Nos. 18-1551, 18-1552

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.

AMGEN INC., AMGEN MANUFACTURING, LIMITED,

Plaintiffs-Appellants,

v.

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

Defendants-Appellees.

Appeals from the United States District Court for the Northern District of California, case nos. 3:14-cv-04741-RS, 3:16-cv-02581-RS, Hon. Richard Seeborg

NON-CONFIDENTIAL BRIEF FOR APPELLEES

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JUNE 22, 2018

CERTIFICATE OF INTEREST

Counsel for appellees certifies the following:

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

Sandoz Inc., Sandoz International GmbH, Sandoz GmbH, Lek Pharmaceuticals d.d.

2. The name of the Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:

N/A

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

Sandoz Inc., Sandoz International GmbH, Sandoz GmbH, and Lek Pharmaceuticals d.d. are indirect subsidiaries of Novartis AG, which trades on the SIX Swiss Exchange under the ticker symbol NOVN and whose American Depository Shares are publicly traded on the New York Stock Exchange under the ticker symbol NVS.

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

Morrison & Foerster LLP (including lawyers no longer with the firm): Rachel Krevans, David C. Doyle, Grant J. Esposito, Anders T. Aannestad, Marc A. Hearron, Stephen D. Keane, Joseph R. Palmore, Julie Y. Park, Lena H. Hughes, Brian M. Kramer, Jessica A. Roberts, James R. Hancock, Nicholas E. Ham, Teresa A. MacLean. Kirkland & Ellis LLP: James F. Hurst, Michael D. Shumsky, John K. Crisham, Reid P. Huefner, James W. Beard, Jeanna M. Wacker, Cristina Q. Almendarez.

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:

None.

Dated: June 22, 2018 /s/ Deanne E. Maynard

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CONFIDENTIAL MATERIAL OMITTED

Pursuant to Federal Circuit Rule 28(d)(2)(B), defendants-appellees prepared this public version of their brief which redacts certain highly confidential, sensitive business information designated as confidential pursuant to the district court's Protective Orders, entered on February 9, 2015 and January 17, 2017. The material omitted on pages 13-16, 20, 30, 41, 52-53 contains highly confidential, sensitive business information concerning the details of defendants-appellees' accused processes. This information was designated confidential by defendants-appellees during discovery under the terms of the Protective Orders and remains confidential.

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STATEMENT OF RELATED CASES

These consolidated appeals are from final judgments of the United States District Court for the Northern District of California in an infringement action filed by plaintiffs-appellants Amgen, Inc., and Amgen Manufacturing, Limited ("Amgen"), in which the court entered judgment of non-infringement in favor of defendants-appellees Sandoz Inc., Sandoz International GmbH, Sandoz GmbH, and Lek Pharmaceuticals d.d. ("Sandoz") regarding the asserted claims of U.S. Patent No. 8,940,878 ("'878 patent") and U.S. Patent No. 6,162,427 ("'427 patent"). This Court previously considered and decided an appeal in this case on July 21, 2015, issuing its mandate on October 23, 2015. *Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347 (Fed. Cir. 2015) (No. 2015-1499) (Judges Newman, Lourie, Chen). The Supreme Court granted the parties' petitions for writs of certiorari, and issued a decision on June 12, 2017. *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 1664 (2017). This Court decided certain issues on remand on December 14, 2017, *Amgen Inc. v. Sandoz Inc.*, 877 F.3d 1315 (Fed. Cir. 2017) (No. 2015-1499) (Judges Newman, Lourie, Chen), issuing its mandate on January 23, 2018.

Counsel for Sandoz knows of no other cases pending in this Court or any other court that will directly affect or be affected by this Court's decision in this appeal.

STATEMENT OF ISSUES

1. Whether Amgen waived its claim construction arguments with respect to claim 7 of the ’878 patent and, regardless, whether the district court correctly held that Sandoz’s one-step, one-solution protein purification process does not infringe the claimed method, which requires three steps and three solutions.

2. Whether the district court did not abuse its broad discretion in denying Amgen’s Rule 56(d) motion for a continuance and additional discovery on claim 7 of the ’878 patent.

3. Whether the district court correctly construed claim 1 of the ’427 patent, concluding that the plain language of a “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.”

INTRODUCTION

The district court correctly rejected Amgen’s attempt to contort its patent claims to try to stop the marketing of Sandoz’s biosimilar products.

As to claim 7 of the ’878 patent, the claim construction arguments Amgen attempts to raise on appeal are waived: it did not contest Sandoz’s arguments regarding separate steps and separate solutions. As the district court observed in its claim construction order, Amgen “did not respond” to Sandoz’s proposed separate steps construction. Amgen’s counsel said it “wasn’t necessary and did not

address it." Having lost its case, Amgen now contends it is entitled to a second chance because the district court supposedly modified its claim constructions at summary judgment. The summary judgment order refutes that contention; the district court extensively quoted its claim construction order, expressly stating that "[n]othing has been offered to suggest the above construction needs modification."

Amgen does not appeal literal infringement under the district court's constructions. Nor could it: claim 7 recites a method for protein purification, but that is about all it has in common with Sandoz's accused process. Claim 7 recites three separate, sequential steps in which each step builds on the last. Amgen's claimed method uses a type of purification, known as "capture purification," because the protein to be purified is captured in the column, then a solution that washes away the impurities is added, and thereafter a different solution that releases and recovers the protein is applied. The undisputed record shows that Sandoz's accused process has no separate steps. It uses one step and one solution; the solution containing the protein is purified in one continuous process. This one-step, one-solution process is a form of purification known as "flow through purification," because the protein flows through the column and becomes separated from the contaminants that are captured and remain in the column.

Recognizing these differences, Amgen resorts to the doctrine of equivalents. But all Amgen has to support that argument is its expert's conclusory allegation.

Amgen's expert backtracked even from that, saying at his deposition that the claimed method and Sandoz's process "might" be equivalent.

Nor did the district court abuse its discretion in refusing Amgen's request for additional discovery on Sandoz's planned change to its purification process. Amgen had ample opportunity to take discovery on that change, including a year and half's notice and Sandoz's disclosure of extensive documentation. The district court properly exercised its discretion to decide non-infringement based on the process expected to be used. And as the district court correctly concluded, the planned change will make no difference: Sandoz's process still will be one step and one solution.

On the '427 patent, Amgen's arguments are a transparent attempt to rewrite its claim. Claim 1 recites two steps. The first drug helps collect stem cells: "hematopoietic stem cell mobilizing." Appx27. The second drug treats a disease, such as cancer: "disease treating." Appx27. Under settled claim construction principles, these two steps have different meanings. That is what the district court correctly held. Despite the plain language of the claim, Amgen says the second drug does not need to treat a disease. Amgen says that both the first and second drug should be administered to help collect stem cells. That is not how the claim is written.

The judgments should be affirmed.

STATEMENT OF THE CASE

This appeal arises from Sandoz's filing of two abbreviated biologics license applications under the Biologics Price Competition and Innovation Act. Sandoz filed its first application in May 2014, seeking FDA approval of Sandoz's biosimilar filgrastim drug, ZARXIO®, for which Amgen's NEUPOGEN® is a reference product. Appx2005. Sandoz's second application, filed in October 2015, sought approval of Sandoz's biosimilar pegfilgrastim, for which Amgen's NEULASTA® is a reference product. Appx7117-7118. Amgen sued Sandoz alleging that Sandoz's filgrastim infringed claims 7, 8, 11, and 13-17 of the '878 patent and claims 1, 2, 3, 4 and 6 of the '427 patent. Appx2040-2046. Amgen later brought a separate suit alleging that Sandoz's pegfilgrastim infringed the same claims of the '878 patent. Appx7130-7132. After claim construction, the district court granted summary judgment of non-infringement on the '878 patent claims, and Amgen stipulated to non-infringement of the '427 patent claims.[1]

A. '878 Patent

As to the '878 patent, Amgen accuses only one purification step in Sandoz's multi-step purification process for filgrastim and pegfilgrastim.

[1] Amgen's second suit alleged that Sandoz's pegfilgrastim infringed U.S. Patent No. 5,824,784. Appx7117. That patent is not on appeal, as Amgen's claims and Sandoz's counterclaims were dismissed without prejudice by joint stipulation. Appx55-56.

1. Capture versus flow through purification

Recombinant protein purification. Filgrastim and pegfilgrastim are recombinant proteins used to address side-effects of cancer treatments like chemotherapy. Recombinant proteins are genetically engineered. Human DNA encoding a protein is introduced into host cells of a different species, and the host cells then produce the protein encoded by the human DNA. Appx34; Appx2725-2739 at Appx2728. These techniques have been used since the 1980s. Appx3795.

A drawback to this process is that the host cells sometimes do not properly fold the expressed protein into its native shape. Appx2728. Expressed proteins that are "misfolded" can accumulate in the host cell to form insoluble aggregates called "inclusion bodies." When this occurs, the proteins are not therapeutically useful.

To remedy this problem, the host cell is broken open to release the inclusion bodies. Appx2728. The inclusion bodies are mixed with various chemicals to solubilize the protein in a solubilization solution. That solution then is combined with a "refold buffer" to form a refold solution, which allows the protein to attain its proper shape. Appx34-35; *see* Appx2728; Appx3795.

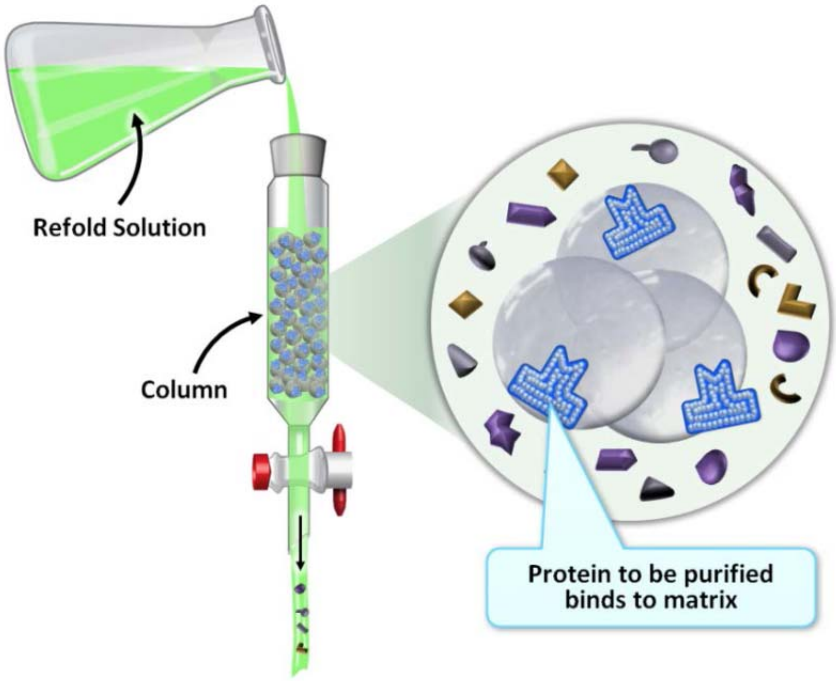
The protein needs to be purified to remove the chemicals from the refolding process and other contaminants. Purification can be accomplished with various chromatography techniques useful for separating mixtures; these techniques have

been a scientific staple for more than 70 years. Appx2728. In many chromatography techniques, a solution in need of purification passes through a "separation matrix." Appx2728. A separation matrix often is a resin, typically in the form of small beads. The resin beads bind to some substances but not others, which can be used to separate the mixture. Appx2728.

Different ways exist to purify proteins using a separation matrix. Two are relevant here: "capture purification" and "flow through purification."

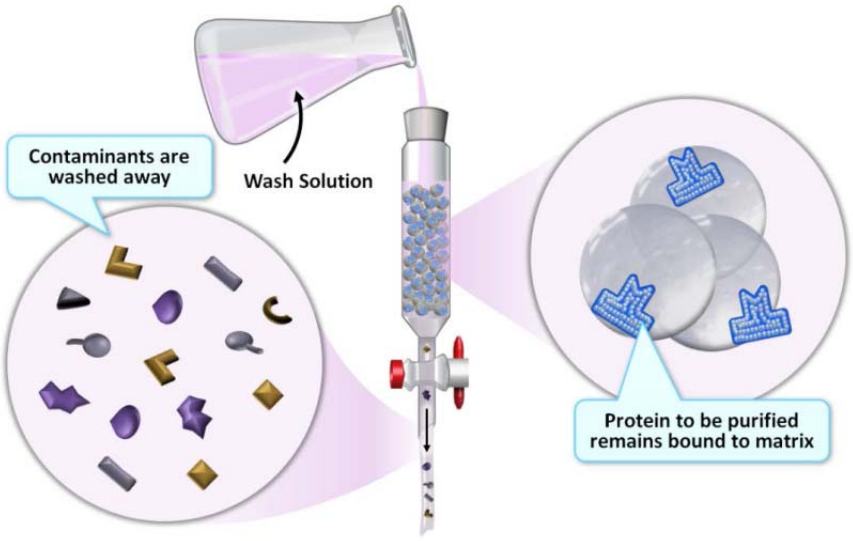
Capture purification. Capture purification of recombinant proteins generally has at least three separate and sequential steps. Appx2737-2738.

First, refold solution is loaded into a column containing a separation matrix. The protein binds to the separation matrix. The chemicals used to solubilize and refold the protein, however, remain in the solution and exit the column (Appx2729-2730):



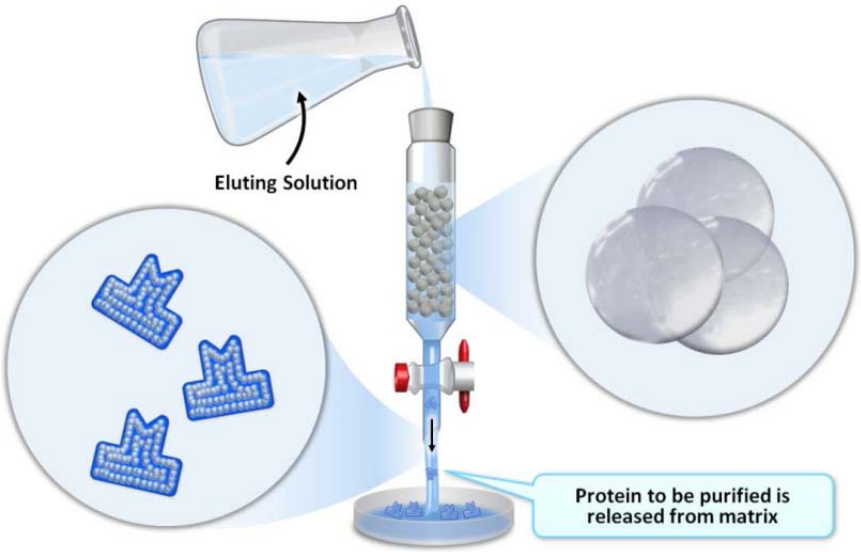
Appx3764.

Second, additional solutions are added into the column to wash the separation matrix. This step removes contaminants that do not bind to the resin but remain in void spaces between the resin beads. Appx2729-2730; Appx2736; Appx3797. During this washing step, the protein remains bound to the separation matrix:



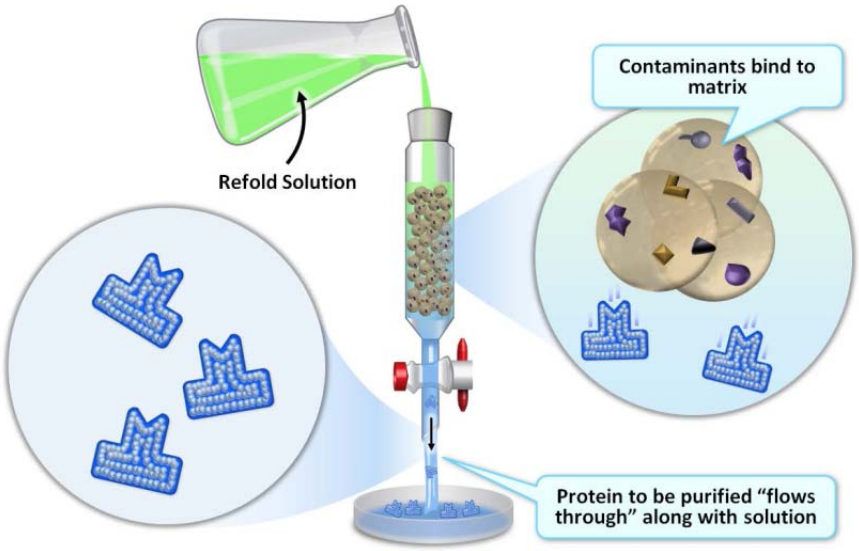
Appx3764.

Third, the protein to be purified is recovered from the separation matrix with a process called "elution" or "eluting." This is done by adding an eluting solution into the column that chemically changes the conditions in the separation matrix so that the purified protein is released (Appx2729-2730):



Appx3764.

Flow through purification. Flow through purification uses the opposite principles. Unlike capture purification, the chemicals used to solubilize and refold the protein bind to the separation matrix. The protein does not. It exits the column as a purified solution (Appx2729):



Appx3763.

Flow through purification can be done in a single, continuous step. It requires no washing or eluting, because the contaminants, not the protein, bind to the separation matrix. Appx2729.

2. The '878 patent's capture purification methods

The '878 patent is titled "Capture Purification Processes for Proteins Expressed in a Non-Mammalian System." Appx60. It claims methods for purifying proteins through "the direct capture of such proteins from a refold mixture or a cell lysate pool by a separation matrix." Appx67 (col.1:14-16).

A purported novelty of the claimed methods is the direct application of the refold solution to the separation matrix. Appx74 (col.15:25-29). The specification states that prior art capture purification methods required dilution or removal of components of the refold solution before applying the refold solution to the separation matrix. Unless this was done, some components of the refold solution would interfere with the protein's binding to the separation matrix. Appx67 (col.1:44-46); *see* Appx68 (col.4:42-46). The claimed methods purport to eliminate this requirement, so the refold solution "is applied directly to the separation matrix, without the need for diluting or removing the components of the solution." Appx74 (col.15:25-29).

At issue here are the steps that follow: the claims require washing the separation matrix and eluting the protein from the separation matrix.

For washing, the specification teaches that "[a]fter the protein of interest has associated with the separation matrix the separation matrix is washed to remove unbound protein, lysate, impurities and unwanted components of the refold solution." Appx74 (col.15:43-46). The washing solution can be "any composition, as long as the composition and pH of the wash buffer is compatible with both the protein and the matrix." Appx74 (col.15:47-49). The specification states that the washing solution to be added to the column is selected to meet certain requirements: the pH range of the washing solution "is chosen to optimize the

chromatography conditions, preserve protein binding, and to retain the desired characteristics of the protein of interest." Appx74 (col.15:55-56). Every example in the specification discloses the addition of a washing solution, distinct from the refold solution, to achieve these ends. Appx75 (col.18:18-19) (Example 1); Appx76 (col.19:16-18) (Example 2); Appx76 (col.20:34-36) (Example 3); Appx77 (col.21:24-25) (Example 4).

For eluting, the specification teaches that "[a]fter the separation matrix with which the protein has associated has been washed, the protein of interest is eluted using an appropriate solution (e.g., a low pH buffered solution or a salt solution) to form an elution pool comprising the protein of interest." Appx74 (col.15:60-64). Unlike washing, the eluting solution is chosen to achieve a different end: "The protein of interest can be eluted using a solution that interferes with the binding of the absorbent component of the separation matrix to the protein," so the protein is released. Appx74 (col.15:65-67). And every example identified involves introduction of an eluting solution, distinct from the refold and washing solutions, to achieve this end. Appx75 (col.18:20-22) (Example 1); Appx76 (col.19:19-20) (Example 2); Appx76 (col.20:36-39) (Example 3); Appx77 (col.21:26-28) (Example 4).

Claim 7 is the only claim Amgen raises on appeal. Claim 7 recites a capture purification method; the last two steps are "washing the separation matrix" and "eluting the protein from the separation matrix":

> **7.** A method of purifying a protein expressed in a nonnative limited solubility form in a non-mammalian expression system comprising:
>
> (a) expressing a protein in a non-native limited solubility form in a non-mammalian cell;
>
> (b) lysing a non-mammalian cell;
>
> (c) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:
>
> (i) a denaturant;
>
> (ii) a reductant; and
>
> (iii) a surfactant;
>
> (d) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:
>
> (i) a denaturant;
>
> (ii) an aggregation suppressor;
>
> (iii) a protein stabilizer; and
>
> (iv) a redox component;
>
> (e) directly applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
>
> (f) *washing the separation matrix*; and
>
> (g) *eluting the protein from the separation matrix*, wherein the separation matrix is a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.

Appx77 (col.22:3-28) (emphasis added).[2]

3. Sandoz's flow through purification step

When Sandoz makes filgrastim and pegfilgrastim, its manufacturing process has several separate purification steps.

The only purification step Amgen accuses of infringement is a flow through purification process: the Anion Exchange Chromatography ("AEX") step. The undisputed record shows that, unlike capture purification, Sandoz's AEX step involves one continuous step, with no separate washing or eluting.[3]

In its AEX step, Sandoz separates the detergent [redacted] from the refold solution. Appx3975. Earlier in its manufacturing process, Sandoz refolds filgrastim in a solution containing the [redacted] Appx3975; Appx3801; Appx3806. [redacted] keeps filgrastim soluble during the refolding process. Appx3986. But [redacted] also interferes with later purification steps in Sandoz's process that remove filgrastim from the refold solution, so Sandoz needs to remove [redacted] before those steps. Appx3986; Appx3801; Appx3873.

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[2] Claims 8, 11, and 13-17 all depend from claim 7, but Amgen's brief (Br. 3) presents only challenges to the judgment as to claim 7. It thus has waived any appeal on the dependent claims. *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1319 (Fed. Cir. 2006) ("[A]rguments not raised in the opening brief are waived.").

[3] The differences between filgrastim and pegfilgrastim are not relevant on appeal. For each, Sandoz's AEX step is identical. Appx3969; Appx3972. Later in the manufacturing process, filgrastim is modified to become pegfilgrastim. Appx3800.

Sandoz starts its AEX step by sanitizing, conditioning, and filling its column with an equilibration solution referred to as [redacted]. Appx3990-3991; Appx3802. Sandoz then continuously loads refold solution containing the filgrastim, [redacted] and other substances into the column. Appx3803; Appx3990-3991. Roughly [redacted] liters of refold solution are loaded into the column during the [redacted] AEX step. It takes [redacted] minutes and [redacted] liters of the refold solution to completely displace the [redacted] equilibration solution. Appx6728-6729.

As refold solution is loaded into the column, negatively charged [redacted] binds to the positively charged separation matrix. Appx3975-3976. The rest of the refold solution, including the filgrastim and other contaminants, are "not retained on the column." Appx3975-3976. Rather, they are "recovered in the column flow-through," which is collected in a single container. Appx3975-3976. At the end of the AEX step, the separation matrix containing the [redacted] is discarded. Appx3975-3976; Appx3803-3804.[4]

As mentioned above, the AEX step is only one of many Sandoz uses to purify its filgrastim. In later steps, Sandoz further purifies the remaining solution containing the filgrastim. Appx3990-3991. For example, after the [redacted] has been

[4] In some instances, more equilibration solution is loaded into the column at the end of the AEX step to displace any remaining refold solution. Appx3803. Amgen acknowledges this additional process does not infringe the '878 patent. Appx3929.

removed, some of Sandoz's later manufacturing steps use capture purification chromatography to separate the filgrastim from the refold solution. Appx3808. Amgen does not accuse any step other than the AEX step of infringement. In essence, the accused AEX step performs the prior art methods the '878 patent sought to avoid; the AEX step removes components (here, [redacted]) from the refold solution that would interfere with the protein's binding to a separation matrix in later purification steps.

4. Sandoz's change in resin

The [redacted] resin Sandoz uses for its separation matrix will be discontinued in late-2018 or 2019. Appx14; Appx3994. In June 2016, Sandoz notified Amgen that Sandoz planned to use a replacement resin; throughout 2017, Sandoz provided Amgen multiple technical documents related to that issue, and Amgen's expert opined on this change in his report and deposition. Appx3947; Appx5277; Appx6426-6428; Appx6430; Appx6432-6529. As Sandoz disclosed, it will replace the [redacted] resin with a different resin called [redacted]. Appx3804-3805; Appx3994. Using [redacted] instead of [redacted] will require Sandoz to make several technical modifications to the AEX step, such as column diameter, bed height, loading time, and residence time. Appx3994-3998. But the undisputed record shows that the AEX step will otherwise remain the same: the same refold solution will be loaded into the separation matrix, and the replacement resin will

bind to and remove [redacted]. Appx4557; Appx3994-3998. As is the case with the current resin, the refold solution and only the refold solution will be added to achieve this result with the new resin. Appx4557.

5. District court proceedings

a. Claim construction

In construing the claims, the district court recognized that claim 7 "discloses a capture method" of protein purification involving "a natural, logical order of steps" that cannot occur "simultaneously." Appx43; Appx46. Amgen attempts to appeal the constructions of the washing and eluting steps.

During claim construction in district court, Sandoz and Amgen agreed that the step of "washing the separation matrix" requires "[a]dding a solution"/"applying a solution" to the separation matrix. Appx2378 (Sandoz: "applying a solution"; Amgen: "[a]dding a solution"). The parties treated "[a]dding a solution"/"applying a solution" the same. Appx2503-2504; Appx2666-2668; Appx2822. The district court agreed. Appx44. Because the claim and specification require that the protein remain bound to the separation matrix during the washing step, the court also held that the washing solution must preserve the protein's binding to the matrix. Appx46. The court thus construed the term "washing the separation matrix" to mean "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.

The court also construed "eluting the protein from the separation matrix." Again, the parties proposed that this step requires "[a]dding a solution"/"applying a solution" to the separation matrix. Appx2378 (Sandoz: "applying a solution"; Amgen: "[a]dding a solution"); Appx2503-2504; Appx2667-2668; Appx2822. The district court agreed. Appx46. The court explained that eluting requires adding a solution that functions differently than the washing solution: the wash buffer must "preserve protein binding" while the eluting solution "interferes with the binding." Appx46 (quoting Appx74 (col.15:55-16:2)). Based on this distinction, the court construed the term to require "[a]pplying a solution that reverses the binding of the purified protein to the separation matrix." Appx45.

As part of its construction, the district court held that the claims require a specific order of separate steps: eluting "must occur after the step of 'washing the separation matrix.'" Appx48. During claim construction, Sandoz contended that the claims required a "logical order and separateness of these steps." Appx2667-2668; Appx2378. In its claim construction briefing, Amgen did not dispute this construction on the merits; rather, it argued only that Sandoz had not presented this issue for construction. Appx2504; Appx2822. When asked by the district court

about Sandoz's construction, Amgen's counsel stated: "We felt that that wasn't necessary and did not address it." Appx3329-3531 at Appx3524; Appx3234-3305.

The district court rejected Amgen's procedural argument: "Sandoz adequately notified Amgen of its intent to seek construction … , as required by the local patent rules." Appx45. Amgen does not appeal this ruling.

The district court then adopted Sandoz's construction, expressly noting that Amgen "did not even respond to Sandoz's argument." Appx45. Relying on this Court's decision in *Mformation Techs., Inc. v. Research in Motion Ltd.*, 764 F.3d 1392 (Fed. Cir. 2014), the court held that the claims required a particular order, where one step must occur after completion of the other. The court explained that the '878 patent states that eluting cannot begin until "'[a]fter the separation matrix with which the protein has associated has been washed.'" Appx46 (quoting Appx74 (col.15:60-62)). The claims require this sequence because "the proteins and the separation matrix should remain associated during the washing process." Appx46. By contrast, "elution involves cleaving the protein from the matrix." Appx46. The court thus concluded that washing and eluting cannot happen at the same time: "If the washing and eluting steps occurred simultaneously, the protein captured by the separation matrix could once again comingle with the contaminants and be washed away." Appx46.

b. Summary judgment

Applying these constructions, the district court granted summary judgment of non-infringement.

Literal infringement. The court held that Sandoz's AEX step does not infringe for two reasons, either of which "independently supports a finding that Sandoz's process does not literally infringe." Appx12.

First, the court concluded that Sandoz's process does not use the washing-then-eluting sequence required by the claims. Appx10. Amgen admitted that washing must happen before eluting. Appx4861. And Amgen's expert conceded he could not determine when Sandoz's washing step ends in relation to when its eluting step begins. Appx3914-3916; Appx4019. Amgen nonetheless argued that the steps need not be separate because the patent did not require that "all washing must be complete before any eluting begins." Appx4861-4862; *see* Appx7019-7084.

The district court rejected Amgen's argument as inconsistent with the court's claim construction. Quoting its claim construction order, the court reiterated its conclusion that the claims require "'*a natural, logical order of steps*,'" in which eluting does not begin until "'[a]fter the separation matrix with which the protein has associated has been washed.'" Appx10 (quoting Appx46; emphasis in summary judgment order). Each of those steps must be separate and

occur in a specific order: "the step of 'eluting the protein from the separation matrix' occurs *after* the step of 'washing the separation matrix.'" Appx10 (quoting Appx46). "Nothing has been offered to suggest the above construction needs modification." Appx10.

In contrast to the claims' multi-step method, Sandoz's accused one-step process "entails continuously pumping a refold solution comprised of filgrastim, a particular detergent ('detergent 1'), and other substances into a column containing a separation matrix. There is no pause in the pumping of the refold solution." Appx10 (footnote omitted); *see* Appx3792-3858. Accordingly, the district court concluded that "[t]here is simply no way to conceive of this continuous pumping process as an eluting step *after* a washing step without straining the language of the patent specification and the claim construction order beyond their reasonable meaning." Appx11.

Second, and as an independent basis for no literal infringement, the court held that Amgen had raised no triable fact issue because Sandoz adds only one solution into the column, whereas the claims require adding different solutions for washing and eluting. Appx10-12. The court rejected Amgen's argument that the patent did not preclude "the refold solution from serving as the solution that is added/applied to the [redacted] column to bring about the washing and eluting functions recited by the claim." Appx4859-4860.

Again, the district court expressly relied on its claim construction order. Appx11-12. The court explained the claims require adding both "a wash buffer that is optimized to preserve protein binding and an eluting solution that interferes with the binding." Appx11 (citing Appx46) (quotations omitted). "The opposite purposes of these two solutions suggests they must indeed be distinct and cannot be, as Amgen contends, a single solution achieving different ends, due to different conditions, at different points in time." Appx11. The court thus concluded Sandoz's process cannot literally infringe: Amgen did not identify "any point at which Sandoz adds a second solution to the column that is compositionally different than the refold." Appx10-11; *see* Appx3740-3764; Appx6241-6259.[5]

Doctrine of equivalents. The court also entered judgment of non-infringement under the doctrine of equivalents. Amgen acknowledged its burden to prove infringement based on the "'individual elements of the claim.'" Appx4862; *see* Appx12. Yet in opposing summary judgment, Amgen did not, instead asserting in general terms that its evidence would "support a finding of literal infringement or infringement under the doctrine of equivalents." Appx4854. Amgen admitted it had presented only two paragraphs of expert testimony on its

[5] The court did not reach two additional, "strong" non-infringement contentions—Sandoz's process could not literally infringe because "the washing step must come after the application of the refold solution, and the solutions required for eluting and washing must be separate and distinct from the refold solution." Appx12.

doctrine-of-equivalents theory. Appx4863-4864. According to Amgen, it need not provide more because Sandoz's process literally infringed. Appx4863-4864.

The district court held Amgen had raised no triable fact issue on equivalency. Appx12-13. Addressing the washing and eluting limitations, the court held Sandoz's accused process performs different functions in different ways than the claimed process. Appx13. The claims involve "'a natural, logical order of steps' in which application of the refold solution is followed by a washing step and then an eluting step." Appx13. Sandoz's process functions in a different way and "involves only one step: the continuous application of a single solution to a separation matrix." Appx13.

Rule 56(d). The district court denied Amgen's motion seeking a continuance. Appx14-15. Amgen argued it needed additional discovery about Sandoz's modified process, beyond what Sandoz already had provided. The court observed Amgen had pointed to no facts, and had requested no information from Sandoz, that would change the infringement analysis: "Sandoz's process will still not contain an eluting step that follows a washing step, as required by claim 7's (f) and (g) elements. It therefore will not infringe." Appx14-15.[6]

[6] The court did not address Sandoz's damages summary judgment motion. Appx13-14.

B. '427 Patent

Amgen appeals the construction of "a disease treating-effective amount of at least one chemotherapeutic agent." In claim 1, a patient is given a protein (such as filgrastim) to facilitate stem cell mobilization followed by at least one chemotherapeutic agent to treat a disease.[7]

1. Pre-chemotherapy stem cell collection

Cancer is a disease that has long been treated with chemotherapy agents, drugs that are toxic to cells that divide rapidly, including tumors. Appx2673. Chemotherapy agents have significant side-effects; they destroy normal, rapidly dividing cells like bone marrow cells. Appx2673. Chemotherapy agents that destroy bone marrow are often referred to as "myeloablative" or "myelotoxic." Appx2673.

Doctors use a process known as autologous stem cell transplantation to ameliorate these negative side effects; it is not itself a treatment for a disease, like cancer. Appx2667; Appx3062. Before chemotherapy, doctors administer a natural protein called G-CSF (granulocyte colony stimulating factor). Appx2674. Filgrastim is a pharmaceutical analog of G-CSF that functions the same way. Appx2674. These proteins "mobilize" hematopoietic stem cells out of the bone

[7] Claims 2-4, and 6 all depend from claim 1, but Amgen's brief (Br. 4) challenges only the judgment as to claim 1. It thus has waived any challenge to the dependent claims. *SmithKline*, 439 F.3d at 1319.

marrow and into the peripheral blood stream that circulates throughout the body. Appx81 (col.1:28-31). Hematopoietic stem cells are self-renewing, blood-forming stem cells that exist naturally in human bone marrow. Appx19.

Next, doctors collect the mobilized stem cells from the patient's peripheral blood in a process called "leukapheresis." Appx2673-2674. The patient then undergoes chemotherapy. After chemotherapy, doctors transplant the collected stem cells into the patient so the bone marrow can make new blood cells. Appx2673-2674; Appx81 (col.1:1-11, 1:18-31, 1:55-61).

2. The '427 patent's claimed method

The '427 patent's method of treating a disease has three requirements: administration of G-CSF; administration of at least one chemotherapeutic agent; and peripheral stem cell transplantation in a patient. Claim 1 recites:

> 1. *A method of treating a disease* requiring peripheral stem cell transplantation in a patient in need of such treatment, comprising administering to the patient *a hematopoietic stem cell mobilizing-effective amount of G-CSF*; and thereafter administering to the patient *a disease treating-effective amount of at least one chemotherapeutic agent*.

Appx85 (col.10:24-29) (emphasis added). The '427 patent is directed to autologous transplants. Appx81 (col.1:4-10); Amgen Br. 28, 60.

3. District court proceedings

In construing the claims, the district court first construed the preamble. The preamble states: "A method of treating a disease requiring peripheral stem cell transplantation in a patient in need of such treatment." Appx85. Both parties agreed this preamble is limiting. Appx24. The parties disagreed whether it meant that peripheral stem cell transplantation is a way to alleviate the side effects of a treatment for a disease (Sandoz's construction) or is itself an independent treatment for a disease (Amgen's construction). Appx24.

The district court agreed with Sandoz. The court explained that the phrase "such treatment" in the preamble refers to "a method of treating a disease," and "peripheral stem cell transplantation" is not a treatment for a disease. Appx24-26. After analyzing the claims and the specification, the court explained that the intrinsic record referred to stem cell transplantation as alleviating the side effects of a disease treatment, "not the disease treatment itself." Appx25. Relying on Sandoz's expert, Dr. Robert Negrin, the court found as fact that the use of peripheral stem cell transplantation to "counteract the negative side effects of disease treatments such as myelotoxic chemotherapy or radiation" is not a disease treatment; it simply "counteract[s] the negative side effects of disease treatments." Appx26 n.3. The court thus construed the preamble to mean: "In the practice of

the method of treating a disease, a patient receives a transplant of peripheral stem cells." Appx47.

Next, the court addressed the phrase Amgen appeals: a "disease treating-effective amount of at least one chemotherapeutic agent." Appx26. Sandoz proposed the following construction: "an amount sufficient to treat a disease for which at least one chemotherapeutic agent is prescribed." Appx26. Amgen argued it meant "an amount of at least one chemotherapeutic agent sufficient to enhance the mobilization of stem cells for recovery from the blood for subsequent peripheral transplantation." Appx26.

The district court adopted Sandoz's construction. Appx26. The court explained that claim 1 has three parts, a preamble and two limitations: "the first limitation is a description of step one (administration of G-CSF); the second limitation is a description of step two (administration of the chemotherapeutic agent)." Appx27. The court noted that claim 1 does not refer "to the two steps of the claimed process as 'stem-cell mobilizing.'" Appx27. Instead, "the patentee chose to use different descriptors for G-CSF and chemotherapeutic agents. G-CSF is 'hematopoietic stem cell mobilizing,' whereas the chemotherapeutic agent is 'disease treating.'" Appx27. The court held this use of different descriptors matters because "[d]ifferent claim terms are presumed to have different meanings." Appx27.

Based on these constructions, Amgen stipulated Sandoz did not infringe. Appx49-54. The court thus entered a non-infringement judgment. Appx2.

SUMMARY OF ARGUMENT

I.A. Amgen waived its claim construction arguments about the '878 patent by not raising them during claim construction in the district court. Seeking to avoid its waiver, Amgen contends the district court modified its constructions of the "washing" and "eluting" steps at summary judgment. The summary judgment order refutes that contention. The court extensively quoted from its claim construction order, expressly stating that it needed no modification. Appx10. Because it did not press its claim construction arguments in district court, Amgen cannot raise them now.

B. Amgen's waiver of its claim construction arguments leaves it with no challenge to the no-literal infringement judgment, which it does not contest on appeal under the district court's construction.

C. Amgen's doctrine-of-equivalents argument fares no better. The district court correctly held that Sandoz's one-step, one-solution process functions in an entirely different way than claim 7's washing and eluting requirements. Amgen bore the burden to demonstrate triable fact issues on a limitation-by-limitation basis, yet it offered little more than its expert's bald allegation of equivalency. Such conclusory statements cannot defeat summary judgment.

D. Even were this Court to consider Amgen's waived claim construction arguments, they fail. A claim requires an ordering of steps, where each needs to be completed before the next begins, when the logic or grammar of the claims or the specification so requires. Here, the claim and the specification dictate that washing must be completed before eluting. To wash, the washing solution must preserve the binding of the protein to the matrix, so the contaminants can be washed away while the protein remains. Eluting requires the opposite: the protein must be released from the matrix. If washing and eluting were not separated, the protein being released and the contaminants being washed would comingle again to form a single solution.

The district court also correctly held that the addition of two solutions is required, one at each step. Washing requires adding a solution that preserves the binding of the protein. Eluting requires applying a solution that reverses the binding of the protein. These opposite requirements preclude a single solution for both steps at the same time.

II. The district court soundly exercised its broad discretion in denying Amgen's Rule 56(d) motion. Amgen had ample opportunity to review technical documents and question witnesses after being informed of Sandoz's replacement resin—almost a year and a half before Amgen filed its motion. Regardless, Amgen

has never explained how the information it seeks would change the infringement analysis. It would not, as Amgen's counsel conceded to the district court.

The district court did not abuse its discretion in basing its non-infringement ruling on the record before it, based on the process expected to be used. As the court correctly held, Sandoz's changed process still will be a one-step, one-solution process that does not infringe Amgen's three-step, three-solution method.

III. The district court also correctly construed the challenged limitation of the '427 patent. Claim 1 has two steps: (1) the administration of G-CSF in a "stem cell mobilizing-effective amount," and (2) the administration of a chemotherapeutic agent in "a disease treating-effective amount." The court's constructions gave meaning to the different language used: the claimed G-CSF is for stem cell mobilizing; the claimed chemotherapeutic agent is for disease treating.

Amgen would eviscerate this distinction. It argues that both G-CSF and a chemotherapeutic agent need to mobilize stem cells, and the chemotherapeutic agent does not need to treat a disease. Amgen's argument runs counter to settled law: different terms are presumed to have different meanings. The court's construction also accords with the specification, while Amgen's imports limitations into the claim.

CONFIDENTIAL MATERIAL REDACTED

STANDARD OF REVIEW

This Court reviews factual findings underlying claim construction for clear error and legal conclusions de novo. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 836-37 (2015). It reviews summary judgment de novo. *Intellectual Sci. & Tech. v. Sony Elecs.*, 589 F.3d 1179, 1183 (Fed. Cir. 2009). It reviews the denial of a Rule 56(d) motion for abuse of discretion. *Family Home & Fin. Ctr. v. Fed. Home Loan Mortg. Corp.*, 525 F.3d 822, 827 (9th Cir. 2008).

ARGUMENT

I. THE DISTRICT COURT CORRECTLY HELD THAT SANDOZ DOES NOT INFRINGE CLAIM 7 OF THE '878 PATENT

The district court correctly held that Sandoz's one-step, flow through purification process does not infringe claim 7 of the '878 patent. Claim 7 recites a capture purification process with three distinct steps and three different solutions. The undisputed record shows that Sandoz's AEX step employs one step and one solution: loading refold solution onto the separation matrix to capture [redacted] while the protein flows through and is collected at the outlet. Because Sandoz's one-step, one-solution process cannot practice Amgen's three-step, three-solution method, the non-infringement judgment should be affirmed.

A. Amgen Waived Its Claim Construction Arguments

Amgen's principal arguments on appeal are founded on a faulty premise: the district court supposedly changed its claim construction at summary judgment.

Br. 3, 36-40. The district court did no such thing. The claim constructions Amgen attempts to appeal were expressly at issue during claim construction proceedings. Amgen made no substantive challenge to them. It is too late to object now.

Amgen first suggests (Br. 38) that the district court's construction—that the eluting "step must occur after the step of 'washing the separation matrix'" (Appx48)—did not "originally" include a limitation that the washing and eluting steps be separate. Not so. As Sandoz explained in proposing that construction, its construction "properly includes *the separateness* and order of steps defined by the claim and the specification." Appx2667 (emphasis added). Sandoz further explained that "[i]f the washing and eluting steps occurred at the same time, the process would not separate the protein from the unwanted components because both the protein and unwanted components would flow over or past the matrix in the solution." Appx2667-2668. Sandoz relied on this Court's decision in *Mformation*, which held the claims there imposed "an ordering-of-the-steps requirement" such that one step had to be completed before the next began. Appx2668 (citing *Mformation*, 764 F.3d at 1398-1400). And Sandoz highlighted that Amgen's claim construction brief "deliberately ignores that logical order *and separateness* of these steps." Appx2668 (emphasis added); *see* Appx2640-2669; Appx3046-3059.

In adopting Sandoz's construction, the district court 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. Appx45-46 (citing *Mformation*). The claim construction order provided: "the specification discloses a natural, logical order of steps. If the washing and eluting steps occurred simultaneously, the protein captured by the separation matrix could once again comingle with the contaminants and components to be washed away." Appx46. At summary judgment, far from altering this construction, the court extensively and expressly quoted it, emphasizing this very language: "*If the washing and eluting steps occurred simultaneously, the protein captured by the separation matrix could once again comingle with the contaminants and components to be washed away.*" Appx10 (quoting Appx46) (emphasis by district court). It rejected Amgen's infringement arguments as "straining the language" of "the claim construction order beyond [its] reasonable meaning." Appx10-11.

The same is true about the other claim construction issue Amgen attempts to appeal (Br. 43): whether claim 7 requires the addition of a washing solution and the addition of a different eluting solution. The parties agreed each step required "[a]dding a solution" or "applying a solution" to the separation matrix. Appx2378 (Sandoz: "applying a solution"; Amgen: "[a]dding a solution"). As Sandoz explained, the patent requires the addition of a washing solution that "*preserve[s]*

protein binding" and then the addition of an eluting solution that "*interferes with* the binding." Appx2666-2667. In its claim construction order, the district court agreed, concluding that each step required the addition of a different solution: for the washing step, "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, for the eluting step, "applying a solution that reverses the binding of the purified protein to the separation matrix." Appx45-46. Again, this is the same construction the court applied at summary judgment, rejecting Amgen's one-solution infringement argument "[f]or similar reasons" that it rejected Amgen's one-step argument. Appx11 (citing Appx46).

Amgen's appeal thus falters on its premise, as the district court did not alter its constructions at summary judgment. The summary judgment order says so itself, after quoting at length from the relevant portion of the claim construction order: "Nothing has been offered to suggest the above construction needs modification." Appx10. Although Amgen acknowledges that "the district court said it was not modifying its earlier claim construction," (Br. 39) Amgen attempts to contest that assertion. But the district court's interpretation of its own order should be given considerable deference; it was in the best position to assess what the parties argued and what it decided. *Avila v. Willits Envtl. Remediation*, 633 F.3d 828, 836 (9th Cir. 2011) ("The district court is the best judge of its own

orders."); *Amado v. Microsoft Corp.*, 517 F.3d 1353, 1358 (Fed. Cir. 2008) (district court's interpretation of its order "was reasonable, and thus worthy of deference").

Once Amgen's premise falters, so does its claim construction appeal. The problem for Amgen is that it did not contest these issues during claim construction. Appx2504; Appx2822. As the district court expressly stated in adopting the separate and sequential steps construction, "Amgen has not offered any reasons to believe" the construction that Sandoz proposed and that it adopted was incorrect. Appx46. Amgen "did not even respond to Sandoz's argument." Appx45. It instead put all its eggs in the procedural basket, arguing Sandoz had not properly identified the terms. Appx2504. Amgen's counsel confirmed this at the claim construction hearing: "There is a separate issue wherein Sandoz wants to put in an order here. We felt that that wasn't necessary and did not address it." Appx3524. But the district court rightly rejected Amgen's procedural argument (Appx45), which Amgen does not appeal. *SmithKline*, 439 F.3d at 1319 ("[A]rguments not raised in the opening brief are waived.").

That leaves Amgen trying to appeal claim constructions it did not properly contest in district court. This Court has barred appellants in like circumstances from advancing such arguments. In *Regents of University of Minnesota v. AGA Medical*, the University argued on appeal that in granting summary judgment, the district court "wrongly allowed translational movement" to satisfy the claim

limitation. 717 F.3d 929, 946 (Fed. Cir. 2013). But this Court agreed with the district court that "its claim construction placed no restriction whatsoever on the type of movement required by the claim." *Id.* "If the University objected to that construction, it should have presented its objection and its alternative construction to the district court," "[b]ut the University's claim construction briefs … never argued that the correct construction required a particular type of movement." *Id.* This Court held "[t]he University has therefore waived any objection to this aspect of the district court's construction." *Id.*

This Court reached the same conclusion in *LizardTech v. Earth Resource Mapping*, 424 F.3d 1336 (Fed. Cir. 2005). There, the patentee argued that "after it agreed to the district court's claim construction, the court materially altered that construction" in granting summary judgment. *Id.* at 1341. This Court disagreed, "discern[ing] no change in the district court's claim interpretation." *Id.* Because the district court's construction had not changed, the Court held the patent owner "cannot now argue against the claim construction." *Id.*

Like the appellants in *Regents* and *LizardTech*, Amgen did not object during claim construction. It is too late for Amgen to do so now.

B. Amgen Does Not Appeal The Judgment Of No Literal Infringement Under The District Court's Claim Constructions

If either of Amgen's claim construction arguments is waived, summary judgment of no literal infringement must be affirmed. Amgen advances arguments

only under what it calls the court's "original" construction (Br. 45-51)—the construction that supposedly does not require separate steps and different solutions. Amgen thus has waived any appeal of the no-literal-infringement judgment under the district court's actual constructions. *SmithKline*, 439 F.3d at 1319 ("[A]rguments not raised in the opening brief are waived.").

Amgen does not challenge the no-literal-infringement judgment for good reason: the undisputed record demonstrates that Sandoz's AEX step does not have a washing step that, once completed, is followed by a separate eluting step. Appx3975-3976. Nor does Sandoz's AEX step add different washing and eluting solutions. Appx3802-3805. Rather, the undisputed evidence shows that Sandoz's process involves only one step and one solution: the continuous application of the refold solution. Appx3975-3976. Indeed, Amgen's expert admitted that Sandoz's process contains no separate and sequential washing and eluting steps. Appx3897; Appx3928; Appx5258; Appx5268. And Amgen acknowledges (Br. 50-51) that Sandoz's process "'entails continuously pumping a refold solution' onto the column" and "'there is no pausing in the pumping of the refold solution.'"

That Amgen advances no argument on appeal under the district court's actual constructions is confirmed by Amgen's passing statement (Br. 51) that, "even if the modified construction is affirmed, Amgen should be given the opportunity to present its infringement case under the narrowed construction." But

even were this Court to conclude the court altered its constructions, there should be no remand. Amgen offers nothing to show it would make a difference. *Monsanto v. Scruggs*, 459 F.3d 1328, 1341 (Fed. Cir. 2006) ("[M]erely stating disagreement with the trial court does not amount to a developed argument."). Regardless, Amgen already had an opportunity to "present its infringement case under the narrowed construction." In response to Sandoz's summary judgment motion (Appx3744), Amgen argued that, even if separate steps were required, its "evidence would still support a finding of literal infringement or infringement under the doctrine of equivalents." Appx4854; *see* Appx4861.[8]

C. Sandoz's One-Step, One-Solution Process Does Not Infringe Claim 7 Under The Doctrine Of Equivalents

Although Amgen does appeal the equivalents ruling under the district court's actual claim constructions (Br. 40, 42, 51-54), the district court correctly rejected Amgen's equivalents theory. Amgen bore the burden of showing "equivalency on a limitation-by-limitation basis." *Akzo Nobel Coatings v. Dow*

[8] Although Amgen accuses (Br. 45) the district court of "fail[ing] to consider" certain evidence, the court did not fail to consider anything; it stated the materials were "not relied on in this order." Appx5. Those materials did not create a factual dispute under the court's constructions—none shows that Sandoz's one-step, one-solution process has separate and sequential washing and eluting steps, or that Sandoz adds a washing solution that preserves protein binding and adds a different eluting solution that reverses protein binding. *E.g.*, Appx4883-4884; Appx4888-4895; Appx4895-4899; Appx4933-4934; Appx4942-4943; Appx4947-4948; Appx4950-4955.

Chem., 811 F.3d 1334, 1342 (Fed. Cir. 2016); *see* Appx12. This requires "particularized testimony and linking argument as to the insubstantiality of the differences between the claimed invention and the accused device or process, or with respect to the function, way, result test when such evidence is presented." *Advanced Steel Recovery v. X-Body Equip.*, 808 F.3d 1313, 1319 (Fed. Cir. 2015).

Amgen raised no triable fact issue of equivalency. As the district court concluded, Sandoz's accused process is substantially different from the claimed washing and eluting limitations. Appx12-13 (applying the function, way, result test). Amgen offered no evidence showing that Sandoz's process functions in substantially the same way as the washing and eluting limitations. Nor could it: "[t]he claimed method 'discloses a natural, logical order of steps' in which application of the refold solution is followed by a washing step and then an eluting step." Appx13. Sandoz's process functions in a substantially different way. There is no washing step followed by an eluting step. Sandoz's process "involves only one step: the continuous application of a single solution to the separation matrix." Appx13.

Even so, Amgen argues (Br. 52) that Sandoz's process functions substantially the same way by "generat[ing] compositionally distinct solutions for washing and eluting within Sandoz's column." According to Amgen (Br. 52), this

purported "*in situ* generation" of different solutions is insubstantially different from the "seriatim addition" of distinct solutions required by the claimed methods.

Amgen's reliance on that attorney argument cannot create a triable fact issue. Nor is it supported by its expert's scant, conclusory opinions. Amgen's expert, Dr. Richard Willson, baldly stated that, even if "the solution applied to the separation matrix must be something other than the refold solution itself, I nevertheless am of the opinion that 'washing the separation matrix'" and "'eluting protein from the separation matrix'" are "met equivalently." Appx5265-5266; Appx5271. Willson offered no justification for this "opinion." He instead provided only a three-sentence paragraph stating the refold solution could perform "substantially the same function" as separate washing and eluting solutions "in the same way" to "achieve substantially the same, if not the same, result." Appx5271-5272; Appx5265-5266. That was it; nothing more. Such conclusory statements cannot defeat summary judgment. *Akzo*, 811 F.3d at 1343; *Genentech v. Wellcome Found.*, 29 F.3d 1555, 1568 (Fed. Cir. 1994) (patentees cannot show equivalency with "speculative" or "conclusory" testimony).[9]

[9] Although Amgen cites (Br. 52) Willson's report and summary judgment declaration, his equivalents statements are word-for-word identical. *Compare* Appx5265-5266, *and* Appx5271-5272, *with* Appx4943-4944, *and* Appx4948-4949.

Indeed, in his deposition, Willson could not explain why the differences are insubstantial. Appx3942-3946. He retreated to his literal infringement theories: "I don't see any elements of the claim as constructed that are not present in the Sandoz process." Appx3942. When pressed, he said, "I think it infringes literally and *might* also infringe equivalently." Appx3943 (emphasis added). In opposing summary judgment, Amgen doubled down on that literal-infringement-based response, arguing that "unless and until the Court alters its current claim construction, there was no reason for Dr. Willson to have answered the questions … any differently." Appx4864. But opinions about literal infringement cannot carry Amgen's burden: "The evidence and argument on the doctrine of equivalents cannot merely be subsumed in plaintiff's case of literal infringement." *Lear Siegler v. Sealy Mattress*, 873 F.2d 1422, 1425 (Fed. Cir. 1989); *see Texas Instruments v. Cypress Semiconductor Corp.*, 90 F.3d 1558, 1567 (Fed. Cir. 1996) (same).

Unable to cite evidence, Amgen puts misplaced reliance (Br. 52) on *In re Omeprazole Patent Litigation*, 536 F.3d 1361 (Fed. Cir. 2008). Amgen argues that when a claim calls for adding a particular composition, the *in situ* generation of that composition is insubstantially different. But *Omeprazole* is not even an equivalents case. And unlike here, *Omeprazole* involved composition claims. *Id.* at 1365-66. That distinction is dispositive. A composition patent can be infringed

regardless of how the claimed compound is made. The Court held that the patentee "did not need to identify the process by which the infringing [compound] was produced; it was sufficient for it to show the presence of the claimed structure." *Id.* at 1371. What is claimed here, however, is *the process*. To infringe a claimed method, the alleged infringer "must have practiced all steps." *Lucent Techs. v. Gateway*, 580 F.3d 1301, 1317 (Fed. Cir. 2009). Amgen thus was required to show something it cannot: that Sandoz's process is equivalent to each limitation of the claimed process.

Amgen asserts (Br. 52-53) that the district court "did not evaluate infringement on a limitation-by-limitation basis." That is backwards. *Amgen* bore that burden. Appx4854; Appx4863-4864. Regardless, the court rejected Amgen's argument because Sandoz's one-step, one-solution process is substantially different from the separate washing and eluting limitations. That is a limitation-by-limitation analysis.

The district court's "way" conclusion is alone sufficient to reject Amgen's equivalents appeal. But the court also correctly held that Sandoz's process does not have similar functions or results to the claimed method, underscoring the significant differences. Appx12-13. Sandoz's flow through purification process removes a contaminant ([redacted]), so it will not interfere with later purification steps. Appx12. That is in essence what the claimed method sought to eliminate with the

requirement of "directly applying the refold solution to a separation matrix." Appx77 (col.22:21-24).

D. Even Were Amgen's Claim Construction Arguments Preserved, They Should Be Rejected And The Judgments Affirmed

Even were this Court to address Amgen's claim construction arguments, the constructions are correct, and the non-infringement judgments should be affirmed.

1. Claim 7 requires separate, sequential "washing" and "eluting" steps

The district court correctly held that claim 7 requires separate, sequential steps for washing and eluting. "[A] claim 'requires an ordering of steps when the claim language, as a matter of logic or grammar, requires that the steps be performed in the order written, or the specification directly or implicitly requires' an order of steps." *Mformation*, 764 F.3d at 1398; *Mantech Environmental Corp. v. Hudson Environmental Servs.*, 152 F.3d 1368, 1376 (Fed. Cir. 1998) (rejecting argument that steps could be performed in any order or at the same time due to the "sequential nature of the claim steps").

In *Mformation*, this Court imposed an order of steps, requiring each step to be completed before the next could begin. The claim stated: "delivering the command from the mailbox at the server to the wireless device by [1] establishing a connection between the wireless device and the server, [2] transmitting the contents of the mailbox from the server to the wireless device …." 764 F.3d at

1394 (emphasis omitted). The patent owner argued that the district court should not have imposed "a requirement that a connection must be completely established *before* the transmitting step begins." *Id.* at 1397. It argued the connection simply needed to be initiated before transmitting could begin, "as long as the connection is later completed." *Id.* This Court disagreed because, as a matter of logic, "connection" had to be established before a mail box can be "transmit[ted]" and that understanding accorded with the specification. *Id.* at 1400.

The same is true here: "as a matter of logic," washing must be completed before eluting. *Id.* at 1398. The reason is straightforward: "washing the separation matrix" requires actual washing. Appx77 (col.22:21-24). To wash away contaminants but not the protein, the washing step must keep the protein bound to the separation matrix. Appx44. Eluting requires the opposite reaction: the protein must be released "from the separation matrix." Appx77 (col.22:25-28). If these two steps occurred at once, "the protein captured by the separation matrix could once again comingle with the contaminants and components to be washed away." Appx46. Amgen thus is wrong in asserting (Br. 41) that "[n]othing in the claims requires that washing and eluting be temporally distinct." The "sequential nature of the claim steps" themselves dictates that requirement. *Mantech*, 152 F.3d at 1376 (finding a sequential nature of steps because "wells" (the first step) needed

to be "provided" before "acetic acid" (the second step) could be introduced "via the wells").

The specification dispels any doubt. *Mformation*, 764 F.3d at 1398 (examining whether "the specification directly or implicitly requires an order of steps" (internal quotation omitted)). It not only explicitly requires a specific order of steps, it dictates they must be separate. The specification states: "After the separation matrix with which the protein has associated has been washed, the protein of interest is eluted using an appropriate solution (e.g., a low pH buffered solution or a salt solution) to form an elution pool comprising the protein of interest." Appx74 (col.15:60-64); Appx76 (col.19:44-46) (same). This means what it says: eluting does not begin until after washing ends—that is, after the separation matrix "has been *washed*." This makes sense: if washing and eluting were to occur contemporaneously, the elution pool would contain far more than the protein of interest; it would contain the contaminants from the refold solution that are being washed off during the washing step.

Nor could the two steps occur at the same time. The specification teaches that the washing step must "preserve protein binding" to separate the contaminants from the protein bound to the separation matrix. Appx74 (col.15:55-57). The eluting step does the opposite: it "interferes with the binding" to release the protein. Appx74 (col.15:56-66); *see* Appx44-46. Even so, Amgen's proposed

construction would require the protein to both bind and unbind to the matrix at the same time. That cannot be correct. Even Amgen's expert, Willson, conceded that these are "opposite" directives. Appx6798 (admitting that "I think their directions are opposite, yes," referring to "preserve binding" and "reverse binding"); *see also* Appx3804-3806 (Sandoz's expert Dr. Nigel Titchener-Hooker) (explaining that if washing and eluting occurred simultaneously both the protein and contaminants would comingle).

Amgen does not confront these problems. Its brief contains little if any developed argument for its assertion that the steps are not separate and sequential. Amgen baldly asserts that the claims do not require it (Br. 41) and that simultaneous washing and eluting must be possible because there is supposedly "no temporal pause or other break between washing and eluting" in Example 3 of the specification (Br. 43 (citing Appx76 (col.20:34-41))). Arguments that are not appropriately developed are waived. *Monsanto*, 459 F.3d at 1341.

Even were these few sentences sufficient, Amgen is mistaken. As discussed, the claim does require it. As for Example 3, Amgen has conceded it is not an embodiment of claim 7. Appx3881-3882; Appx6399-6400. Regardless, like the rest of the intrinsic record, Example 3 teaches three separate, sequential steps with three distinct solutions. First, Example 3 states that washing occurs "[a]fter loading" of the refold solution, so the loading of the refold solution cannot be "the

adding" of the washing solution. Appx76 (col.20:34). It further explains that the column is washed two times with two different solutions. Appx76 (col.20:34-36). And it teaches that "[t]he protein of interest was recovered from the resin by gradient elution." Appx76 (col.20:36-41). This elution involves the sequential introduction of a new solution containing an increasing salt concentration, not the washing solution (which has no salt). Entirely missing from Example 3 is any indication that these steps occurred contemporaneously.[10]

Given this requirement of separate, sequential steps, the district court correctly rejected Amgen's infringement arguments (*supra* Parts I.B, I.C)—a sufficient ground to affirm.

2. The "washing" and "eluting" steps require adding different solutions

The district court also correctly concluded that the washing and eluting steps each require adding a solution with an opposite directive, so the same solution cannot be added for both. Appx48. The intrinsic record compels this construction. The specification teaches that the relevant solutions do different things. They interact with the matrix in different ways once the refold solution, containing the protein to be purified and contaminants, has been applied to the matrix and the

[10] Although Amgen accuses the district court of "ignor[ing]" this example (Br. 43), the court cannot be faulted for not mentioning what Amgen never briefed. Amgen made only a passing reference to Example 3 during the summary judgment hearing, when its counsel acknowledged "[t]his was not in the briefs." Appx7038.

protein has bound to the resin. Appx74 (col.15:43-44). The specification explains that the wash buffer must be "compatible with both the protein and the matrix." Appx74 (col.15:48-49). In particular, the wash buffer is "chosen to optimize the chromatography conditions, preserve protein binding, and to retain the desired characteristic of the protein of interest." Appx74 (col.15:55-57). These characteristics are important: by being chosen to preserve protein binding, the washing solution ensures that only the contaminants from the refold solution are washed away.[11]

The specification teaches the opposite for eluting. Eluting requires "a solution that interferes with the binding of the adsorbent component of the separation matrix to the protein." Appx74 (col.15:47-16:9). Unlike the washing solution, the eluting solution must stop the binding between the protein and the matrix, so the protein can be recovered separately in "an elution pool comprising the protein of interest." Appx74 (col.15:62-63). Given the opposite interactions these two solutions must have with the protein and the matrix, the district court

[11] Amgen nit-picks the district court: "The specification does not say that the wash buffer is 'optimized to preserve protein binding,' even though the district court puts that phrase in quotation marks." Br. 43. But the specification states 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." Appx74 (col.15:55-57). Regardless of whether the buffer is chosen to "preserve protein binding" or "optimized to preserve protein binding," the specification teaches that it must preserve protein binding.

rightly concluded that the two solutions could not be the same. Appx44-45 ("washing the separation matrix" requires a solution that "preserv[es] binding of the protein to be purified"); Appx48 (eluting solution "reverses the binding of the purified protein to the separation matrix").

Amgen argues (Br. 41) that claim 7 does not "specify what solutions are used for washing and eluting" and does "not even use the word 'solution' but merely refer[s] to the actions of 'washing[']and 'eluting.'" But *Amgen* proposed the phrase "adding a solution" in its constructions for washing and eluting. Appx44-45. And Amgen did not propose that any solution could meet the washing and eluting requirements. Like Sandoz, Amgen recognized that washing and eluting require solutions with certain characteristics. Appx44-45 (Amgen arguing that the washing solution "remove[s] materials in the refold solution that do not interact with the separation matrix" and the eluting solution "revers[es] the interactions between protein and the separation matrix"). Amgen cannot disavow those positions now. *Conoco v. Energy & Envtl. Int'l*, 460 F.3d 1349, 1358-59 (Fed. Cir. 2006) (holding that a party cannot "alter the scope of the claim construction positions it took below").

Regardless, Amgen is wrong because the district court's constructions do not require the application of a specific solution. Amgen asserts (in another argument it never made to the district court) that when the inventors wanted to limit a claim

to a specific solution, they knew how to do so. Br. 41. Amgen points to dependent claim 18, which recites: "[t]he method of claim 1 or 7, further comprising the step of washing the separation matrix with a regeneration agent." Appx77 (col.22:62-63). But even were claim differentiation applied to claims 7 and 18, Amgen's argument would mean only that claim 7 encompasses more washing solutions than "a regeneration agent." The district court's construction accords with that notion. It 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. Appx48. Amgen nowhere explains how the application of a single solution could meet those opposite requirements. And skilled artisans knew no such solution existed. Appx3796-3809 (Titchener-Hooker).[12]

Amgen also suggests (Br. 42) that the specification's reference to "any composition" for washing and an "appropriate solution" for eluting means the washing and eluting solutions can be almost anything. Not so. Those phrases do not mean that a single solution can be added for washing *and* eluting, or that the washing or eluting solution could be the refold solution that was introduced earlier

[12] Amgen's reliance on claim 18 is wrong for another reason. Claim 18's "further comprising" language recites an additional washing step to clean and preserve the separation matrix for future use, after the protein already has been recovered. Appx67-68 (col.2:60-3:6); Appx75 (col.17:8-46). This additional step has nothing to do with claim 7's washing requirement.

in the claim. It means that the adding of any new solution that meets the respective requirements of either the washing or the eluting step practices that particular step of the claim.

Amgen argues (Br. 42) that the specification provides an example where a single solution "gradually changes over time to achieve washing and eluting." According to Amgen (Br. 44), one solution becomes a different solution "*in situ*"—that is, the solution evolves to accomplish both purposes. Amgen says Example 3 discloses such a "gradient elution," where "eluting begins with the *same* solution used to wash the column—30 mM MES solution at pH 6.0—and then the salt concentration is gradually increased to cause the protein to become unbound." Br. 42-43 (footnote omitted).

But in Example 3, no single solution is applied to the column for both washing and eluting. Rather, the matrix is washed twice: "with 30 mM MES, pH 4.5" and "30 mM MES; pH 6.0." Appx76 (col.20:34-36). Eluting follows with the application of a gradient elution "between 30 mM MES; pH 6.0 and 30 mM MES, 500 mM NaCL; pH 6.0." Appx76 (col.20:38-39). These solutions have different compositions. The eluting solution has NaCL—*i.e.*, salt. The washing solution does not. The washing solution therefore does not become the eluting solution *in situ*; eluting only begins when salt is added. Appx76 (col.20:34-41).

Indeed, Amgen admits as much. *E.g.*, Br. 42 (eluting occurs "by increasing the salt concentration"), 43.[13]

Given claim 7's requirement of adding different solutions at each of the washing and eluting steps, the district court correctly held this was an independent basis to reject Amgen's infringement arguments (*supra* Parts I.A., I.B)—another independent basis to affirm.

II. THE DISTRICT COURT DID NOT ABUSE ITS DISCRETION IN DENYING AMGEN'S RULE 56(D) MOTION

The district court properly exercised its broad discretion in denying Amgen's Rule 56(d) motion. Amgen had ample opportunity to take discovery regarding Sandoz's plans to replace the resin in its separation matrix, and the district court correctly concluded that the planned process would not infringe.

Rule 56(d) required Amgen to show that "(1) it has set forth in affidavit form the specific facts it hopes to elicit from further discovery; (2) the facts sought exist; and (3) the sought-after facts are essential to oppose summary judgment." *Family Home*, 525 F.3d at 827. "The mere hope that further evidence may develop

[13] In the other examples, the washing and eluting solutions also are indisputably different. Appx75 (col.18:12-21) (Example 1: washing with "10 mM Tris; pH 8.0"; eluting with "50 mM sodium acetate, pH 3.1"); Appx76 (col.19:16-18) (Example 2: washing with "25 mM Tris, 100 Mm sodium chloride; pH 7.4, or similar buffered solution"; eluting with "100 mM sodium acetate, pH 3.7"); Appx77 (col.21:15-28) (Example 4: washing with "25 mM Tris, 100 mM sodium chloride; pH 7.4"; eluting with "100 mM sodium acetate, pH 3.7").

prior to trial is an insufficient basis for a continuance." *Cont'l Mar. of S.F. v. Pacific Coast Metal*, 817 F.2d 1391, 1395 (9th Cir. 1987).

The district court correctly held that Amgen did not meet these requirements. The specific facts Amgen hopes to elicit—changes to Sandoz's "column diameter, bed height, loading time and residence time"—are "not material" to infringement. Appx14. Even with a different resin, "Sandoz's process will still not contain an eluting step that follows a washing step, as required by claim 7's (f) and (g) elements." Appx14-15. Sandoz's process still will add "only one continuous step and only one solution." Appx14.

Amgen nonetheless contends (Br. 55-57) that it could not oppose summary judgment until Sandoz submits information to the FDA concerning the new resin and Amgen obtains unnamed "source documents" and "technical details." Amgen's own expert refutes that contention. Willson did not need additional documents or technical details to opine that Sandoz's AEX step, using either [redacted] or [redacted], would infringe claim 7. Willson stated that Sandoz's old and new resins are [redacted] Appx6426-6428. Even if the new resin requires different [redacted] and [redacted] Willson's infringement analysis would not change. Appx5277; Appx3947.

Having not demonstrated that any additional facts would have made a difference, Amgen argues process, wrongly asserting it was denied "the

opportunity to take discovery essential to its opposition." Br. 55 (citing *Baron Services v. Media Weather Innovations*, 717 F.3d 907 (Fed. Cir. 2013)). But Amgen had every opportunity to take discovery on the change in resin; it cannot argue surprise. Sandoz informed Amgen of its plans to use a replacement resin in June 2016—more than 17 months before Amgen filed its Rule 56(d) motion. Appx6430. Amgen did not respond. In March 2017, Sandoz provided Amgen a 98-page scientific report related to the change in resin. Appx6432-6529. Again, Amgen did not respond. Even so, Amgen deposed several of Sandoz's witnesses about the scientific report, among other "[d]etails regarding any proposed or actual changes to the use of [redacted] in the AEX step." Appx6536; *see* Appx6548-6558; Appx6564-6574; Appx6582-6612. After those depositions, Sandoz produced still more information, giving Amgen batch records for Sandoz's commercial-scale process using the replacement resin as well as four laboratory notebooks. Appx6419; Appx5029-5030.

Amgen has never explained how additional discovery is essential to opposing summary judgment. Nor has it explained its lack of diligence during discovery, which is reason alone to affirm the district court: "A [Rule 56(d)] movant cannot complain if it fails diligently to pursue discovery before summary judgment." *Mackey v. Pioneer Nat'l Bank*, 867 F.2d 520, 524 (9th Cir. 1989); *see*

Cornwell v. Electra Cent. Credit Union, 439 F.3d 1018, 1026 (9th Cir. 2006) (same).

Amgen ignores these facts, which readily distinguish this case from *Baron*. Unlike here, the *Baron* district court granted summary judgment of non-infringement before construing the disputed patent, before plaintiff could review crucial evidence (the allegedly infringing source code), and before plaintiff could depose any witnesses. *Baron*, 717 F.3d at 910-12. It did so even though plaintiff "diligently pursued that discovery" and "adequately explained how that additional discovery was relevant and essential for its opposition." *Id.* at 912-14. None of that happened here.

Amgen also suggests (Br. 56-57) the district court's ruling will preclude it from alleging infringement in the future, "even if Sandoz makes further, entirely new changes to the modified process." Were Amgen's concerns correct, that could be said of any non-infringement ruling. But as the district court explained to Amgen's counsel at the summary judgment hearing, a non-infringement ruling "doesn't preclude you from arguing that your patent is subsequently infringed." Appx7059. "If this becomes a material alteration on their part, … your rights are not negatively impacted; you bring a new claim." Appx7059. Amgen's counsel acknowledged as much, Appx7059, stating that "if Your Honor were to rule

against us, but then there was a material change, we would come back." Appx7060.

Amgen is likewise mistaken in asserting a violation of 35 U.S.C. § 271(e)(2)(C), which Amgen argues requires "a comparison of the patent claims to the process that Sandoz will likely use to make its products." Br. 57. In the Hatch-Waxman context, this Court has held that "[t]he only difference in actions brought under § 271(e)(2) is that the allegedly infringing drug has not yet been marketed and therefore the question of infringement must focus on what the ANDA applicant will likely market if its application is approved, an act that has not yet occurred." *Glaxo v. Novopharm*, 110 F. 3d 1562, 1569 (Fed. Cir. 1997). Even assuming that analysis applies here, the district court complied with it. It based its non-infringement ruling on "[w]hat is likely to be sold, or, preferably, what will be sold." *Id*. at 1570; *see* Appx14. Amgen possessed and presented to the district court information related to Sandoz's abbreviated biologics license application, materials Sandoz submitted to the FDA, "and other pertinent evidence provided by the parties," including the information regarding Sandoz's planned change in resin. *Glaxo*, 110 F.3d at 1570; *see* Appx5207; Appx5287-5291. Based on that evidence, the district court concluded that Sandoz's process did not infringe, regardless of the resin Sandoz used. Appx14-15. This is so because

Sandoz's process involves, and will continue to involve, one step and one solution, not the multiple steps and multiple solutions that claim 7 requires. Appx14-15.[14]

Indeed, Amgen's counsel conceded that a change in resin would make no difference on the issues here. At the summary judgment hearing, he told the district court: if "the Court concludes that there has to be three discre[te] solutions added at the top, then I think that's a difference that would not be implicated." Appx7056-7057. He continued, "[i]f this is being decided on the issue of claim construction, I don't think it makes – makes any difference." Appx7057. Amgen's concession is fatal to its arguments on appeal. The district court acted well within its wide discretion in denying Amgen's request for delay.

III. THE DISTRICT COURT CORRECTLY CONSTRUED THE CHALLENGED LIMITATION OF THE '427 PATENT, UNDER WHICH AMGEN STIPULATED TO NON-INFRINGEMENT

The district court also correctly construed the challenged limitation of claim 1 of the '427 patent. The claim recites a "method of treating a disease," like cancer. Appx85 (col.10:24). It has two steps: (1) the administration of G-CSF in a "stem cell mobilizing-effective amount," and (2) the administration of a

[14] Contrary to Amgen's suggestion (Br. 33, 57), this case is unlike *Sunovion Pharmaceuticals v. Teva Pharmaceuticals*, 731 F.3d 1271 (Fed. Cir. 2013). There, the ANDA application infringed the asserted claims, and this Court held that "[s]imply saying 'But I won't do it' is not enough to avoid infringement." *Id.* at 1280. Here, Sandoz's application, the materials it has submitted to the FDA, and all the other record evidence demonstrate that Sandoz's process, regardless of the resin used, does not infringe claim 7.

chemotherapeutic agent in "a disease treating-effective amount." Appx85 (col.10:26-30).

Despite the different language in these steps, Amgen argues that both G-CSF and a chemotherapeutic agent need to be administered in an amount to mobilize stem cells. It further contends that a chemotherapeutic agent does not need to be administered in an amount effective to treat a disease, like cancer. Amgen's construction would eliminate the claim's distinction between G-CSF and a chemotherapeutic agent. It would read "disease treating" out of the claim. This Court should reject Amgen's attempt to rewrite its claim.[15]

A. Claim 1's Plain Language Dictates The District Court's Construction

The district court's construction follows from the settled rule that, absent contrary evidence, "different terms have different meanings." *PPC Broadband v. Corning Optical Commc'ns*, 815 F.3d 747, 752-53 (Fed. Cir. 2016); *Augme Techs. v. Yahoo!*, 755 F.3d 1326, 1333-34 (Fed. Cir. 2014).

In *Augme*, this Court applied that rule: the claims recited an "embedded first code module" and a second code module that is "retrieved" or "downloaded." 755 F.3d at 1332. The Court held this "distinction creates a presumption that

[15] Although Amgen's Statement of Issues refers to claim 1's "chemotherapeutic agent" (Br. 4), Amgen makes no argument about that term's construction. Amgen's argument is directed to the term "disease treating-effective amount of at least one chemotherapeutic agent."

'embedded' means something different than 'retrieved' or 'downloaded.'" *Id.* at 1333. The specification reinforced that distinction by describing an "embedded code module" in ways that would make little sense if (as the patent owner contended) "embedded code" *included* code that was separately "retrieved" or "downloaded." *Id.* The Court thus rejected a construction of the claims that "would render meaningless the distinction between the embedded first code module and the downloaded or retrieved second code module." *Id.*

So too here. Claim 1 uses different terms to describe the administration of G-CSF and a chemotherapeutic agent. The administration of G-CSF requires an amount effective for "hematopoietic stem cell mobilizing." Appx85 (col.10:28). The administration of a chemotherapeutic agent requires a "disease treating-effective amount." Appx85 (col.10:29-30). Based on these differences, the district court correctly held that the terms have different meanings. Appx27 ("Here, the patentee chose to use two different words, and thus the two terms presumably carry different meanings."). The claimed G-CSF is for stem cell mobilizing; the claimed chemotherapeutic agent is for disease treating. Appx27. The district court rejected Amgen's construction (Appx27), which would eliminate "disease treating" from the claimed method: "an amount of at least one chemotherapeutic agent sufficient to enhance the mobilization of stem cells for recovery from the blood for subsequent peripheral transplantation." Appx26 (Amgen's construction).

The preamble reinforces the district court's construction, emphasizing that the claimed method is directed to treating a *disease*. The preamble states: "A method of treating a disease requiring peripheral stem cell transplantation in a patient in need of such treatment." Appx85 (col.10:24-25). Peripheral stem cell transplantation, as recited in the claim, is not itself an independent treatment for a disease. Skilled artisans knew (and the district court found as fact) that the type of peripheral stem cell transplantation in the claimed method only counteracts the side effects of chemotherapy. It does not independently treat a disease. Appx2684-2685.

Relying on Sandoz's expert Dr. Negrin, the district court found as fact that there are "two types of stem-cell transplants: allogeneic transplants and autologous transplants." Appx26 n.3; *see* Appx2670-2690; Appx3060-3070. Allogeneic transplants are disease-treating. In allogeneic transplants, stem cells are collected from a healthy donor and transplanted into the patient to treat certain cancers. Appx26 n.3; *see* Appx3062-3063. The transplanted stem cells from the healthy donor will exhibit an immune response against tumor cells in the recipient patient. Appx3063. But autologous transplants are not disease treating; "autologous transplants involve using the patient's own stem cells" and "do not treat diseases; they counteract the negative side effects of disease treatments such as myletoxic chemotherapy or radiation." Appx26 n.3; *see* Appx3062-3063. Amgen has not

challenged this finding as clearly erroneous, *Teva*, 135 S. Ct. at 836-37, and it is too late now, *SmithKline*, 439 F.3d at 1319.

That finding further supported the district court's conclusion that claim 1's stem cell transplantation is not itself a treatment for a disease. The court recognized that "[t]he '427 Patent obviously addresses autologous transplants, not allogenic transplants." Appx26 n.3. The claimed method addresses only the transplantation of a patient's own stem cells, and the patent discloses no other type of transplant. Appx81 (col.1:44-47) (citing "investigations on the use of G-CSF in association with high-dosage chemotherapies in autologous bone marrow transplantations"); Amgen Br. 28, 60. Amgen thus cannot be right that "disease treating" refers to mobilization of stem cells, as mobilization is not itself a disease treatment.

Amgen likewise is mistaken in relying on *Abbott Labs. v. Baxter Pharm. Prod.*, 334 F.3d 1274 (Fed. Cir. 2003), and *Geneva Pharm.* v. *GlaxoSmithKline*, 349 F.3d 1373 (Fed Cir. 2003). Amgen argues (Br. 68) that those decisions hold that an "effective amount" is a term of art "that indicates the amount administered is the amount effective to achieve the goal of the claimed method." But those decisions are about *how much* a claim requires to effectuate a goal. *Geneva*, 349 F.3d at 1383; *Abbott*, 334 F.3d at 1277. The dispute here is about what *the goal* is: treating a disease or enhancing stem cell mobilization. Here, the district

court correctly held that because stem cell transplantation is not itself a disease treatment, claim 1 requires an amount effective to treat the disease for which the chemotherapeutic agent is prescribed.

Amgen also mistakenly argues (Br. 69) that dependent claim 4 supports its construction, asserting that claim "specifies a mechanism of action by which the chemotherapeutic agent is participating in the enhancement of stem cell mobilization." Claim 4 recites: "wherein at least one chemotherapeutic agent opens the endothelial barrier of the patient to render the endothelial barrier permeable for stem cells." Appx85 (col.10:35-39). The district court construed this limitation to mean "[d]isrupt the bone marrow endothelial barrier to facilitate permeability of the endothelial barrier for stem cells." Appx47. Claim 4 thus requires the chemotherapeutic agent to accomplish an *additional* function: disrupt the endothelial barrier. But as a dependent claim, it does not eliminate the requirement that a chemotherapeutic agent be administered in a "disease treating-effective amount." Amgen has offered no evidence that a disease treating-effective amount of a chemotherapeutic agent would not disrupt the endothelial barrier.

Regardless, Amgen's premise is wrong. Claim 4 is not directed to making it easier to collect stem cells from the peripheral blood. *Contra* Br. 69. Amgen lost that argument at claim construction and does not appeal it. Amgen argued that the additional limitation of claim 4 means: "Enhances the transit of stem cells from

the bone marrow to the peripheral blood." Appx2495. The district court rejected that proposal as contrary to the intrinsic record. Appx33 ("The trouble with Amgen's proposed construction is the fact it untethers the claim from the specification and the prosecution history.").

As Negrin explained, the scientific evidence upon which Amgen relied—three articles cited in the specification—merely hypothesized the effect the disruption of the endothelial barrier would have on the transit of stem cells. Appx2688-2689. If anything, these articles cut against Amgen. They all state that the disruption of the endothelial barrier would facilitate the transit of stem cells in the opposite direction: from the peripheral blood into the bone marrow. Appx2688-2689. For example, in discussing "transplantations," the specification cites Shirota as teaching that a "cytostatic agent facilitates the permeability of the endothelial barrier for stem cells." Appx81 (col.1:51-54) (citing Shirota et al. 1991 Exp. Hematol. 19:369-373). As Negrin explained, Shirota's abstract states: "We conclude that the cytotoxic conditioning regime, given with different objectives, may facilitate the traffic of transplanted cells into the compartment of the marrow." Appx2689. Facilitating the transplantation of stem cells into the bone marrow

after a chemotherapy agent has been administered to treat a disease is consistent with the district court's construction.[16]

B. Amgen's Specification-Based Arguments Cannot Rewrite Claim 1

Undeterred by the claim language, Amgen argues (Br. 63) that "disease treating-effective amount" refers "simply to the amount of chemotherapeutic agent used to enhance mobilization and not a purpose related to treatment of the underlying disease." Amgen resorts to the specification (Br. 64-65), citing some examples and statements where a chemotherapeutic agent is administered to enhance stem cell mobilization.

The specification is consistent with the district court's construction. The specification defines "chemotherapeutic agents" in terms of their disease-treating function: "exogenous substances suited and used to damage or destroy microorganisms, parasites or tumor cells." Appx81 (col.2:37-39); *see* Appx28-30. The specification teaches that stem cell transplantation addresses the side effects of treating cancer (a disease) with chemotherapy. "The use of high-dosage

[16] Amgen argues that the PCT Examiner "stated that the claims cover 'the use of *a combination of G-CSF and chemotherapy* (cyclophosphamide) *to mobilize stem cells* in the treatment of malignant diseases requiring peripheral stem cell transplantation.'" Br. 66 (quoting Appx2570-2571) (Amgen's bolding omitted). But that does not refer to the '427 patent; it refers to the PCT application's claims (PCT/EP96/05568), which Amgen did not make part of this case's record. Appx2567-2572. The Court should not accept Amgen's unfounded suggestion that the claims are the same.

chemotherapy or bone marrow ablation by irradiation requires subsequent incorporation of hematopoietic stem cells into the patient, in which case recovery of such cells is required." Appx81 (col.1:18-21). The specification thus teaches that cancer-treating doses of chemotherapy are part of the method: transplantation occurs only *after* a patient receives a "disease treating-effective amount" of a chemotherapeutic agent.

The parts of the specification Amgen cites are not to the contrary. They merely indicate a chemotherapy agent can *also* be administered to enhance stem cell mobilization; this is just an additional step not recited in claim 1. Br. 64-65. None of the passages Amgen cites precludes administration of a "disease treating-effective amount" (cancer-treating) of a chemotherapeutic agent as part of the claimed method. Nor would they: even under Amgen's reading of the specification, such a chemotherapeutic agent is administered (to treat a disease like cancer) *after* stem cell mobilization and leukapheresis, but *before* stem cell transplantation.

Thus, even assuming Amgen were correct about what the '427 patent discloses, that is not what the patent claims. Rather than draft a narrow claim that recited all the steps disclosed in the specification, the inventors decided to draft a broader one. "[T]he court may not rewrite unambiguous patent claim language."

Adams Respiratory Therapeutics v. Perrigo Co., 616 F.3d 1283, 1290 (Fed. Cir. 2010).

Amgen tried to correct this now-perceived deficiency by proposing a convoluted construction of "comprising." Amgen's proposed construction would rewrite claim 1 to make the disease-treating amount of a chemotherapeutic agent to be an unwritten additional step supposedly encompassed by comprising:

> G-CSF and the at least one chemotherapeutic agent are given in combination for purposes of stem cell mobilization, and the order in which G-CSF and the chemotherapeutic agent(s) are administered for that purpose is G-CSF first followed by the chemotherapeutic agent(s). Other than the foregoing stem cell mobilization step, the method for treating a disease requiring peripheral stem cell transplantation involves additional steps such as collection of cells by leukapheresis, myeloablative and/or myelotoxic therapy, and transplanting the collected peripheral stem cells back into the patient. The term "comprising" allows for these additional steps.

Appx2373-2374. According to Amgen, leukapheresis, myeloablative and/or myelotoxic therapy (such as a "disease treating-effective amount" of a chemotherapy agent), and transplanting the collected peripheral stem cells back into the patient, are the unclaimed "additional steps." The district court rightly rejected this convoluted interpretation of "comprising." Appx31. "Comprising" means "including but not limited to." Appx31 (quoting *Exergen Corp. v. Wal-Mart Stores*, 575 F.3d 1312, 1319 (Fed. Cir. 2009)). It is not an invitation to

import limitations from the specification into the claims. Appx31; *see Hill-Rom Servs. v. Stryker Corp.*, 755 F. 3d 1367, 1371 (Fed. Cir. 2014) ("While we read claims in view of the specification, of which they are a part, we do not read limitations from the embodiments in the specification into the claims.").

For similar reasons, Amgen is wrong when it argues that the district court's construction "improperly exclude[s] situations where the chemotherapeutic agent is prescribed only for stem cell mobilization rather than treatment of an underlying disease." Br. 63. Nothing in claim 1 precludes the administration of an additional chemotherapeutic agent. The court's construction expressly contemplated that possibility: "[t]he word 'comprising' means 'including but not limited to,' and allows for additional steps before, in between, and after the steps recited in the claim." Appx47.[17]

For all these reasons, the district court's construction of the challenged limitation should be affirmed. Under that construction, Amgen stipulated to non-infringement. Appx49-53.

CONCLUSION

The judgments should be affirmed.

[17] Amgen cites (Br. 69) another district court's construction of "disease treating-effective amount." But there, Apotex did not dispute Amgen's construction. *Amgen v. Apotex*, No. 15-61631-CIV, 2016 WL 1375566, at *6 (S.D. Fla. April 7, 2016). Regardless, this Court is not bound by that decision.

Dated: June 22, 2018

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the appellate CM/ECF system on June 22, 2018.

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I certify that the confidential version of this brief has been served, by agreement of the parties, on counsel for appellants at the following e-mail addresses:

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CERTIFICATE OF COMPLIANCE WITH RULE 32(a)

This brief complies with the type-volume limitation of Rule 32(a) of the Federal Rules of Appellate Procedure because it contains 13,975 words.

Dated: June 22, 2018 /s/ Deanne E. Maynard

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UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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