Judge Sleet, who had been critical. App. at A49 (Feb. 24, 2017 Hearing Tr. in Case No. 17-cv-165-GMS) at 22:24-25:21. Amgen's venue strategy failed. *Amgen, Inc. v. Genentech Inc. et al.*, 2018 WL 910198 (C.D. Cal. Jan. 11, 2018), *confirmed*, 2018 WL 718418 (C.D. Cal. Feb 2, 2018) (dismissing case as "highly anticipatory").

of infringing processes and intended to file a new BPCIA lawsuit directed to the ARI product.[6]

8. The ARI Application disclosed that Amgen had [redacted] t Genentech invented and patented in U.S. Patent No. 9,493,744 ("Shiratori").[7] It is undisputed that the manufacturing process described in the ATO Application and approved by the FDA in September 2017 [redacted],[8] and so Shiratori was not on the list of potentially infringed patents that Genentech served pursuant to 42 U.S.C. § 262(*l*)(3) as part of the first BPCIA "patent dance" in 2017.

9. Genentech therefore served a new list of patents pursuant to § 262(*l*)(3)(A) that it reasonably believed could be infringed by the ARI [redacted]. The list included some but not all of the patents on Genentech's prior list, and added new patents like Shiratori. Under the BPCIA Amgen had sixty days to serve responsive contentions. On Day 58 Amgen announced it would not do so nor otherwise participate in the "patent dance." App. at A45. Although a biosimilar applicant may give (*l*)(8) notice any time after filing, *Sandoz II*, 137 S. Ct. at 1677-78, Amgen has never done so with respect to the Mvasi licensed under the ARI Application.

10. Following Amgen's refusal to participate in the "patent dance," Genentech received the Court's permission to file this litigation, Case No. 17-cv-1407-CFC, D.I. 318, and did so on March 29, 2019. In the interim, the FDA notified Amgen that "[w]e have completed our review of this supplemental biologics license application, as amended" and approved the ARI Application on December 11, 2018. App. at A113.

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[6] *See* App. at A61 at 122:15-17 ("So we've gotten that application. We are reviewing it. The [BPCIA] gives us a period of time."); *id.* at 122:18-24 (Genentech's counsel explaining that Amgen's new application would result in a third lawsuit between the parties).

[7] *See also* App. at A105-A112 ([redacted]); *id.* at A380-A381.

[8] *See, e.g.*, App. at A405 [redacted]

C. The Revised Labeling Application

11. Amgen not only changed its manufacturing site [redacted], it also changed its Mvasi label. The ATO Application the FDA approved in September 2017 proposed a label identical to the Avastin label with respect to the treatment of patients who develop hypertension. The "Warnings and Precautions" section offered the following guidance:

> Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend [MVASI] if not medically controlled. Discontinue [MVASI] for hypertensive crisis or hypertensive encephalopathy.

Id. at A65. The "Dose Modifications" section of the label then directed "[t]here are no recommended dose reductions," but providers should "[d]iscontinue [MVASI] for . . . [h]ypertensive crisis or hypertensive encephalopathy" and should "[t]emporarily suspend [MVASI] for . . . [s]evere hypertension not controlled with medical management." *Id.* at A68-69. The FDA approved this version of Amgen's label when it approved the ATO Application in September 2017. *See id.* at A3; *id.* at A8-A43 (approved label).

12. The Patent Office issued Fyfe on October 24, 2017. It claims, among other things, a method of treating cancer in a patient who "has a grade III hypertensive event resulting from the bevacizumab administration," "comprising administering to the patient an antihypertensive agent in an amount sufficient to manage the grade III hypertensive event while continuing to treat the patient with bevacizumab, the continued bevacizumab treatment being carried out without altering the dosage regimen." *Id.* at A558 at 53:8-16.

13. Because its approved label obviously induced physicians to infringe Fyfe, Amgen amended the label language in in an effort to mitigate that risk ("Revised Labeling Application"). Amgen tweaked the "Warnings and Precautions" language quoted above, substituting the language "if not" with the word "until":

> Hypertension: Monitor blood pressure and treat hypertension. Withhold ~~if not~~

> *until* medically controlled; resume once controlled. Discontinue for hypertensive crisis or hypertensive encephalopathy.

Id. at A116. It similarly edited the "Dose Modifications" section to direct that in cases of "severe" hypertension one should "[w]ithhold MVASI *until* controlled with medical management" and "resume once controlled" and also added a parenthetical that "severe" hypertension is hypertension "such as Grade 3 and above." *Id.* at A120.[9] The FDA approved the application in June 2019.

14. [redacted].

15. Though the FDA [redacted], *id.* at A150, A153, ultimately, it allowed Amgen's slight change to the "Warnings and Precautions" and "Dose Modifications" sections [redacted], *id.* at A223, A226. FDA approved the Revised Labeling Application with the other proposed changes on June 24, 2019 and licensed Amgen to market a version of Mvasi that is made at ARI and accompanied by the revised label. *Id.* at A218.

D. Amgen's Discovery Failures

16. Genentech has been trying to obtain deposition testimony about Amgen's launch plans and the Revised Labeling Application since April 2019.

[9] [redacted] the "temporarily suspend" language recited above was replaced with the term "withhold." App. at A116, A120. The substitution of the word "until" and the addition of language about "Grade 3" hypertension, however, depart from the Avastin label.

17. After weeks of prodding by Genentech, Amgen finally agreed to produce two regulatory witnesses (Narae Bae and Katherine Lew, [redacted]) for depositions on June 21 and 28. Amgen also agreed to produce witnesses on the proposed marketing of Mvasi (Molly Benson and Rob Jacobson) on June 14 and 19.

18. Then, just days before the Benson, Jacobson, and Bae depositions, Amgen unilaterally cancelled them. Several days later, it cancelled Ms. Lew's deposition (and the June 25 deposition of a former Amgen employee, Margaret Karow, [redacted]). Amgen justified its actions by citing the Court's privilege-waiver ruling, [redacted].

19. Genentech objected and demanded these depositions go forward or be promptly rescheduled. Amgen refused, citing not just the privilege waiver-ruling but also the company's policy to give all employees the week of July 4 off.

20. To date, Genentech has not received any deposition discovery regarding [redacted]. Amgen has not proposed new dates for the depositions of the witnesses listed above.

21. Amgen also has thwarted full discovery into its ARI manufacturing process. By forgoing the "patent dance" as to the ARI Application and moving to dismiss the Complaint asserting patents infringed there—including the Shiratori patent that was not and could not have been asserted against Amgen's ATO Application—Amgen has avoided producing discovery and serving the infringement or invalidity contentions that the BPCIA envisions the innovator company would have well-prior to any possible launch of a biosimilar product.

ARGUMENT

The Mvasi Amgen apparently plans to start marketing is different from the product the FDA licensed in September 2017 and Amgen referenced in the (*l*)(8) notice it served a month

later. The parties' dispute thus reduces to a single question of statutory interpretation: does Amgen's October 2017 notice satisfy the BPCIA's requirement with respect to a subsequent product made at a new location, [redacted] with a new label, and that required new FDA approvals before Amgen could sell it? The only answer consistent with the statutory language and orderly adjudication of patent disputes under the BPCIA is "no."

I. THE BPCIA REQUIRES 180-DAY NOTICE PRIOR TO MARKETING OF NEW PRODUCTS.

Approval of biological products is governed by 42 U.S.C. § 262. Subsection (a) specifies the substantial hurdles innovators face when they apply for approval of a new product. The BPCIA added subsection (k), specifying the lesser showing required for a "biosimilar" application, and subsection (*l*), establishing procedures for the orderly resolution of patent disputes. Subsection (*l*)(8)(A) requires a biosimilar, or "subsection (k) applicant," to "provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)."

[redacted]. App. at A513.[10] This Mvasi is a new product made by [redacted] accompanied by a new label, and the subject of separate applications, FDA reviews, and FDA approvals. It is therefore a distinct "product licensed under subsection (k)" requiring its own (*l*)(8) notice.

[10] *See* App. at A513, [redacted] *Id.* at column D, rows 2-5 [redacted]

A. The BPCIA's Plain Text Compels Notice for Each Product Licensed Under Subsection (k)

Amgen apparently contends that it has only one biological product "licensed under subsection (k)" and that the notice it served in October 2017 suffices for any and all versions of Mvasi for which it subsequently seeks FDA licensure. This cannot be correct.

1. When FDA approved Amgen's aBLA in September 2017, the resulting license authorized Amgen to manufacture drug substance only at Amgen Thousand Oaks, App. at A3, and to sell Mvasi only "for use as recommended in the enclosed agreed-upon labeling text," *id.* at A3, A8-A43 (enclosing approved labeling). That is the product Amgen described in its October 2017 notice, *id.* at 1, and was statutorily permitted to sell (subject to an injunction for infringement) beginning in April 2018. [redacted] could have been "licensed under subsection (k)" when Amgen gave (*l*)(8) notice in October 2017, or even 180 days later, because Amgen did not file its supplemental applications until later in 2018.

This is not just a matter of common sense. The BPCIA makes clear that a biological product "licensed under subsection (k)" is limited to particular manufacturing facilities and labeling. *See* 42 U.S.C. § 262(k)(2). Subsection (k)(2)(A) lists the information that must be submitted to FDA to obtain approval for a "biological product' under subsection (k). As pertinent here, the biosimilar applicant must specify the manufacturing location, 42 U.S.C. § 262(k)(2)(A)(i)(V), and "consent[] to the inspection of *the facility that is the subject of the application*," *id.* § 262(k)(3)(B) (emphasis added).[11] Subsection (k)(2)(A)(i)(III) requires the

[11] Recognizing this requirement for its ARI Application, Amgen permitted inspection of that facility [redacted]. App. at A411.

biosimilar applicant to identify the conditions of use of the drug—the label. These are requirements that define a biological product "licensed under subsection (k)." Consistent with FDA's guidance that "[d]ifferent manufacturing processes may alter a protein product in a way that could affect the safety or effectiveness of the product,"[12] Amgen was required to obtain approval before it was authorized to sell this distinct product made at a different manufacturing facility or under its new label, [13] and it did so pursuant to subsection (k). The product initially licensed under subsection (k) is not the same as the distinct product, separately "licensed under subsection (k)," that incorporates those changes.

2. The interplay between (*l*)(8) and other provisions of the BPCIA reinforces the conclusion. The statute does not authorize an innovator to bring suit or otherwise seek redress over an infringing biologic before an application for approval has been filed, and before that time, no Article III case or controversy exists. 42 U.S.C. § 262(*l*)(9); 35 U.S.C. § 271(e)(2)(C); *Sandoz, Inc. v. Amgen Inc*., 773 F. 3d 1274, 1279-82 (Fed. Cir. 2014) ("*Sandoz 2014*"). The corollary is that a biosimilar manufacturer may not serve effective (*l*)(8)(A) notice for a product the FDA has not even been asked to approve. 42 U.S.C. § 262(*l*)(1)(A), *id.* § 262(*l*)(8); *see Sandoz I*, 794 F.3d at 1358-59; *Sandoz II*, 137 S. Ct. at 1677. Any suggestion otherwise contradicts the BPCIA's definition of a "subsection (k) applicant"—the party that may serve notice—as "a person that *submits an application* under subsection (k)." 42 U.S.C. § 262(*l*)(1)(A) (emphasis added).

The BPCIA confirms that "[a]fter receiving the notice under subparagraph (A) and before

[12] App. at A568 (FDA Guidance for Industry).

[13] Indeed, FDA's approval letter for Amgen's Revised Labeling Application refers Amgen to its "supplemental biologics license application (sBLA) . . . *submitted under section 351(k)* of the Public Health Service Act for Mvasi (bevacizumab-awwb) injection." App. at A218 (emphasis added).

such date of the first commercial marketing of such biologic product, the reference product sponsor may seek a preliminary injunction." 42 U.S.C. § 262(*l*)(8)(B). Amgen's interpretation, permitting its 2017 notice to be effective for applications it subsequently filed in 2018, would render this right illusory. Even if courts *had* jurisdiction, only innovators with crystal balls could divine the contents of future applications and seek to enjoin marketing of an infringing product that does not yet exist. A product like the version of Mvasi Amgen plans to sell, one made by a [redacted] a different plant and to be marketed with a different label, all requiring additional FDA approval, cannot possibly be covered by an (*l*)(8) notice served nearly a year before the applications for its approval were put on file.

3. This interpretation finds further support in the use of different language in a related portion of the BPCIA. In subsection 262(k)(7), the BPCIA defines a period of regulatory exclusivity during which FDA will not approve any biosimilars. Having settled on twelve years, Congress took care to define when the twelve-year period starts, providing that FDA may not approve a subsection (k) application "until the date that is 12 years after the date on which the reference product was *first* licensed." 42 U.S.C. § 262(k)(7)(A) (emphasis added). Congress recognized that a licensed reference product frequently changes as a result of supplemental filings.[14] It therefore made clear that the twelve-year period "shall not apply to a license for or approval of . . . a supplement for the biological product that is the reference product." *Id.* § (k)(7)(C)(i). In other words, biological products can change as a result of supplemental

[14] Congress was acutely aware of the importance of manufacturing processes for biologic drugs and thus certainly considered that changes in manufacturing processes could result in supplemental filings. Congressional recognition of manufacturing's elevated importance for biologics is evidenced by the fact that process patents are explicitly integrated into the BPCIA, *see* 42 U.S.C. §§ 262(*l*)(2)(A), (*l*)(3)(A)(i), while such patents may not be listed in the "Orange Book" that controls Hatch-Waxman litigation over small-molecule drugs, 21 C.F.R. § 314.53(b)(1).

applications, and when it wished to do so, Congress knew how to exempt such changes from time periods in which certain activities may not occur.

"Where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion." *Russello v. United States*, 464 U.S. 16, 23 (1983) (quotation omitted). Here (*l*)(8)'s proscription against marketing for 180 days does not contain the exclusionary language included in (k)(7) to exempt biological products licensed via supplemental applications. To the contrary, "first" in subsection (*l*)(8) modifies "commercial marketing," not "biological product." Well aware that an applicant may be licensed under subsection (k) to make more than one biological product referencing an innovator's product, Congress required notice before the "first" marketing of each of them. The provision's reference to "*the* biological product" rather than "*a* biological product" reinforces this construction. The latter wording, were it enacted, would have allowed a single notice for multiple products requiring, as here, supplemental applications each requiring FDA approval.[15]

B. Amgen's Interpretation Eliminates the BPCIA's Mandated Opportunity to Obtain Pre-Marketing Relief.

Because the plain text of the BPCIA requires (*l*)(8) notice for each biological product "licensed under subsection (k)," the Court need not address the purpose behind this provision. *Sandoz II*, 137 S. Ct. at 1678. To the extent the Court concludes the text is in any way

[15] *See, e.g.*, *Am. Bus Ass'n v. Slater*, 231 F.3d 1, 4-5 (D.C. Cir. 2000) ("[I]t is a rule of law well established that the definite article 'the' particularizes the subject which it precedes. It is a word of limitation as opposed to the indefinite or generalizing force of 'a' or 'an.'" (quotation omitted)).

Not every supplemental application requires FDA approval. App. at A595 (FDA Draft Guidance for Industry). It is undisputed that Amgen's supplemental applications at issue did require FDA approval. *See* 21 C.F.R. § 601.12(b) (changes requiring prior approval); *id.* at § 601.12(f) (labeling changes); App. at A626 (FDA Draft Guidance recommending change in manufacturing location be reported in prior approval supplement).

ambiguous, the plain purpose of (*l*)(8) notice within Congress' "carefully calibrated scheme," *id.* at 1670, requires that notice be provided for each biological product licensed under subsection (k).

Often the problem with ascertaining Congressional purpose is that the usual sources produce disagreement, not consensus. Not so here. Congress' purpose in requiring (*l*)(8) notice was to "provide[] a defined statutory window during which the court and the parties can fairly assess the parties' rights prior to the launch of the biosimilar product." *Sandoz I*, 794 F.3d at 1358, *rev'd on other grounds, Sandoz II*, 137 S. Ct. 1664; *Apotex*, 827 F.3d at 1060. Requiring (*l*)(8) notice for each new product licensed under subsection (k) furthers that purpose; dispensing with it does not.

As illustrated by the facts outlined above, a supplemental biologics license application can change substantially how a product is made or how it is used. Where biologic products are concerned, "it is often said that the product is the process—that is, the biopharmaceutical is determined by the process by which it was produced."[16] FDA's guidance recognizes that "[d]ifferent manufacturing processes may alter a protein product in a way that could affect the safety or effectiveness of the product."[17] Amgen's ARI Application not only changed its manufacturing site, [redacted] in ways that implicated new Genentech patent rights. For example, Genentech's Shiratori patent claims a process that protects manufacturing sites from catastrophic viral contamination. Amgen [redacted]. Absent (*l*)(8) notice of intent to market a product made via Amgen's ARI [redacted], Genentech has no opportunity for the orderly adjudication of its rights, such as Shiratori,

[16] App. at A632 (Ivo Abraham et al., *Biosimilars in 3D: Definition, Development and Differentiation* et al., *Biosimilars in 3D: Definition, Development and Differentiation,* 4(4) Bioengineered 203, 204 (2013)).

[17] App. at A568.

that the BPCIA is designed to guarantee. *See Apotex*, 827 F.3d at 1065 (noting that unless a patentee can enforce its (*l*)(8) notice right via injunction, "[t]he reference product sponsor will have to race to court for immediate relief to avoid irreparable harm").

Similarly, Genentech has a patent concerning the use of Avastin in treating certain ovarian cancers, U.S. Patent No. 8,778,340 ("Dupont"). Because Amgen has omitted deliberately from its label the ovarian cancer indications and other text relevant to Dupont, Genentech cannot assert Dupont in any pending case. [redacted] prior to the expiry of Dupont, Genentech will assert its patent. Properly interpreted, subsection (*l*)(8) should require Amgen to provide 180-day notice before it begins marketing with a label that includes the ovarian cancer uses, and that time period will be critical to adjudicating any patent dispute in an orderly manner. But if (*l*)(8) is interpreted as Amgen now urges, the stage will be set for exactly the type of chaotic temporary restraining order proceedings that Congress sought to avoid. *Apotex*, 827 F.3d at 1065.

Pronouncing such a rule would not just undermine orderly proceedings but also incentivize gamesmanship. Subsection (k) applicants would be encouraged to apply first for a license to market whatever version of their product implicates the fewest patents, serve (*l*)(8) notice while that application is pending, and then file supplemental applications to obtain approval for products that infringe more patents. This strategy would deprive the reference product sponsor of the BPCIA's guarantee of an orderly patent adjudication process and, possibly, conceal the infringement entirely if the applicant never turns over its supplemental applications.[18] Even a patentee who anticipated that something like this was occurring could not

[18] Amgen's pending motion to dismiss the Complaint in this case disputes any obligation under the BPCIA to provide the innovator company with supplemental applications. In Amgen's view,

protect itself by seeking a declaratory judgment on its other patents because such a lawsuit would not be ripe until the supplemental applications were filed. *See Sandoz 2014*, 773 F.3d at 1279 (no jurisdiction to adjudicate dispute regarding patent infringement and validity regarding an application that had not yet been filed).

Were the Court to adopt Amgen's interpretation of (*l*)(8), "the parties and the court, in dealing with a request for a temporary restraining order or a preliminary injunction, will engage in precisely the hurried motion practice that (8)(A) is designed to replace by ensuring a defined amount of time for pre-launch litigation." *Apotex*, 827 F.3d at 1065. This would not serve the BPCIA's goal of orderly and timely adjudication of patent rights. Under the only analogous patent adjudication system—the Hatch-Waxman Act—FDA prohibits generic drug manufacturers from employing such tactics, instead requiring an "appropriate patent certification or statement with a 505(b)(2) or ANDA supplement,"[19] and prompt notice to the patent owner, 21 C.F.R. § 314.95(d). Confirming that subsection (k) applicants must provide (*l*)(8) notices for each product licensed under subsection (k) will enforce the statutory text as written and ensure the same result.

II. THE BPCIA'S NOTICE PROVISION IS ENFORCEABLE.

Although compliance with some BPCIA provisions is optional,[20] providing notice under

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an innovator receives supplemental applications only if there is pending litigation over a prior application and an outstanding Rule 34 request calling for their production. D.I. 16 at 6.

[19] App. at A636. FDA is well aware of the chicanery a contrary policy could encourage; in 2016, it declined to adopt a proposed rule limiting the supplemental ANDAs that required patent certifications due to concern that "an ANDA applicant could circumvent the patent certification requirements by seeking approval of a noninfringing product that the applicant does not intend to market followed by a supplement for a modified form of the active ingredient or a different formulation of the drug product that the applicant intends to market." *Id.*

[20] Section 262(*l*)(2)(A) is not enforceable by federal injunction. *Sandoz II*, 137 S. Ct. at 1674.

§ 262(*l*)(8)(A) is not. *See Sandoz II*, 137 S. Ct. at 1677; *see also Apotex*, 827 F.3d at 1066. Nor is there any question about the remedy for non-compliance: a court order requiring that the applicant provide notice and wait 180 days before launching its product.

This is best illustrated by the proceedings in Amgen's case against Sandoz over the latter's plans to market a biosimilar of Neupogen. Sandoz served two notices-of-commercial-marketing, one before receiving FDA approval and one immediately afterward. The Federal Circuit held the first was inoperative because it was served prior to approval, and then enjoined commercial marketing of Sandoz's biosimilar until 180 days after Sandoz served the second. *Sandoz I*, 794 F.3d at 1357-58, 1360. The Supreme Court overruled the holding as to the first notice, construing the BPCIA as permitting notice prior to approval, *Sandoz II*, 137 S. Ct. at 1677, but had no occasion to review and left untouched the holding that compliance can and should be enforced by injunction against marketing until 180 days have elapsed following proper notice.

The Federal Circuit did not rely on the traditional four-factor analysis before enforcing compliance, App. at A559-A560 (*Amgen, Inc. v. Sandoz, Inc.*, 2015-1499, D.I. 105 (Fed. Cir. May 5, 2015)); *Sandoz I*, 794 F.3d at 1358-60, nor did it need to do so. Where the operative statute provides a "clear and valid legislative command," and "in so many words, or by a necessary and inescapable inference, restricts the court's jurisdiction in equity," orders enforcing compliance must issue. *Weinberger v. Romero–Barcelo*, 456 U.S. 305, 313 (1982) (quoting *Porter v. Warner Holding Co.*, 328 U.S. 395, 398, (1946)). Here, the command is clear—the "applicant shall provide notice" 180 days before starting sales—and there may be no other

remedy for non-compliance if it is not enjoined. *Apotex*, 827 F.3d at 1063-64.[21]

Apotex reinforces the propriety of enforcing (*l*)(8) here. 827 F.3d 1052. Affirming an injunction against marketing without (*l*)(8) notice, the Federal Circuit had no occasion to consider whether Amgen would suffer irreparable harm absent the injunction because the parties stipulated that it would. 827 F.3d at 1060. Having sought and obtained orders enforcing (*l*)(8) in two separate litigations (*Apotex* and *Sandoz I-II*), it is difficult to credit any suggestion by Amgen in this case that it is free to launch without serving (*l*)(8) notice unless Genentech shows that that irreparable harm would follow.

In any event there is, if necessary, abundant evidence of irreparable harm should Amgen start competing head-to-head with Avastin before the law allows. Avastin is one of Genentech's most important products, with U.S. sales alone of nearly $3 billion, and a critical source of funds for the company's operations, including its research and development activities. As explained in the attached declaration of Harvard economist and physician Anupam B. Jena ("Jena Decl."), an unlawful launch of Mvasi would inflict, *inter alia*, price-erosion, loss of market share, and damage to Genentech's good-will, Jena Decl. ¶¶ 35-57, none of which can be repaired even if the BPCIA authorized damages for an (*l*)(8) violation, and all of which the Federal Circuit and courts in this district have cited to justify an injunction against sales of an unlawful competing product.[22] No court has yet addressed whether violations of (*l*)(8) are redressable by damages at

[21] In analogous circumstances under the Hatch-Waxman Act, the court directly enforces Congress' statutory commands when it modifies the length of the 30-month stay. *See, e.g.*, *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 2008 WL 4809963 (S.D. Ind. Oct. 29, 2008) (granting "Motion for Extension of Statutory Stay"), *aff'd* 557 F.3d 1346 (Fed. Cir. 2009).

[22] *See, e.g.*, *Celsis in Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 930-31 (Fed. Cir. 2012); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382-83 (Fed. Cir. 2006); *Research Found. of State Univ. of New York v. Mylan Pharm. Inc.*, 723 F. Supp. 2d 638, 658-60 (D. Del. 2010). Amgen has made the same arguments as an innovator seeking to enjoin a biosimilar manufacturer who violated the BPCIA. Jena Decl. ¶ 68.

trial. If the answer is "no," the unavailability of money damages makes this harm *per se* irreparable. *See, e.g., Metalcraft of Mayville, Inc. v. The Toro Co.*, 848 F.3d 1358, 1368 (Fed. Cir. 2017).

For the same reasons, the balance of hardships favors injunctive relief. An improper launch by Amgen would devastate Genentech's Avastin market and be nearly impossible to redress either on appeal or at trial. Amgen has acted strategically to sequence its applications in a manner designed to skirt FDA's biosimilarity requirements and obstruct Genentech's ability to assert its patent rights, and it has compounded the problem with its behavior during discovery. It can wait the time prescribed by the BPCIA until this Court, and the court of appeals, assesses the consequences of its conduct.

CONCLUSION

For the reasons set forth above, the Court should enter an order prohibiting Amgen from selling Mvasi manufactured at ARI or with the label approved via its supplemental Application until Amgen complies with the notice requirements set forth in 42 U.S.C. § 262(*l*)(8)(A) and the 180-day period elapses.

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Respectfully submitted,

OF COUNSEL:

Paul B. Gaffney
David I. Berl
Thomas S. Fletcher
Kyle E. Thomason
Teagan J. Gregory
Charles L. McCloud
Kathryn S. Kayali
Jonathan S. Sidhu

WILLIAMS & CONNOLLY LLP
725 Twelfth St. NW
Washington, DC 20005
(202) 434-5000

Attorneys for Plaintiff Genentech, Inc.

Daralyn J. Durie
Adam R. Brausa
Eric C. Wiener
Eneda Hoxha
DURIE TANGRI
271 Leidesdorff Street
San Francisco, CA 94111

Attorneys for Plaintiffs Genentech, Inc. and City of Hope

MCCARTER & ENGLISH, LLP

/s/ Daniel M. Silver
Michael P. Kelly (# 2295)
Daniel M. Silver (# 4758)
Renaissance Centre
405 N. King Street, 8th Floor
Wilmington, Delaware 19801
Tel.: (302) 984-6300
Fax: (302) 984-6399
mkelly@mccarter.com
dsilver@mccarter.com

Attorneys for Plaintiffs Genentech, Inc. and City of Hope

CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that true and correct copies of the foregoing document were caused to be served on July 10, 2019 on the following counsel in the manner indicated:

VIA EMAIL:

Melanie K. Sharp
James L. Higgins
YOUNG CONAWAY STARGATT & TAYLOR, LLP
1000 North King Street
Wilmington, DE 19801
(302) 571-6600
msharp@ycst.com
jhiggins@ycst.com

Amir A. Naini
Siegmund Gutman
Michelle M. Ovanesian
PROSKAUER LLP
2029 Century Park East, Suite 2400
Los Angeles, CA 90067-3010
(310) 284-5641
anaini@proskauer.com
sgutman@proskauer.com
movanesian@proskauer.com

Attorneys for Immunex Rhode Island Corp. and Amgen Inc.

Dated: July 10, 2019

/s/ Daniel M. Silver
Daniel M. Silver (#4758)