Appeal Nos. 2018-1551, 2018-1552

United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING, LIMITED,

Plaintiffs-Appellants,

– v. –

SANDOZ INC., SANDOZ INTERNATIONAL GMBH, SANDOZ GMBH,

Defendants-Appellees.

Appeal from the United States District Court for the Northern District of California in No. 3:14-cv-04741-RS, Judge Richard Seeborg

AMGEN INC., AMGEN MANUFACTURING, LIMITED,

Plaintiffs-Appellants,

– v. –

SANDOZ INC., SANDOZ INTERNATIONAL GMBH, SANDOZ GMBH, LEK PHARMACEUTICALS, D.D.,

Defendants-Appellees.

Appeal from the United States District Court for the Northern District of California in No. 3:16-cv-02581-RS, Judge Richard Seeborg

NON-CONFIDENTIAL REPLY BRIEF FOR PLAINTIFFS-APPELLANTS AMGEN INC. AND AMGEN MANUFACTURING, LIMITED

(For Appearances See Inside Cover)

July 20, 2018

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CERTIFICATE OF INTEREST

1. The full name of every party represented by me is:

   AMGEN INC. and AMGEN MANUFACTURING, LIMITED

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

   AMGEN INC. and AMGEN MANUFACTURING, LIMITED

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party represented by me are:

   AMGEN INC.

4. The names of all law firms and the partners and associates that appeared for the party now represented by me in the trial court or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are

   SIDLEY AUSTIN LLP: Vernon M. Winters, Sue Wang, and Alexander David Baxter who is no longer with the firm

   PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP: Michael T. Wu and Ana J. Friedman who are each no longer with the firm

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47.4(a)(5) and 47.5(b).

   None

Date: July 20, 2018

/s/ Nicholas Groombridge
Nicholas Groombridge

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CONFIDENTIAL MATERIAL OMITTED

Pursuant to Federal Circuit Rule 28(d)(2)(B), Plaintiffs-Appellants prepared this public version of their brief which redacts certain information designated confidential pursuant to the district court's Protective Orders, entered on February 9, 2015 and January 17, 2017. Specifically, the material omitted on pages 17, 21, and 22 contains references to Defendants-Appellees' accused processes, and was designated confidential by Defendants-Appellees during discovery under the terms of the Protective Orders. Prior to filing the public version of Plaintiffs-Appellants' Blue Brief, counsel for Plaintiffs-Appellants conferred with counsel for Defendants-Appellees, and Defendants-Appellees confirmed that they continue to consider the omitted material to be confidential. Additionally, Defendants-Appellees omitted the same material from their Red Brief as "highly confidential, sensitive business information concerning the details of defendants-appellees' accused processes."

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INTRODUCTION

The '878 Patent. The district court erred in changing its claim construction at summary judgment to impose two additional requirements: first, that there must be a temporal break between washing and eluting; and second, that washing and eluting must be accomplished by applying compositionally different solutions. Notably missing from Sandoz's Red Brief is any argument that these limitations are expressly present in the district court's original construction. (Red Br. at 32-33.) And, the claim construction that applies in this action is that given by the district court, and not the arguments made by Sandoz in its briefs.

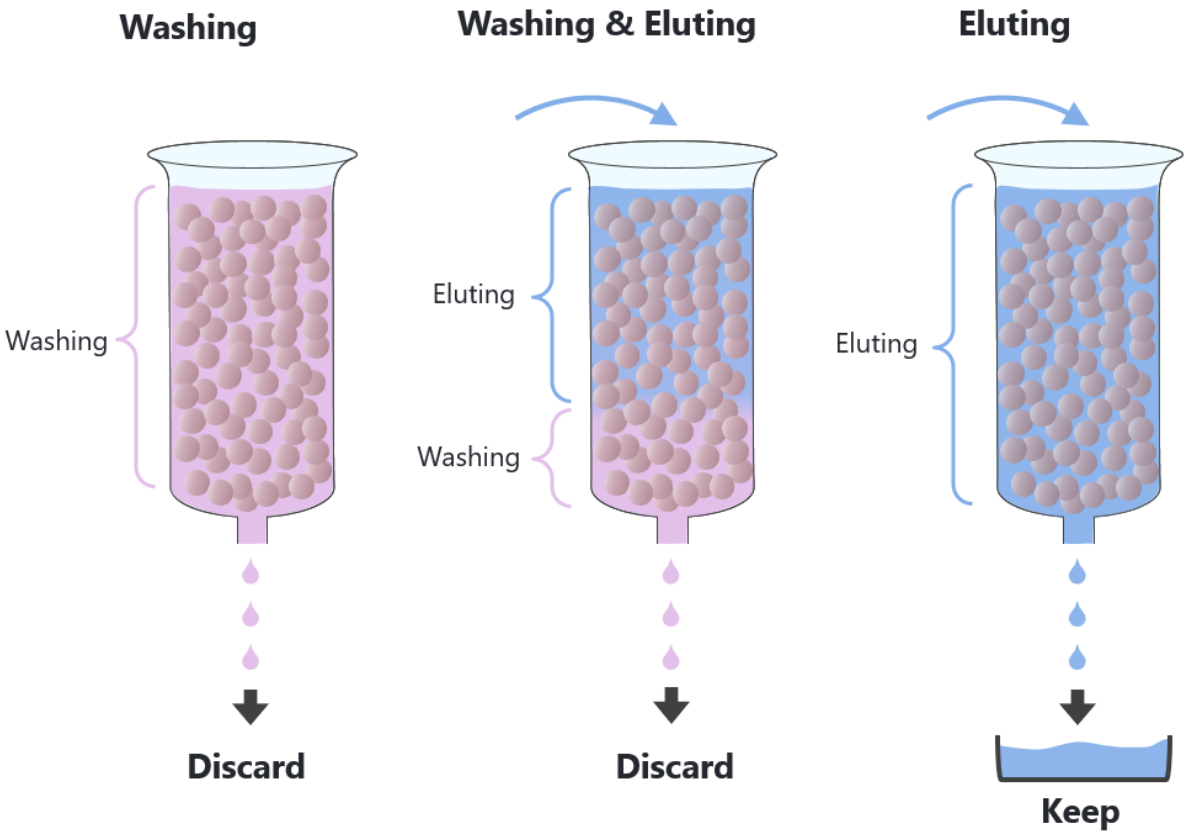
Following the Claim Construction Order, Amgen's expert faithfully applied what is stated in the Claim Construction Order to reach an opinion that there is infringement. (Blue Br. at 46-51; Appx4920-4951.) Sandoz has no substantive response to the Amgen expert testimony. Instead, Sandoz raises procedural arguments—principally waiver—and the suggestion that the opinions of Amgen's expert can be swept aside as merely speculative and conclusory. Nothing could be further from the truth: Amgen's expert, Dr. Willson, provided a lengthy analysis in painstaking detail of what happens inside the chromatography column used in the Sandoz purification process. This analysis consists of more than 120 paragraphs of detailed explanation, replete with calculations and figures. (Appx4914-4949, ¶¶ 118-230.) Dr. Willson describes how, in the Sandoz process,

filgrastim binds to the separation matrix (Appx4926-4936, ¶¶ 148-179); impurities are washed away and discarded (Appx4936-4944, ¶¶ 180-210); and then the filgrastim is eluted off the column (Appx4944-4948, ¶¶ 211-228). If this testimony is credited, as it should be on summary judgment, the decision below must be reversed.

With respect to the temporal break limitation, the key question is not whether washing must precede eluting—Dr. Willson showed that in the Sandoz process it does—but whether ***all*** washing must be completed before eluting begins ***anywhere*** on the column.

The sole rationale advanced by Sandoz to add a temporal break limitation to the claim language is that for there to be purification, it is logically necessary for eluting to occur after washing to prevent any ***comingling*** of the protein from impurities. (Red Br. at 43.) This rationale—avoiding any comingling—does not justify imposing a limitation that all washing be complete throughout the entire column before eluting begins at any point in the column. Under the district court's original construction, there is no comingling of the initial impurities washed away at the bottom of the column before the protein elutes, as Amgen has demonstrated. As shown in the diagram below, when eluting begins at the top of the column, the "washed" impurities at the bottom of the column are discarded and thus never

comingled with the eluted protein. (Appx4936-4949.) The district court erred in not crediting this evidence.



Similarly, there is no basis for the second requirement added by the district court, that washing and eluting must be carried out by applying compositionally different solutions to the column. The language of claim 7 simply requires "washing" and "eluting"—there is absolutely nothing in the claim limiting how these functions are to be accomplished. Dr. Willson showed how there are different solutions that cause washing and eluting in the Sandoz process, and the difference arises because of changes that occur as the refold solution flows through the column. (*See* Appx4937-4938, Appx4945-4948.) That these different

solutions are formed *in situ* rather than being pre-mixed outside the column is immaterial to the question of whether washing occurs followed by elution.

Nor is there any merit to Sandoz's waiver argument. Neither of the two added claim requirements was mentioned during the original claim construction proceedings: they were first presented when Sandoz moved for summary judgment. (*See* Appx3751.) At that point, Amgen responded by laying out its position and providing the testimony of Dr. Willson. (*See* Appx4859-4872.) This is not a situation in which Amgen is attempting to raise on appeal an argument never presented below. And if Sandoz is now suggesting that at claim construction Amgen should have responded to a non-infringement argument that had not yet even been made, there is simply no authority for such a proposition.

The '427 Patent. The district court erred in holding that "disease treating-effective amount" requires the chemotherapeutic agent to be used—indeed, "prescribed"—***for*** disease treatment; and further erred by failing to construe the term "disease treating" as a modifier for "amount." The claims do not impose a functional requirement that the chemotherapeutic-agent amount must be prescribed to treat a disease, as the intrinsic evidence confirms. It is Sandoz, and not Amgen, that is attempting to "rewrite unambiguous patent claim language." (Red Br. at 64.) Sandoz, like the district court, incorrectly focuses only on the adjective describing the chemotherapeutic agent's ***amount*** to determine the

chemotherapeutic agent's ***purpose*** in the claimed method. The "disease treating" adjective simply modifies the "effective amount," and does not define or impose a requirement as to purpose. The ***purpose*** of the chemotherapeutic agent is exclusively and repeatedly identified in the specification as the enhancement of stem cell mobilization. (Blue Br. at 64-65 (citing and quoting, *e.g.*, '427 Patent, abstract, 1:5-9, 1:11-18, 1:62-65, 1:66-2:4, 3:7-17).)

Accordingly, Amgen respectfully requests that the district court's judgments be reversed, vacated, and/or remanded.

ARGUMENT

I. The District Court Erred in Construing Claim 7 of the '878 Patent to Require a Temporal Break Between Washing and Eluting, and That Compositionally Different Solutions Be Added for Washing and Eluting

A. The District Court Revised its Claim Construction in its Summary Judgment Order

1. The Claim Construction Order Requires Only That Eluting "Occur After" Washing

The Claim Construction Order held in relevant part that "[t]his [eluting] step must occur after the step of 'washing the separation matrix.'" (Appx45.) The Summary Judgment Order then added two limitations to the earlier claim construction: (1) a requirement of a temporal break between washing and eluting such that all washing is completed in the column before eluting begins, *i.e.*, a "pause in the pumping of the refold solution" (Appx10), and (2) a requirement that

there be compositionally distinct washing and eluting solutions added to the column, *i.e.*, "Sandoz's argument that the washing and eluting solutions must be distinct is equally compelling and provides an additional ground on which to conclude that Sandoz's process does not literally infringe the claimed method" (Appx11).

Sandoz argues that the Claim Construction Order "made clear that the steps not only had to occur in a particular order, ***but also that the washing must be completed before the eluting begins***." (Red Br. at 32 (emphasis added).) But nowhere do those emphasized words appear in the Claim Construction Order. Nor do the claims themselves impose such a requirement. Sandoz argues that the district court's Claim Construction Order nevertheless requires a temporal break between washing and eluting and the addition of compositionally distinct washing and eluting solutions because Sandoz explained in its responsive claim construction brief that its construction includes the "separateness and order of steps." (Red Br. at 31 (quoting Appx2667).) This is a red herring. On the same page of its responsive claim construction brief in which Sandoz made that assertion, Sandoz made clear in the chart that its proposed construction was simply that "This [eluting] step must occur after the step of 'washing the separation matrix.'" (Appx2667.) Notably, this chart did not indicate that (1) the two steps

must be separated by a temporal break between washing and eluting, or (2) the added washing and eluting solutions must be compositionally distinct.

Further, the district court's claim construction is contained in the words of the construction itself—it does not also include whatever arguments Sandoz made in support of its proposed construction. Had the district court intended to impose additional limitations into this construction (or Sandoz intended to argue that its proposal encompassed additional limitations), then Amgen respectfully submits that those limitations should have been spelled out in the construction, and not implicitly read into the patent claims at the summary-judgment stage.

Sandoz argues that the district court did not further construe the claim terms during summary judgment because the "summary judgment order says so," and this statement should be given deference. (Red Br. at 33.) This elevates form over substance. A district court's own statement that it did not modify its claim construction is not controlling, and Sandoz does not cite any authority holding otherwise. *Avila* merely stated that the district court is in the best position to explain the scope of its own order extending a discovery deadline. 633 F.3d 828, 835-36 (9th Cir. 2011). And *Amado* deferred to a district court in interpreting the word "appeal" to include petitions for certiorari in an order staying an injunction. 517 F.3d 1353, 1358 (Fed. Cir. 2008).

2. Washing Does Not Need to Be Completed Before Eluting Begins in the Column, and Different Solutions for Washing and Eluting Do Not Need to Be Added to the Column, to Avoid Comingling

Sandoz attempts to read in a temporal break limitation ***by implication*** on the ground that completion of washing must occur before eluting to avoid any comingling of the protein captured by the separation matrix with the contaminants to be washed away. (Red. Br. at 32 (quoting Appx46).) This fails. Under the district court's original construction and as demonstrated by Amgen's infringement evidence, eluting of filgrastim from Sandoz's column occurs after impurities initially at the bottom of Sandoz's column are washed off the column. (*See* Blue Br. at 20-21 (citing, *e.g.*, Appx4888, Appx4898).) There is no comingling of these washed-away impurities with the eluted protein because they are discarded before Sandoz begins to collect fractions containing filgrastim. (*See id.*)

In Sandoz's process, although there is no temporal break between the addition of the washing and eluting solution, there is an increasing salt concentration over time in the column that causes the protein to elute and exit the Sandoz column. (*See* Blue Br. at 49-51 (citing, *e.g.*, Appx4946-4947).) During this gradual change in the column, washing continues until the salt concentration changes such that elution occurs; the impurities washed away at the bottom of the column are discarded rather than comingling with the subsequently eluted and collected filgrastim. (*Id.*) In this circumstance, eluting follows washing in the

column ***without*** comingling of the eluted protein with the impurities that have been washed away and discarded.

Similarly, the fact that Sandoz does not apply different solutions for washing and eluting does not mean that there is comingling of the eluted protein and the impurities that have been washed away and discarded. Amgen presented these facts to the district court (Appx4866-4872), submitting evidence that "at any given location in the column where filgrastim binds, the washing step and the eluting step are occurring sequentially consistent with claim 7" (Appx11). The district court erred in not crediting such facts, and instead granting summary judgment of non-infringement by further construing the claims to require completion of all washing before any eluting and requiring that the solutions added to column for washing and eluting be compositionally distinct. (Appx10-11.)

Further, Sandoz does not dispute that the claimed process covers partial purification—*i.e.*, where some impurities have been removed but others still comingle with the protein that has been collected. '878 Patent, 6:64-7:3. And Sandoz does not dispute that the district court's Summary Judgment Order misreads claim 7 to require complete purification—a requirement not found in the Claim Construction Order. (Blue Br. at 47; Appx13.)

B. Amgen Has Not Waived its Appeal, Even Assuming That the Original Claim Construction Order Imposed the Additional Limitations the Summary Judgment Order Required

Even assuming that the district court did ***not*** change its claim construction as Sandoz argues, Amgen has plainly not waived its challenge to the district court's construction in its Claim Construction Order. Indeed, Amgen's Notices of Appeal expressly appealed from the Claim Construction Order which is an underlying decision to the ultimate summary judgment of non-infringement. (Appx87, Appx91.)

Sandoz, however, asserts waiver on the ground that Amgen did not "contest these issues during claim construction." (Red Br. at 34.) This is incorrect. At the Claim Construction Hearing, the parties focused on whether "this [eluting] step must occur after the step of washing the separation matrix." (Appx3524-3530.) Sandoz did not propose there that the construction must include a requirement that there be a temporal break between washing and eluting, or that the washing and eluting solutions applied to the column must be compositionally distinct.

Further, Amgen made clear that adopting this construction could be material but not resolve the parties dispute for example because:

> if there is a single step -- and this is fairly common in this -- where a fluid is run through the column and it employs was [sic, what] is called a gradient where some characteristic like pH is increased as the fluid runs through. And the first part of that is effecting a washing step, and then once it passes a certain point of ph [sic], it is now

> effecting an eluting step. Is that two steps or one? Are we going to get in a fight over ***after***?

(Appx3526-3527.) Now, the parties have a factual dispute about whether the use of what in effect is gradient elution in Sandoz's process means eluting comes ***after*** the washing step. There is no waiver in these circumstances.

The cases Sandoz cites are inapposite. (Red Br. at 34.) *Regents of University of Minnesota v. AGA Medical Corporation* addressed whether the patentee's "interpretation of the claim limitation [was] inconsistent with the district court's construction" where the patentee did not object to the constructions during the *Markman* proceedings or summary judgment proceedings. 717 F.3d 929, 946 (Fed. Cir. 2013). *LizardTech, Incorporated v. Earth Resource Mapping, Incorporated* involved a patentee that agreed to a district court's claim construction during the *Markman* phase, and objected after the construction resulted in an adverse ruling on summary judgment. 424 F.3d 1336, 1341 (Fed. Cir. 2005). That is not the case here, where the district court imposed additional limitations at the summary-judgment stage that were not present in the Claim Construction Order.

Sandoz incorrectly argues Amgen had the opportunity to present infringement arguments under the narrower modified construction used by the district court in its summary judgment opinion. (Red Br. at 37.) Amgen cannot be faulted for not challenging—or found to have waived its objection to—a claim construction that was never proposed by Sandoz or adopted by the district court

during the claim construction proceedings. Further, Amgen vigorously objected to Sandoz's interpretation of the district court's claim constructions (requiring the addition of two different solutions for washing and eluting and that washing be completed before eluting) during summary judgment proceedings. (*See, e.g.*, Appx7024-7025, Appx4859-4864.)

C. The District Court Erred in Its Construction

Sandoz argues that the district court's construction in its Summary Judgment Order is nevertheless correct. (Red Br. at 42-51.) Sandoz's arguments fail.

First, Sandoz incorrectly argues that *Mformation Technologies, Incorporated v. Research in Motion Limited* and *Mantech Environmental Corporation v. Hudson Environmental Services, Incorporated* compel importing a temporal break requirement into the claims here. (Red Br. at 31, 42-44.) In each of the disputed claims in those cases, the previous step had to be completed because the following step depended on it. *Mformation* held that the claimed step of "establishing a connection between the wireless device and the server" needed to be completed before transmission of mailbox information from the server to the wireless device. 764 F.3d 1392, 1399 (Fed. Cir. 2014). Similarly, *Mantech* held that the claimed steps had to be sequential based on the claim language. 152 F.3d 1368, 1375-76 (Fed. Cir. 1998). That is not the case here: the claimed washing does not have to be completed throughout the column before elution can occur, and

elution of protein begins after impurities have been washed off the column and discarded.

Sandoz argues that Amgen's Blue Brief contains only a "bald[ ] assert[ion]" that the washing and eluting steps are not separate and sequential. (Red Br. at 45.) This is incorrect. As Amgen stated in its Blue Brief, the claims and specification both support Amgen's position because they do not impose requirements for a temporal break between washing and eluting or that different solutions be added to the column for washing and eluting. (Blue Br. at 40-42.) Contrary to Sandoz's argument, the specification teaches that "protein of interest associates with the matrix in the presence of the components of refold buffer, impurities are washed away and the protein is eluted." '878 Patent, 4:52-55. Nothing in the patent requires that one step be completed throughout the entire column before the next step begins.

Second, the district court erred in adopting a claim construction that requires the addition of different solutions to effect washing and eluting. According to the district court and Sandoz, the specification says that "the wash buffer is 'chosen to optimize the chromatography conditions, preserve protein binding, and to retain the desired characteristic of the protein of interest.'" (Red Br. at 46-47, 47 n.11.) This misreads the patent. The patent actually states that "[t]he pH range is chosen to optimize chromatography conditions, preserve protein binding, and to retain the

desired characteristics of the protein." '878 Patent at 15:55-57. In other words, the wash buffer must be of a pH that, among other things, preserves protein binding. The patent does not teach that the wash buffer itself must optimize protein binding, nor does the district court's original claim construction require so. As Amgen explained in both its opposition to Sandoz's motion for summary judgment and in its Blue Brief, a single solution being added to the column, namely Sandoz's refold solution, can act to first wash away impurities and then elute the protein as the conditions in the column change. (Blue Br. at 45-50; Appx4867-4872.) Additionally, Sandoz cannot import a limitation for compositionally distinct solutions based on the examples of the specification, which use distinct solutions. Nothing in the claims so limits the invention.

Sandoz says that Amgen is reversing its position on what solution is required for washing and eluting (Red Br. at 48), and also that Amgen believes the washing and eluting solution "can be almost anything." (*Id.* at 49-50.) This is a red herring. Amgen has consistently argued that washing and eluting are accomplished using solutions that are defined by their function (to wash or elute, respectively). This is confirmed by the claims and specification which define washing and eluting as functional steps. (*See* Blue Br. at 41-42.) Nothing in the claims requires the addition of a solution, let alone a specific solution, for washing and the addition of a different solution for eluting. Nor does the Claim

Construction Order impose such limitations on the claims. (Appx44-47.) Sandoz concedes that the district court's claim construction "does not limit the washing and eluting solutions to any particular solutions; it requires each solution to meet the requirements of its respective step—one preserving the binding, the other reversing the binding." (Red Br. at 49.) This is entirely true, and Sandoz's assertions otherwise fail. (*Id.* at 49.) Amgen and its expert Dr. Willson set forth in detail how Sandoz's process meets the claimed limitations as discussed below and in the Blue Brief at 45-51. Sandoz ignores these facts as did the district court.

In addition, Sandoz misreads Example 3 as teaching three, separate, sequential steps using different solutions. (Red Br. at 45-46, 50-51.) Example 3 describes washing and gradient elution, which begins using the same solution, namely 30mM MES; pH 6.0. Sandoz concedes the elution solution begins with no salt, thus making it the same as the wash solution, and then "the salt concentration is gradually increased." (*Id.* at 50.) Thus, the patent expressly teaches that elution can begin with a solution that is identical to the wash solution. (*Id.* at 46.) Sandoz then says that "entirely missing from Example 3 is any indication that these steps occurred contemporaneously." (*Id.*) The question is not whether these steps occurred at the same time at the same point in the column; rather, in Example 3 washing and eluting can occur at the same time at different locations of the column due to changing conditions in the column from the gradient. (Blue Br. at 48.)

Further, the differences between Example 3 and the claimed invention are unrelated to washing or eluting, which Sandoz also ignores. (Red Br. at 45 (citing Appx3881-3882, Appx6399-6400).)

II. The District Court Erred as a Matter of Law in Granting Summary Judgment that Sandoz Does Not Infringe Claim 7 of the '878 Patent

A. Under the Original Claim Construction, Ample Evidence of Literal Infringement Was Provided

Amgen submitted ample factual evidence that Sandoz's process includes washing and eluting—occurring in that order—which literally satisfies the claims as construed in the Claim Construction Order. (Blue Br. at 16-26, 45-51.) Specifically, Amgen's expert Dr. Willson provided extensive testimony that the conditions in Sandoz's column change such that compositionally distinct solutions form *in situ* in the column. (Appx4893-4894, Appx4937-4938.) The testimony of Amgen's expert must be credited at the summary-judgment stage, and not ignored as the district court erroneously did here.

Sandoz argues that Dr. Willson's testimony is not material because "Sandoz's process involves only one step and one solution: the continuous application of the refold solution." (Red Br. at 35-36.) This, however, does not resolve the question of whether the Sandoz process meets the originally construed claims that the eluting step occurs after the washing step. As Dr. Willson made clear, this limitation is met in the Sandoz process. Sandoz also misstates

Dr. Willson's testimony when it claims that he "admitted that Sandoz's process contains no separate and sequential washing and eluting steps." (*Id.* at 36.) In the pages cited by Sandoz for this point, Dr. Willson says:

- "[A] lot happens along the length of that column." (Appx3897.)
- The wash solution and elution solution "don't coexist at any place in the column." (Appx3927-3928.)
- Both a washing solution and an eluting solution "are generated sequentially along the length of the column." (Appx3928.)
- ". . . [F]ilgrastim binds to the [redacted] resin for a period of time while other materials in [the refold solution] separate from the bound filgrastim and are washed off the column in advance of the first filgrastim molecules to elute." (Appx5258.)
- ". . . [A]s Sandoz continues to apply the [refold solution] to the [redacted] column, after it has served to wash the matrix (as construed by the Court and discussed above), the conditions on the [redacted] column continue to change . . . such that the binding of filgrastim is reversed . . . ." (Appx5268 (footnote omitted).)

Thus, based on Dr. Willson's testimony, Amgen has established that Sandoz washes by "adding a solution to the separation matrix to remove materials in the refold solution while preserving binding of the protein to be purified" (Appx44-45) and, after washing, elutes by "applying a solution that reverses the binding of the purified protein to the separation matrix" (Appx46).

B. Under the District Court's Summary-Judgment Construction, There Is Evidence Raising a Genuine Issue of Material Fact of Sandoz's Infringement Under the Doctrine of Equivalents

Sandoz argues that "Amgen offered no evidence showing that Sandoz's process functions in substantially the same way as the washing and eluting limitations." (Red Br. at 38.) This is incorrect because it ignores the detailed testimony of Dr. Willson which is based on Sandoz's own documents and his extensive analysis of those materials—not speculative or conclusory as Sandoz asserts. (Appx4937-4949.) Dr. Willson explained that the application of the refold solution (having a higher salt concentration) to the column equilibrated with a lower salt concentration equilibration buffer performs the same function, way, and result as (and is insubstantially different from) the application of temporally and compositionally distinct solutions for washing and eluting. (Appx4893-4894, Appx4943, Appx4948-4949.) Specifically, the continued application of the refold solution (with a higher salt concentration) to the column equilibrated with a lower salt concentration equilibration buffer causes the conditions in the column to change, which results in washing and eluting as if those steps occurred via the addition of compositionally and temporally distinct solutions for washing and eluting. (Appx4893-4894, Appx4943, Appx4948-4949.) His testimony is evidence of infringement under the doctrine of equivalents under the narrower modified construction—it is not mere attorney argument. (Blue Br. at 51-52.)

And, contrary to Sandoz's assertion (Red Br. at 41), Amgen did argue infringement, both literally and under doctrine of equivalents, on a claim-by-claim basis. (Appx4862-4864, Appx4867-4872, Appx4936-4949.)

Sandoz asserts "opinions about literal infringement cannot carry Amgen's burden" based on two pre-*Warner-Jenkinson* cases. (Red Br. at 40.) Those cases do not apply here where Amgen argued for literal infringement under the Claim Construction Order, and the district court later changed its claim construction in granting summary judgment. In other words, what changed is not the facts but the legal framework to which those facts are being applied. If indeed the claims require application of different solutions formed outside the column, Dr. Willson's explanation of the changing conditions within the column is particularized testimony and linking argument to show the equivalents are insubstantially different; it is more than sufficient to meet Amgen's burden of showing that the same scientific processes are at work, *i.e.*, the differences between the claimed and practiced processes are insubstantial.

Sandoz attempts to distinguish *In re Omeprazole* on the basis that it involved composition claims rather than process claims and does not address equivalence. (Red Br. at 40-41.) This misses the point. *In re Omeprazole* supports Amgen's argument that when a claim calls for a particular composition, it does not matter whether that composition forms *in situ*. (Blue Br. at 52.) Here, both washing and

eluting occur in Sandoz's process, sequentially, using solutions that form *in situ* rather than two solutions that are added seriatim to the column. The district court incorrectly rejected such infringement evidence on summary judgment.

III. The District Court Erred in Granting Summary Judgment of Non-Infringement as to Sandoz's Yet-To-Be Submitted Modified Process for Making Its Biosimilar Products

The district court's decision is incorrect because it essentially gives Sandoz a blank check to modify its process without regard to whether it infringes. (Blue Br. at 56-57.) Because the district court has already found that the unfinished process is non-infringing, Sandoz is essentially free to make changes that would bring the process within the scope of the patent claims under any interpretation of those claims. (*Id.*) The appropriate inquiry is the process for which FDA approval will be sought, and not an unspecified process. (*Id.* at 57.) Indeed, it is not clear whether Sandoz would be bound by its representations here that the new process is not materially different from the existing process. (*Id.* at 57-58.)

Sandoz argues that the district court complied with *Glaxo Inc. v. Novopharm Limited* under § 271(e)(2) because it focused its infringement analysis on what the applicant will market if the FDA approves its application. (Red Br. at 55-56.) This is wrong for the reasons stated in Amgen's Blue Brief at 57-58. Until Sandoz actually submits its updated process to FDA for approval, an infringement analysis cannot focus on what is in the application. Moreover, Sandoz has not even

provided draft FDA submissions for the [redacted] process. And, "Simply saying 'But I won't do it' is not enough [for an ANDA applicant] to avoid infringement." *Sunovion Pharms. Inc. v. Teva Pharms. Inc.*, 731 F.3d 1271, 1280 (Fed. Cir. 2013).

Sandoz then argues that the district court's ruling does not preclude Amgen from asserting infringement against Sandoz if Sandoz further changes its process. (Red Br. at 54.) But without the discovery that Amgen seeks, Amgen cannot determine the details of the modified process as approved by the FDA (when/if it is approved by the FDA) and thus can only give a preliminary infringement analysis. And, if Sandoz further changes the details of its modified process, which, as far as Amgen knows, Sandoz has not yet submitted to the FDA, Amgen will not know anything about those changes unless Sandoz provides discovery.

In addition, Sandoz argues that Amgen does not need additional information in order to determine whether the modified process infringes, and that Amgen did not demonstrate that additional facts would have made a difference. (*Id.* at 52-53.) This is incorrect. In order to evaluate infringement, Amgen asked for samples of the liquid exiting the column at various points in time of the original [redacted] process, which would demonstrate that impurities exit the column before filgrastim. (Appx5411-5414, Appx5419.) Sandoz, however, refused. (*See* Appx5346-5347.) Thus, Dr. Willson calculated the retention time of filgrastim in the [redacted] column to show that it bound to the column while impurities were

washed out of the column (and discarded) before filgrastim eluted. (Appx4931-4944.) For the modified process, Dr. Willson made similar preliminary calculations for the [redacted] column relying on assumptions of similarities between the [redacted] process and the [redacted] process, but he did not have the information from Sandoz that could confirm those assumptions because Sandoz once again refused to provide it. (Appx4949-4951.)

Further, Sandoz incorrectly argues that Amgen's "lack of diligence during discovery" is reason enough to affirm the district court. (Red Br. at 53.) The district court did not find that Amgen lacked diligence during discovery, and Sandoz's attempt to have the Federal Circuit make that finding in the first instance should be rejected. (Appx14-15.) In any event, Amgen diligently pursued discovery in the face of Sandoz's lack of cooperation. Specifically, Amgen requested the discovery when it learned that documentation of the [redacted] process existed during depositions of Sandoz's fact witnesses in June 2017. (Appx5152-5153.) Amgen then continued to press for the discovery in the face of Sandoz's delay and failure to cooperate up to the time Amgen filed its Rule 56(d) motion. (Appx5153-5160.) Because Amgen acted diligently, *Baron Services, Inc. v. Media Weather Innovations LLC* is indeed on point. (Red Br. at 54.) As in *Baron*, Amgen lacks discovery "without which 'it cannot present facts essential to justify

its opposition'" to summary judgment despite its diligence in pursuing that discovery. *See* 717 F.3d 907, 912 (Fed. Cir. 2013).

Further, contrary to Sandoz's assertion, Amgen has not "conceded that a change in resin would make no difference on the issues here." (Red Br. at 56.) The issue being discussed in this context was whether the modified process would affect the analysis where the patent claims require a temporal break between the washing and eluting steps, and whether the patent claims also require different solutions to be added for washing and eluting. (*See* Appx7057.) This is not a concession that the modified process would not make a difference for infringement under the district court's original claim construction. As demonstrated by Dr. Willson's analysis, it would. (Appx4937-4951.)

IV. The District Court Erred in Construing Claim 1 of the '427 Patent

A. "Disease Treating" Specifies the Amount of Chemotherapeutic Agent Used in the Claimed Method; It Does Not Impose a Requirement That the Agent Be Prescribed for Disease Treatment

The district court erred in holding that "disease-treating-effective amount" of at least one chemotherapeutic agent means "an amount sufficient to treat a disease for which at least one chemotherapeutic agent is prescribed." (Appx47.) First, the district court's construction requires the chemotherapeutic agent to be used—indeed, "prescribed"—***for*** disease treatment. (*Id.*, Appx27 ("[T]he chemotherapeutic agent ***is*** 'disease treating.'"), Appx25 ("[O]ne substance

mobilizes stem cells, while the other ***treats a disease***."), Appx28 ("[T]he patentee claimed the ***disease-treating function*** of chemotherapeutic agents.") (emphases added).) This is incorrect. Nothing in the intrinsic evidence suggests that the chemotherapeutic agent is required to be prescribed for disease treatment. (Blue Br. at 62-69.) Indeed, the specification makes clear that this chemotherapeutic agent administered after G-CSF enhances mobilization, and is distinct from the high-dosage chemotherapy or bone marrow ablation by radiation, administered subsequent to leukapheresis. '427 Patent 1:4-10, 18-21. The district court erred by construing the term to read out the actual invention of disease treatment by administrating G-CSF and a chemotherapeutic agent in that order where the chemotherapeutic agent is used solely for stem cell mobilization. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (*en banc*) ("Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim.").

Second, the term "disease treating" is a modifier for "amount." It does not define or impose a requirement as to purpose or function of the chemotherapeutic agent. Defining the ***amount*** of chemotherapeutic agent by reference to a functionality that is not required by the claims (disease treatment) makes sense where, as here, the patent broadly defines chemotherapeutic agents to mean a wide

range of materials. '427 Patent, 2:39-54. The term "disease treating" modifies the word "amount"; it is not a requirement that the amount be prescribed ***for*** disease treatment. The district court erred in holding otherwise.

B. The Intrinsic Evidence Supports Amgen's Construction

1. The Claims

As the district court recognized, chemotherapeutic agents may be used for stem-cell mobilization (Appx20, Appx27-28); however, it found that these disclosures were overcome by the claim language that uses "disease treating" as to the chemotherapeutic agent and "stem cell mobilizing" as to G-CSF. (Appx27-28.) Sandoz also argues that the plain language of the claims requires that the chemotherapeutic agent have a functional requirement of "disease treating." (Red Br. at 58.) This is incorrect. "Disease treating" simply defines the amount of the chemotherapeutic agent that is used consistent with the claims and specification.

Sandoz asserts that Amgen's construction "would eliminate 'disease treating' from the claimed method." (*Id.* at 57-58.) Not so. Under Amgen's construction, the administration of the chemotherapeutic agent achieves the goal of the claimed method, *i.e.*, "treating a disease requiring peripheral stem cell transplantation," by enhancing the mobilization of stem cells in combination with G-CSF. The chemotherapeutic agent is administered in an "amount effective to treat diseases requiring stem cell transplants," which, as the specification makes

abundantly clear, is ***not*** an amount for the treatment of the underlying disease, but instead an amount for the enhancement of stem cell mobilization in combination with G-CSF. (Blue Br. at 67.) And Sandoz's criticism of *Abbott* and *Geneva* fails. (Red Br. at 60-61.) Sandoz does not appear to dispute that those cases support Amgen's argument that the claim term "effective amount" typically indicates "*how much* a claim requires to effectuate a goal." (Red Br. at 60 (emphasis in original).)

Contrary to Sandoz's argument (Red Br. at 57-58), Amgen's construction gives each term meaning. The reason that the claims specify a "disease treating" effective amount of a chemotherapeutic agent compared to a "stem cell mobilizing" amount of G-CSF is because not all chemotherapeutic agents (as defined in the patent specification) were known at the time of the invention to mobilize stem cells on their own. (Blue Br. at 66-67 (citing '427 Patent, 1:35-37).) For such chemotherapeutic agents, a "stem cell mobilizing-effective amount" would not exist. The claim language thus reflects the understanding of the applicants at the time of the invention that unlike G-CSF which was known to cause the mobilization of stem cells, not all chemotherapeutic agents were known to have that function. The claims are broad enough to cover the use of chemotherapeutic agents that, when working with G-CSF, enhance mobilization, but, when working alone, may not. And Sandoz's cited cases are inapposite because Amgen's construction does not "render meaningless the distinction

between" a stem cell mobilizing-effective amount and a disease treating-effective amount. (*See* Red Br. at 57-58.)

Sandoz argues that dependent claim 4 requires an additional function of disrupting the endothelial barrier but does not eliminate the requirement that the chemotherapeutic agent treat a disease. (Red Br. at 61.) This misses the point. Amgen is not contending that the requirement in claim 4 supplants the independent claim requirement that the chemotherapeutic agent be administered in an "disease treating-effective amount." Rather, claim 4 simply specifies one mechanism of action for the chemotherapeutic agent to enable stem cell mobilization (opening the endothelial barrier)—a function that is permitted under Amgen's construction of the claim term. Contrary to the district court's argument (Appx28), claim 4 does not mean that the chemotherapeutic agent of claim 1 must itself treat a disease.

2. The Specification.

Sandoz concedes that the specification describes administering a chemotherapeutic agent to enhance stem cell mobilization. (Red Br. at 63.) But Sandoz then suggests that these portions be ignored, and criticizes Amgen for "resort[ing] to the specification." (*Id.*) The law is otherwise: the specification of a patent is the single best tool for interpreting claims and is usually "dispositive." *See Phillips*, 415 F.3d at 1315. Sandoz also argues that those portions of the specification "merely indicate a chemotherapy agent can also be administered to

enhance stem cell mobilization." (Red Br. at 64.) But administering a chemotherapeutic agent in combination with G-CSF ***for stem cell mobilization*** in a ***particular order*** to improve ***stem cell collection*** is the invention of the '427 Patent, as the district court recognized in its decision. (Appx20-21.) Moreover, in the specification, the inventors recognized, and distinguished their invention from, the prior-art method of using G-CSF alone for stem cell mobilization and using chemotherapy (or radiation) for the ablation of the cells in the patient's bone marrow. '427 Patent, 1:32-34, 3:24-30; (Appx20.) Sandoz's and the district court's construction thus disconnects the invention from the claims, and instead covers the prior-art methods that the inventors had purposefully distinguished.

In addition, Sandoz mischaracterizes the portions of the specification that it does cite. (Red Br. 63-64.) First, Sandoz points to where the specification identifies and lists types of "chemotherapeutic agents." (*Id.* at 63 (quoting '427 Patent, 2:37-39).) This is not where the specification discusses the purpose of the chemotherapeutic agent in the claimed method. Notably, Sandoz skips the specification's immediately-prior disclosure that "[a]s chemotherapeutic agents in the meaning of the invention those therapeutic agents may be used which open the endothelial barrier, rendering it permeable for stem cells." '427 Patent, 2:34-36.

Sandoz also states, without any support, that the specification "teaches that stem cell transplantation addresses the side effects of treating cancer (a disease)

with chemotherapy." (Red Br. at 63.) This is incorrect. The specification teaches that certain diseases "requir[e] peripheral stem cell transplantation" for treatment. *E.g.*, '427 Patent 1:5-11, 1:66-2:4, 2:12-14; (*see* Appx2833-2834.) More fundamentally, stem-cell transplantation does ***not*** merely address the side effects of treating cancer. Rather, stem-cell transplantation is performed as part of the treatment of certain diseases, such as cancers of the blood or bone marrow. (Appx2833-2835.) Generally, stem cells are mobilized from a patient's bone marrow to the patient's peripheral blood, and then collected by a process called leukapheresis for storage. (*Id.*) During the next part of the treatment—high-dosage chemotherapy or bone marrow ablation by radiation—the hematopoietic and non-hematopoietic cells in patient's bone marrow are destroyed, in effect, clearing out the bone marrow to make it ready to receive the collected stem cells. (*Id.*)

Next, Sandoz attempts to equate the specification's reference to the stem cell transplantation's "high-dosage chemotherapy" for ablation of the bone marrow (*i.e.*, "antitumor therapy") with the chemotherapeutic agent(s) of the claim. (Red. Br. at 63-64.) This fails. The specification distinguishes the chemotherapeutic agent of the claim from whatever is used to ablate the bone barrow. '427 Patent, 1:4-10, 3:24-26. Indeed, the specification states (in the very portion cited by Sandoz) that the antitumor therapy can be accomplished using high-dose

chemotherapy ***or radiation***. '427 Patent, 1:18-21. Nowhere does the claim or specification say that the chemotherapeutic agent is given for the purpose of disease treatment, let alone that the chemotherapeutic agent is "prescribed" for disease treatment. And Sandoz does not attempt to explain how the word "prescribed" is supported by the evidence; neither did the district court.

3. The Prosecution History

Sandoz does not dispute that the PCT examiner describes the chemotherapeutic agent as being used with G-CSF for the purpose of mobilizing stem cells. Instead, Sandoz warns the Court not to accept Amgen's arguments regarding the claims of the PCT application. (Red Br. at 63 n.16.) But the PCT report cited by Amgen, which is part of the file history of the '427 Patent, can be used by the Court in determining what the invention is. *Phillips*, 415 F.3d at 1317.

4. Sandoz's Remaining Arguments Fail

Sandoz relies on extrinsic evidence to assert that "disease treating" does not refer to mobilization of stem cells. (Red Br. 59-60.) This cannot overcome the teachings of the specification, for example, that describe the use of chemotherapeutic agents for enhanced mobilization of stem cells in the treatment of diseases. *E.g.*, '427 Patent, 1:5-11. In addition, Sandoz argues that Amgen is proposing a convoluted construction of "comprising." (Red. Br. at 65.) But that is not Amgen's argument. Tellingly, Sandoz does not cite to Amgen's Blue Brief on

this point because there is nothing to cite: Amgen is not proposing to rewrite claim 1 to include an unwritten additional step. Rather, Amgen is asking the Court to construe "disease treating" not to require the chemotherapeutic agent to be used for disease treatment, as supported by the claims and specification.

Finally, Sandoz suggests that the construction of the same patent term by another district court should be ignored because the construction was not disputed there. (Red Br. at 66 n.17.) But Apotex did dispute whether the term is indefinite there, and the district court rejected that argument, correctly holding instead that a "person of ordinary skill in the art would understand that a dose of chemotherapeutic agent within [the range given in the specification], when administered after G-CSF, would be the 'disease treating-effective amount' needed ***to achieve the goal of enhancing stem cell mobilization*** for recovery from blood and subsequent transplantation." *Amgen v. Apotex*, No. 15-61631-CIV, 2016 WL 1375566, at *6 (S.D. Fla. April 7, 2016) (Appx2791) (emphasis added).

CONCLUSION

For the foregoing reasons, Amgen respectfully requests that this Court reverse, vacate, and/or remand the district court judgments.

Dated: July 20, 2018

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on this 20th of July, 2018, I caused the REPLY BRIEF FOR PLAINTIFFS-APPELLANTS AMGEN INC. AND AMGEN MANUFACTURING, LIMITED (CONFIDENTIAL AND NON-CONFIDENTIAL) to be filed with the Clerk of the Court using the NextGen System. I also caused a true and correct copy of the REPLY BRIEF FOR PLAINTIFFS-APPELLANTS AMGEN INC. AND AMGEN MANUFACTURING, LIMITED (CONFIDENTIAL AND NON-CONFIDENTIAL) to be electronically served, pursuant to agreement of the parties, on Defendants-Appellees Sandoz Inc., Sandoz International GmbH, Sandoz GmbH, and Lek Pharmaceuticals, d.d.'s counsel of record as follows:

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UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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