No. 2017-1010

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

AMGEN INC. AND AMGEN MANUFACTURING LTD.,

Plaintiffs-Appellants,

v.

APOTEX INC. AND APOTEX CORP.,

Defendants-Appellees.

On appeal from the United States District Court for the Southern District of Florida, Case No. 15-61631-CIV-COHN/SELTZER (Consolidated with 15-62081-CIV-COHN/SELTZER), Judge James I. Cohn

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RESPONSIVE BRIEF FOR DEFENDANTS-APPELLEES APOTEX INC. AND APOTEX CORP.

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CERTIFICATE OF INTEREST

Counsel for Appellees Apotex Inc. and Apotex Corp. certify the following:

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

   Apotex Inc. and Apotex Corp.

2. The names of the real parties in interest represented by me is:

   Apotex Inc. and Apotex Corp.

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

   Apotex Inc. is an Ontario corporation, and is wholly owned by Apotex Pharmaceuticals Holdings Inc. (APHI), which itself is wholly owned by Apotex Holdings, Inc. (AHI). Both APHI and AHI are Ontario corporations. Apotex Corp. is a Delaware corporation and is ultimately wholly owned by AHI. Neither Apotex Inc., Apotex Corp., APHI, nor AHI are publicly traded companies.

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 or agency or are expected to appear in this court are:

   COZEN O'CONNOR: Barry P. Golob, Kerry B. McTigue, W. Blake Coblentz, Aaron S. Lukas, Milton A. Marquis, Donald R. McPhail, Keri L. Schaubert, Ryan P. Bottegal, Eric J. Choi, Ryan Blaney, Martin B. Pavane, Marilyn Neiman, Simeon Brier, Matthew B. Criscuolo, and Julia Kim*

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Dated: January 17, 2017

/s/Barry P. Golob
Barry P. Golob

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TABLE OF ABBREVIATIONS

’138 Patent	U.S. Patent No. 8,952,138
aBLA	abbreviated Biologics License Application
Amgen	Amgen Inc. and Amgen Manufacturing Ltd.
ANDA	Abbreviated New Drug Application
Apotex	Apotex Inc. and Apotex Corp.
BPCIA	Biologics Price Competition and Innovation Act (2009) (codified at 42 U.S.C. § 262 *et seq*.)
FDA	U.S. Food & Drug Administration
g/L	grams per Liter (a unit of weight to volume)
L	Liter (a unit of volume)
mg/mL	milligrams per milliliter (a unit of weight to volume)
mL	milliliter (a unit of volume)
mM	milliMolar or milliMoles per Liter (a unit of concentration based on number of moles per unit volume)
NDA	New Drug Application
PTO	U.S. Patent & Trademark Office
w/v	weight to volume
w/w	weight to weight

STATEMENT OF RELATED CASES

This Court (Judges Wallach, Bryson, and Taranto) previously considered Apotex's appeal of the district court's grant of a preliminary injunction in the same action at issue in this appeal. *See Amgen Inc. v. Apotex Inc.*, 827 F.3d 1052 (Fed. Cir. 2016) (No. 16-1308). In that case, this Court issued an opinion on July 5, 2016, the mandate issued on August 11, 2016, and Apotex petitioned the Supreme Court for a writ of certiorari, which has been denied. *See Apotex Inc. v. Amgen Inc.*, No. 16-332, 2016 WL 4944497 (U.S. Dec. 12, 2016).

U.S. Patent No. 8,952,138 is currently the subject of a petition for inter partes review: *Apotex Inc. v. Amgen Inc.*, IPR2016-01542 (filed Aug. 5, 2016). As of the filing of this brief, the Patent Trial and Appeal Board has yet to determine whether to institute trial. No other related cases are known to counsel for Apotex to be pending in this or any other court that will directly affect or be affected by this Court's decision on appeal.

STATEMENT OF THE ISSUES

Pursuant to Federal Circuit Rule 28(b), Apotex disagrees with Amgen's Statement of the Issues, and therefore submits the following Statement of the Issues with respect to the specific areas of disagreement:

1. Did the district court clearly err in holding that Amgen did not meet its burden to show that the protein concentration in Apotex's refolding process is "at or above about 1 g/L" and thus Apotex does not infringe the asserted claims of the '138 Patent?

    a. Did the district court clearly err in holding that statements in Apotex's pre-litigation letters pursuant to the BPCIA information exchange are not binding and not probative of infringement?

    b. Under the doctrine of judicial estoppel, is Amgen precluded from arguing for a different construction of the term "protein" from that which it successfully argued for at the district court?

2. Under the correct claim construction, does claim 1 of the '138 Patent require "a protein . . . present in a volume at a concentration of 2.0 g/L or greater" to be present where protein refolding occurs—in the "refold mixture"?

3. Did the district court clearly err in holding that Amgen did not meet its burden to show that Apotex's refolding process does not use an equivalent of the claimed redox buffer strength?

4. Under the correct claim construction, does claim 1 of the ’138 Patent require that the “redox buffer strength” be determined by the relevant concentrations of oxidant and reductant in the refold mixture, and does the specification of the ’138 Patent effectively limit the redox buffer strength at a maximum concentration of 100 mM?

STATEMENT OF THE CASE

Per the March 2016 version of the Federal Circuit Rules of Practice, the Statement of the Case includes the facts relevant to the issues. Fed. Cir. R. 28(a)(7). Because Apotex disagrees with Amgen's Statement of the Facts and Amgen also failed to include facts relevant to the issues, Apotex includes the following Statement of the Case. Fed. Cir. R. 28(b).

I. The District Court's Findings of Fact Regarding Apotex's Manufacturing Process

The district court made the following factual findings concerning Apotex's manufacturing process based on the uncontroverted evidence presented at trial.

Apotex's manufacturing process includes an "upstream" process and a "downstream" process. (Appx18; *see* Appx3602; Appx5556-5561; Appx5868-5873.) During the upstream process, Apotex performs multiple washes of the inclusion bodies with a buffer and water, and those washing steps result in wet insoluble inclusion bodies. (Appx18; *see* Appx3610-3611; Appx5558-5559; Appx5870-5871.) The wet inclusion bodies are weighed at the conclusion of the upstream process and then frozen. (Appx18; *see* Appx3612-3613; Appx5587; Appx5896.) The inclusion bodies remain frozen in storage until they are used in Apotex's downstream process. (Appx18; *see* Appx3611; Appx5558; Appx5870.)

Apotex's aBLAs specify that between 144 and 216 grams of inclusion bodies are used to begin Apotex's downstream process. (Appx18; *see* Appx3612-

3613; Appx5592-5593; Appx5900-5901.) In addition to specifying the wet (i.e., including water) weight of inclusion bodies carried from the upstream process into Apotex's downstream process, Apotex's aBLAs also specify the amount of inclusion bodies as a concentration, which is equivalent to 0.9 to 1.4 g/L of Apotex's "Refolding Buffer" (described below). (Appx18; *see* Appx3612-3613; Appx5592-5594; Appx5900-5902.) This concentration is determined by dividing the lowest and highest amounts of inclusion bodies—144 grams and 216 grams, respectively—by the nominal volume of the refold buffer tank, which is 160 Liters. (Appx19; *see* Appx3613-3615; Appx4790.)

The first step in Apotex's downstream process is solubilization of the inclusion bodies. (Appx19; *see* Appx3611-3612; Appx5561; Appx5592; Appx5873; Appx5900.) To begin the solubilization process, the pre-weighed frozen inclusion bodies are thawed and re-suspended in a small amount of water, and then mixed with Apotex's solubilization buffer, which dissolves (i.e., solubilizes) the inclusion bodies in a solution having a volume of 7.2 L. (Appx19; *see* Appx3616-3617; Appx5592-5593; Appx5900-5901.) The solubilized inclusion bodies are then reacted with dithiothreitol ("DTT") to reduce the proteins into their primary, unfolded structure. (Appx19; *see* Appx5593; Appx5901.)

Apotex's aBLAs specify that filgrastim is present in the solubilization buffer at a concentration of 4.24 to 11.80 milligrams per milliliter ("mg/mL"), which is

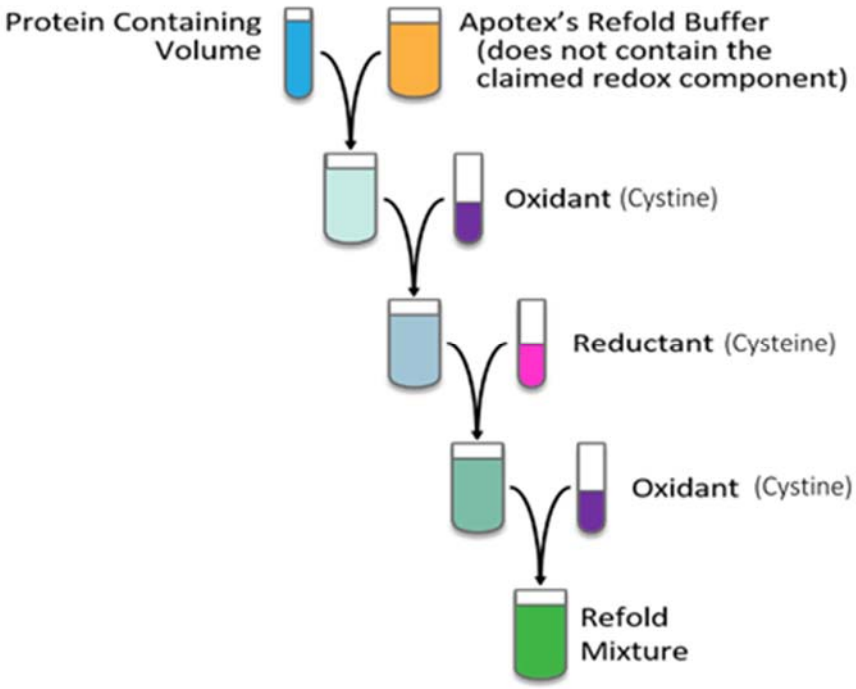
the same as 4.24 to 11.80 grams per Liter ("g/L"). (Appx19; *see* Appx3617-3618; Appx5592; Appx5595; Appx5900; Appx5902.)

Apotex's specification for the filgrastim concentration in Apotex's solubilization buffer limits the concentration of filgrastim that can be present in subsequent manufacturing processes, such as during protein refolding. (Appx19; Appx25; *see* Appx3618.) For example, the solubilization buffer (which has a volume of 7.2 L) is subsequently diluted to form the refold mixture (which has a volume of 160 L). (*See* Appx5593; Appx5901.) The maximum filgrastim concentration in Apotex's refold mixture is 0.531 g/L. (Appx19; *see* Appx3618; Appx4790.) This is calculated by simply taking the highest possible concentration of filgrastim in the solubilization buffer—11.80 mg/mL (or 11.80 g/L)—and multiplying by the volume of the solubilization buffer, which is 7.2 L, and then dividing by the volume of the refold mixture, which is 160 L. (Appx19-20; *see* Appx3618-3619; Appx4790.)

Apotex's aBLAs also specify that in the solubilization buffer, at least 75% of the total protein present must be filgrastim. (Appx20; *see* Appx3619-3620; Appx5595; Appx5902.) This specification for the filgrastim purity limits the amount of total protein in Apotex's refold mixture to a maximum of 0.708 g/L. (Appx20; *see* Appx3620; Appx4790.) This total protein amount is calculated by

dividing the maximum filgrastim concentration (0.531 g/L) by 0.75 (or dividing by 75%). (Appx20; *see* Appx3620-3621; Appx4790.)

After solubilization and reduction of the inclusion bodies, the refolding process begins the next step of the downstream process. (Appx20; *see* Appx3622; Appx5597; Appx5904.) Apotex's overview of its refolding process was shown at trial by the following schematic:



(Appx20). The composition and quantity of ingredients in Apotex's "Refolding Buffer", "Cystine Solution", and "Cysteine Solution" are shown below:

Table S.2.2-33: Refolding – Solution Composition

Solution	Component	Quantity
Refolding Buffer, pH 9.0 ± 0.2, Conductivity 17.5 ± 1.5 mS/cm	Arginine base	16.8 ± 0.02 kg
	Tris base	1940.00 ± 0.02 g
	Sorbitol	8.0 ± 0.8 kg
	EDTA disodium dihydrate	118.80 ± 0.02 g
	WFI Ph. Eur., IP, USP	q.s. to 168.0 kg
Cystine Solution	Cystine	13.2 ± 3.6 g
	0.2 N Hydrochloric Acid	440 ± 4 mL
Cysteine Solution	Cysteine	2.500 ± 0.025 g
	WFI Ph. Eur., IP, USP	32.00 ± 0.32 mL

Tris = Tris (hydroxymethyl) aminomethane; WFI = Water for Injection; USP: United State Pharmacopoeia

(Appx21; *see* Appx3622-3623; Appx5600; Appx5906).

The first step in Apotex's refolding process is to create Apotex's Refolding Buffer (orange) and to add it to the refolding vessel. (Appx21; *see* Appx3622.) The next step in Apotex's refolding process is the slow addition of solubilized and reduced inclusion bodies (royal blue) to Apotex's Refolding Buffer over 90 minutes. (Appx21; *see* Appx3438; Appx3623-3624.)

After the solubilized and reduced inclusion bodies are added to Apotex's Refolding Buffer, the Cystine Solution (purple) and Cysteine Solution (pink) are added in a stepwise manner. (Appx21; *see* Appx3442-3446; Appx3627.) According to the aBLAs, first 360 mL of the Cystine Solution (purple) is added to Apotex's Refolding Buffer. (Appx21; *see* Appx5597-5598; Appx5904-5905.) Next, 32 mL of the Cysteine Solution (pink) is added to Apotex's Refolding Buffer. (Appx21; *see* Appx5597-5598; Appx5904-5905.) Finally, 80 mL of Cystine Solution is added. (Appx21; *see* Appx5597-5598; Appx5904-5905.)

According to Apotex's aBLAs, the Cystine Solution and Cysteine Solution are added separately and in a stepwise manner for specifically defined reasons: the first Cystine addition is to "neutralize the DTT[,]" next, Cysteine is added to "break S-H (thiosulfide) bonds[,]" and the second Cystine addition is to "reduce the free S moieties so they [are] not available to form intramolecular disulfide bonds after refolding." (Appx21; Appx5969; Appx7150; *see* Appx3442-3446; Appx3627-3629.)

After the stepwise addition of the Cystine and Cysteine Solutions, Apotex incubates the refold mixture for at least 18 hours. (Appx21; *see* Appx3446-3447.) Following the incubation period, Apotex isolates the filgrastim protein using a series of purification steps. (Appx21; *see* Appx3447-3448.)

II. The District Court's Findings of Fact Regarding Infringement

A. Amgen Did Not Prove That Apotex's Specification for Inclusion Bodies Defines the Protein Concentration in the Refold Mixture

The district court did not find that Apotex's inclusion bodies are substantially pure protein. (Appx24.) Instead, the district court credited the testimony of Apotex witnesses, Dr. Jason Dowd and Dr. Anne Robinson, that Apotex's inclusion bodies are composed of approximately two-thirds water at the time they are weighed. (*Id.*) The district court found Amgen's theory that Apotex's inclusion body specification defines protein concentration, as explained

by its expert, Dr. Willson, does not sufficiently account for the water weight present in the inclusion bodies at the time of weighing. (*Id.*)

The district court found that Amgen "knew or should have known" that Apotex's inclusion bodies contained water. (*Id.*) Further, the district court found that Apotex's pre-litigation letters are not probative of the issue of protein concentration, are not filed with FDA or part of Apotex's aBLAs, and thus are not binding on Apotex. (*Id.*; *see* Appx34.) The district court also credited Dr. Dowd's trial testimony that the statements at issue in the pre-litigation letters are factually incorrect. (Appx24.)

The district court found that Apotex's aBLAs' specifications of 0.9 to 1.4 g/L merely require an amount of inclusion bodies to be used as an input in Apotex's refolding process, but do not specify the amount of protein present in those inclusion bodies. (Appx25.) Thus, the district court weighed the evidence and determined that Amgen failed to meet its burden to show by a preponderance of the evidence that Apotex's refolding process literally infringes the "refold mixture" limitation of claim 1 of the '138 Patent. (*Id.*)

B. Apotex's aBLAs' Specifications Specify a Protein Concentration Separate From an Inclusion Body Concentration

The district court determined that the maximum protein concentration in Apotex's refold mixture is limited by Apotex's aBLAs' specifications to 0.708 g/L. (*Id.*) The district court determined that the upper limit of the filgrastim

concentration in Apotex's refold mixture is 0.531 g/L. (*Id.*) The district court credited the testimony of Dr. Dowd in determining that if Apotex's manufacturing process was to deviate from the amount and quantity of filgrastim as specified in the Apotex aBLAs submitted to FDA, Apotex would be required to discard that batch. (Appx26.)

The district court found that Amgen cited no evidence to contradict Apotex's aBLAs' specifications which limit the maximum protein concentration in Apotex's refold mixture to 0.708 g/L. (*Id.*) Further, the district court found no infringement because these specifications directly address the infringement inquiry and define a protein refolding process having a total protein concentration in the refold mixture of less than "at or above about 1 g/L." (*Id.*)

C. Apotex's Refolding Process Does Not Include a Redox Component Having a Redox Buffer Strength of 2 to 100 mM or Its Equivalent

The district court found that it was undisputed that Apotex's process does not literally include the claimed redox component that has an oxidant (Cystine) and reductant (Cysteine) combined together outside the refold mixture. (Appx29.) The district court also found that there was no dispute that Apotex's process does not literally include the claimed redox buffer strength. (*Id.*) In reaching its non-infringement holding regarding the redox buffer strength limitation, the district court assumed, without deciding, that the Cysteine and Cystine solutions added in

a stepwise manner in Apotex's process is the equivalent of the claimed redox component. (*Id.*)

The district court found that Amgen did not prove by a preponderance of the evidence that Apotex's "hypothetical" redox component has a redox buffer strength that is equivalent to claim 1 of the '138 Patent. (*Id.*) The district court's finding was based on the court's determination that Amgen did not prove that the redox buffer strength of Apotex's hypothetical redox component was insubstantially different from the claimed redox buffer strength of 2 to 100 mM. (*Id.*) The district court determined that since the maximum volume of Apotex's hypothetical redox component is 476.32 mL, the redox buffer strength is 214 to 340 mM. (Appx29-30.) The district court found that to practice claim 1 of the '138 Patent, one would need to change Apotex's process and increase the total volume of the redox component to 1.0 to 1.6 L in order to deliver the same number of molecules of Cystine and Cysteine to the refold mixture as in Apotex's process. (Appx30.) The district court found that a volume of 1.0 to 1.6 L is two to three times greater than the volume of Apotex's hypothetical redox component. (*Id.*)

The district court found the difference between a volume of a redox component of 476.32 mL and a volume of 1.0 to 1.6 L, particularly when its components are added in a stepwise manner as in Apotex's process, is substantial. (*Id.*) The district court determined Amgen's evidence was insufficient that simply

increasing the redox component volume will serve substantially the same function in substantially the same way to achieve substantially the same result as practicing a volume with the claimed redox buffer strength. (*Id.*) In support of its conclusion, the district court stated that Amgen's expert, Dr. Willson, (1) did not specify what liquid would be used to increase the volume of Apotex's hypothetical redox component; (2) did not know where equivalence would be lost by increasing the volume of the redox component volume; and (3) did not perform experiments or present any evidence that increasing the volume of the redox component would result in an insubstantial difference. (Appx30-31.)

Finally, the district court found that a redox component volume of 1.0 to 1.6 L was not possible under Apotex's aBLAs. (Appx31.)

SUMMARY OF THE ARGUMENT

First, the district court did not clearly err in holding that Amgen failed to prove by a preponderance of the evidence that Apotex's refolding process uses a protein concentration "at or above about 1 g/L" in the refold mixture. (*See* Appx33-36.) After hearing the evidence submitted by Amgen and Apotex at trial, the district court found that Apotex's inclusion bodies are not wholly protein, but instead are on average about two-thirds water. (Appx23.) Additionally, because Apotex's inclusion bodies are wet at the time they are weighed (and contain mostly water), Apotex's aBLAs' specifications (0.9 to 1.4 g/L) for inclusion body

concentration in the refold mixture are not reliable for determining protein concentration in the refold mixture. (*Id.*) Further, as the district court held, this fact cannot be changed merely because Apotex's pre-litigation letters sent to Amgen pursuant to 42 U.S.C. § 262(*l*)(3)(B) incorrectly referred to inclusion body concentration as protein concentration, which is a determination that was not made in clear error. (Appx34-35.)

At trial, Amgen waived any evidentiary objections to the district court's findings of fact on these issues, and cannot show that the district court clearly erred in any of its findings. Instead, Amgen now attempts to conjure legal issues where none exist. For instance, even after admitting at closing arguments that Apotex is not bound by statements in its optional pre-litigation letters, Amgen now asks this Court to give those same pre-litigation letters evidentiary weight as a matter of law. (*See* Op. Br. at 45-46.) For the reasons discussed herein, the district court's findings that Amgen did not meet its burden of proof should be affirmed.

Second, the district court admitted documentary evidence and heard testimony that Apotex's aBLAs specify a process for protein refolding in which "the maximum total protein concentration allowable in Apotex's refold mixture is restricted at 0.708 g/L." (Appx25-26; Appx35.) Based on this evidence, the district court did not err in concluding that "Apotex's aBLAs['] specifications directly address the infringement inquiry and define a protein refolding process

having a total protein concentration less than 'at or above about 1 g/L protein.'" (Appx35 (citing *Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1279-80 (Fed. Cir. 2013)).)

Amgen does not dispute that Apotex's aBLAs define a maximum protein concentration of 0.708 g/L in the refold mixture, but argues that it is "entirely possible" that Apotex can exceed this maximum because its specifications are not so limiting. (Op. Br. at 61-64.) If that were so, then Apotex's aBLAs' specifications do not resolve the question of infringement, and under this Court's precedent, the proper analysis is to examine records reflective of Apotex's protein refolding process in order to determine whether Apotex is likely to manufacture its pegfilgrastim and filgrastim proteins by an infringing process. Upon consideration of Apotex's batch records, the district court found that each step in Apotex's manufacturing process is outlined therein, and heard uncontroverted testimony that "in the 91 times that Apotex has run its manufacturing process, the highest protein concentration in the refold mixture has been 0.56 g/L . . . ." (Appx27-28; Appx35-36.) Therefore, the district court did not clearly err in holding that "even if Apotex's aBLAs had been silent on the issue of protein concentration, Apotex's batch records show that the drug products it intends to market are manufactured by a non-infringing process." (Appx35.)

Third, the district court did not err in determining that Amgen did not meet its burden of showing that Apotex has a redox buffer strength that is equivalent to the redox buffer strength of claim 1 of the '138 Patent. (Appx36-38.) Amgen's equivalence theory requires an equivalent of an equivalent, and is thus incorrect as a matter of law. Further, Amgen failed to perform the correct analysis when it focused on equivalence in the refold mixture, not the redox component. (Appx37.) Finally, Amgen's equivalence theory has no boundary and would require Apotex to change its process and specifications, which Apotex is not allowed to do. (Appx38.)

ARGUMENT

I. The District Court's Rejection of Amgen's Infringement Theory That Was Based on Inclusion Body Concentration Should Be Affirmed

The district court did not clearly err in holding that Amgen failed to prove by a preponderance of the evidence that Apotex's refolding process uses a protein concentration "at or above about 1 g/L" in the refold mixture. (*See* Appx33-36.) Infringement is a question of fact, which this Court reviews for clear error. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1339 (Fed. Cir. 2003). A factual finding is only clearly erroneous if, despite some supporting evidence, the reviewing court is left with the "definite and firm conviction" that a mistake has been made. *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006); *see also*

Polaroid Corp. v. Eastman Kodak Co., 789 F.2d 1556, 1559 (Fed. Cir. 1986) ("The burden of overcoming the district court's factual findings is, as it should be, a heavy one.").

At trial, Amgen waived any evidentiary objections to the district court's findings of fact on these issues and cannot show that the district court clearly erred in any of its findings. Instead, Amgen now attempts to conjure legal issues where none exist. For the reasons discussed herein, the district court's findings that Amgen did not meet its burden of proof should be affirmed.

A. Apotex's Process Specifications for Inclusion Bodies in Its aBLAs Do Not Define Protein Concentration in Apotex's Refold Mixture

Amgen's infringement theory hinged upon its expert's conclusion that Apotex's inclusion bodies are equivalent to protein (Appx23-24), which the district court appropriately rejected based on the evidence presented at trial. (Appx24-25.) In concluding that Apotex's inclusion bodies contain mostly water, the district court considered and relied upon testimony from fact and expert witnesses concerning Apotex's aBLAs and batch records. (Appx24.) Further, the district court expressly rejected Amgen's proffered testimony that Apotex's aBLAs' specifications for inclusion bodies were interchangeable with protein concentration in the refold mixture, because Amgen's expert, Dr. Willson, did "not sufficiently account for the water weight present in the inclusion bodies at the time of weighing." (*Id.*) A district court has broad discretion in determining witness

credibility, and the reviewing court gives great deference to those determinations. *See Energy Capital Corp. v. United States*, 302 F.3d 1314, 1329 (Fed. Cir. 2002); *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1378-79 (Fed. Cir. 2000) (quoting *Carroll Touch, Inc. v. Electro Mech. Sys., Inc.*, 15 F.3d 1573, 1580 (Fed. Cir. 1993)). This Court should therefore affirm the district court's judgment that Amgen failed to prove infringement by a preponderance of the evidence, because the district court's factual findings that directly contradict Amgen's infringement theory are not clearly erroneous.

On appeal, Amgen does not dispute that Apotex's inclusion bodies contain mostly water. (*See* Op. Br. at 64.) Instead, Amgen argues this fact is irrelevant because Apotex's aBLAs do not include a specification for the water that is admittedly present in Apotex's inclusion bodies. (*Id.*) However, to be clear, Amgen admits that the aBLAs' specifications it relies upon are for inclusion body concentration—not protein. (*See, e.g.*, *id.* at 51.) Instead, it was merely Amgen's assertion that Apotex's inclusion bodies were primarily, if not wholly, protein. (Appx34.) Having heard the evidence and weighed the credibility of Amgen's expert under cross-examination, the district court did not clearly err in rejecting Amgen's assertions. (Appx22-25; Appx34.)

It was always Amgen's burden, under its only infringement theory, to prove that Apotex's inclusion bodies are wholly protein. *See Glaxo, Inc. v. Novopharm,*

Ltd., 110 F.3d 1562, 1568 (Fed. Cir. 1997) (holding that the burden of proving infringement is never shifted to the alleged infringer). As noted above, Apotex's aBLAs' specifications that Amgen chose to rely upon include no requirement for any amount of protein or water to be present in the inclusion bodies. Because the aBLAs' specifications that Amgen chose to rely upon are silent as to their protein concentration, Amgen's infringement case hinged on the credibility of its expert's analysis. As the district court found, not in clear error, Amgen's expert failed to account for the water present in Apotex's inclusion bodies. (Appx23-24; *see* Appx3192-3193; Appx3551-3552.) Further, Amgen elected not to conduct any independent analysis of Apotex's inclusion bodies. (Appx3188 at 73:17-19.)

Amgen's claims of surprise that Apotex's inclusion bodies are not wholly protein ring hollow, as Amgen had ample time to review Apotex's aBLAs and batch records. (*See, e.g.*, Op. Br. at 24.) Indeed, when asked whether he did not account for the water (present in Apotex's inclusion bodies) for any calculation of a protein concentration between 0.9 and 1.4 g/L, Amgen's expert testified that:

> I think that's true. I'll note that there are places where Apotex talks about water, and *I was a bit worried about it*. And there are places where there's a great deal of water and places where there is less water, but you're correct, I think.

(Appx3192-3193 at 77:22-78:2 (emphasis added).) Thus, Amgen can hardly claim that Apotex's "water theory" (which is not a theory at all, but instead a fact) was first presented in Apotex's rebuttal case. (*See* Op. Br. at 56.)

For these reasons, the district court's judgment that Amgen failed to meet its burden of proving infringement because Apotex's inclusion bodies are not wholly protein should be affirmed.

B. The District Court Did Not Clearly Err in Finding That Apotex's Pre-Litigation Letters Are Not Probative of Infringement, and Amgen's Argument That These Letters Are Binding Has Been Waived

Amgen's infringement case also relied upon pre-litigation letters that Apotex's counsel sent to Amgen's counsel pursuant to the optional pre-litigation exchange of the BPCIA (42 U.S.C. § 262(*l*)(3)-(5), (*l*)(3)(B)). (Appx3085-3086 (discussing Appx7396 and Appx7447).) It is undisputed that these optional pre-litigation letters are not part of Apotex's aBLAs, were never filed with FDA, and do not impact Apotex's process or the product that FDA may approve. (Appx34.) Thus, the district court did not clearly err in finding that the pre-litigation letters are not probative of infringement, because it is Apotex's aBLA documents and batch records that are relevant to this inquiry. *See Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002) (stating that the relevant inquiry is whether the specifications set forth in an applicant's FDA regulatory filings define a drug

product that falls within the scope of an issued patent); *see also Ferring B.V. v. Watson Labs., Inc.-Fla*., 764 F.3d 1401, 1408-09 (Fed. Cir. 2014).

Amgen does not dispute that the statements in Apotex's pre-litigation letters are factually incorrect and plainly contradicted by Apotex's batch records, which reflect a maximum protein concentration of 0.56 g/L. (Op. Br. at 42; Appx19; *see* Appx3645-3646; Appx3666.) Instead, Amgen argues that the district court erred in crediting Dr. Dowd's testimony concerning the pre-litigation letters because he did not prepare the letters and had no knowledge of them prior to trial. (Op. Br. at 42, 48-49.) This is a red herring, as the pre-litigation letters have no bearing on the underlying facts concerning Apotex's manufacturing process as set forth in Apotex's aBLAs. (Appx34-35.) What is more, Amgen has waived any objection to the district court's consideration of Dr. Dowd's testimony that the pre-litigation letters were "factually incorrect." (Op. Br. at 49; Appx24); *see, e.g., Robert Bosch LLC v. Pylon Mgf. Corp.*, 659 F.3d 1142, 1154 n.5 (Fed. Cir. 2011) ("Because evidentiary objections not raised before the trial court are deemed waived, and we otherwise do not discern any plain error in the admission of this testimony, we do not accept [defendant's] arguments." (citing *Failla v. City of Passaic*, 146 F.3d 149, 159-60 (3d Cir. 1998))). Indeed, the testimony that Amgen takes issue with was elicited through Amgen's cross-examination of Dr. Dowd, and Amgen made no attempt to impeach Dr. Dowd or to strike his answers as non-responsive. (*See*

Appx3665-3668.) Further, Dr. Dowd's testimony was not speculative, but instead based on his personal knowledge of Apotex's manufacturing process—a process that he designed. (Appx3603-3605; Appx3667 at 84:6-21; *see* Appx3654 at 71:14-20.) Because district courts have broad discretion in determining witness credibility, this Court should defer to the district court's reliance upon Dr. Dowd's testimony—testimony that Amgen itself elicited. *Energy Capital*, 302 F.3d at 1329; *Ecolochem*, 227 F.3d at 1378-79 (quoting *Carroll*, 15 F.3d at 1580). For these reasons the district court's finding that Apotex's pre-litigation letters are not probative of infringement should be affirmed.

Recognizing its heavy burden to show that the district court's finding was incorrect, Amgen frames the evidentiary consideration of Apotex's pre-litigation letters as a question of law. (Op. Br. at 45-46.) Specifically, Amgen asks this Court to hold that facts asserted in a detailed statement under paragraph 262(*l*)(3)(B) are entitled to weight as a matter of law.[1] (*Id.* at 23-24, 45-46.) This argument has been waived. "Waiver is the intentional relinquishment and abandonment of a known right, which precludes appellate review." *United States*

[1] Amgen notably does not use the word "binding" in its request that this Court hold pre-litigation statements under paragraph 262(*l*)(3)(B) to be given "weight as a matter of law." (Op. Br. at 24.) However—to be clear—in seeking to override the district court's role in admitting and weighing evidence, Amgen now asks this Court to hold that pre-litigation statements under paragraph 262(*l*)(3)(B) be treated as binding party admissions.

v. Parker, 469 F.3d 1074, 1079 (7th Cir. 2006) (citing *United States v. Thigpen*, 456 F.3d 766, 769 (7th Cir. 2006)). In *Parker*, defendant's counsel admitted during closing argument a legal finding was satisfied, which foreclosed defendant's argument on appeal. *See id.* Here, at closing arguments, Amgen's counsel admitted that:

> *[I]n the letters from Apotex's counsel, I would like to be clear, we are not suggesting that those are in some way binding*; in other words, Apotex is precluded from raising different arguments. What we are saying is that the lawyers addressed this very issue looking at the documents that were submitted to the FDA and came up with an answer that is radically different from the one that they're now putting forth. That is, may not be limiting, but it is highly persuasive evidence that the new theory is not correct.

(Appx3807 (emphasis added).)[2] Thus, Amgen clearly waived any argument that statements made in pre-litigation letters under paragraph 262(*l*)(3)(B) are binding—or, in Amgen's phrasing—"entitled to weight as a matter of law[.]" (Op. Br. at 24.)

Nonetheless, should this Court find that Amgen has not waived this argument, then Apotex submits that there is no basis in the law for *de novo* review

[2] Apotex also notes that Amgen did not present the same infringement theory in its paragraph (*l*)(3)(C) statement as it relates to the redox buffer strength of 2 mM or greater limitation of claim 1 of the '138 Patent as it did at trial. (Appx11227-11228; *compare* Appx11272, *with* Appx3869-3879.) Thus, Apotex also finds Amgen's argument that parties should be held to its pre-litigation letters as disingenuous.

of the probative value of Apotex's pre-litigation letters. Despite Amgen's assertions, this is an evidentiary issue, not a statutory question. "Evidentiary rulings 'generally are committed to the very broad discretion of the trial judge, and they may constitute an abuse of discretion only if based on an erroneous conclusion of law, a clearly erroneous finding of fact or a manifest error in judgment.'" *United States v. Keck*, 643 F.3d 789, 795 (10th Cir. 2011) (quoting *Webb v. ABF Freight Sys., Inc.*, 155 F.3d 1230, 1246 (10th Cir. 1998)); *see Cook ex rel. Estate of Tessier v. Sheriff of Monroe Cty., Fla.*, 402 F.3d 1092, 1103-04 (11th Cir. 2005). None of these situations are present here. Moreover, affording any evidence weight as a matter of law is prohibited by Federal Rule of Evidence 104(e), which explicitly permits a party "to introduce before [the fact finder] evidence relevant to weight or credibility." Fed. R. Evid. 104(e); *see United States v. Dominguez*, No. 09-20989, 2010 WL 431877, at *1-2 (S.D. Fla. Feb. 2, 2010) (holding that a court's finding that evidence is admissible "does not prevent the defense from challenging this evidence at trial, in terms of any factors which bear upon the weight that the jury should accord such evidence.").

Here, once admitted as evidence, the district court found that Apotex's pre-litigation letters had no probative value precisely because other documents—namely, Apotex's aBLAs and batch records—contradicted Amgen's assertions. (Appx24.) If Apotex's pre-litigation letters were to be accorded evidentiary weight

as a matter of law, this would directly contradict the Federal Rules of Evidence that allow a party to introduce testimony that bears upon the weight of the evidence and require the finder of fact to accord evidentiary weight. Thus, there is no basis in the Federal Rules or law for Amgen's contention that the probative value of Apotex's pre-litigation letters is a question of law entitled to *de novo* review and should be accorded weight as a matter of law.

Nonetheless, Apotex submits there is no basis in the law for Amgen's contention that the optional pre-litigation letters outlined in paragraph (*l*)(3) of the BPCIA should be treated as binding admissions by a party. (Op. Br. at 45.) Indeed, as this Court has long held, litigants in the pharmaceutical arts who are statutorily required to provide notice to patent owners prior to litigation may freely modify or add claims and defenses in litigation. *See Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 549 F.3d 1381, 1389-90 (Fed. Cir. 2008) ("It is clear from the district court's opinion that it was not faulting Alphapharm or Mylan for the act of filing an ANDA that challenged the pioglitazone patent, nor did it limit the filers to the theories raised in their certification letters."). Further, Amgen incorrectly suggests that the factual basis for a certification made under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) is filed with FDA. (Op. Br. at 47.) In reality, the factual and legal bases underlying a "P-IV certification" is included in a letter and accompanied with a detailed statement that is sent only to the NDA holder and

patent owner—not filed with FDA. *See* 21 U.S.C. § 355(j)(2)(B) *et seq*. Moreover, notice letters are statutorily mandated, whereas the BPCIA's pre-litigation exchange is wholly optional. *See Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347, 1354-57 (Fed. Cir. 2015). It defies logic that an optional disclosure should be binding on a party when precedent holds that an analogous mandatory disclosure is non-binding. And, as this Court must surely recognize, holding that optional pre-litigation letters are binding would eliminate any reason for an aBLA-filer to follow these provisions of the BPCIA, effectively rendering these sections of the BPCIA superfluous.

Similar to an ANDA filer's notice under 21 U.S.C. § 355(j)(2)(B), Apotex's pre-litigation letters outlined Apotex's counsel's legal theories based on information available at that time. Notably, Apotex provided Amgen with its pre-litigation letters without the benefit of any disclosure from Amgen concerning its bases for infringement, its proposed claim constructions, or any discovery. (*See* Appx2048.) As Amgen acknowledges, Apotex could not have known that Amgen would argue for a claim construction whereby the only concentration limitation recited in claim 1 of the '138 Patent—"2.0 g/L or greater"—has nothing to do with protein refolding, or that the district court would insert a limitation into claim 1 requiring a "high protein concentration at or above 1 g/L" during protein refolding.

(*See* Op. Br. at 48.)[3] Nor could Apotex have known Amgen's position on the construction of the term "protein" in claim 1 of the '138 Patent. Therefore, aBLA filers, like ANDA filers, should not be precluded from modifying and adding claims and defenses during litigation, as this Court held in *Takeda*. *See* 549 F.3d at 1389-90.

Finally, Amgen's argument that Apotex did not assert additional legal theories, but sought to change facts, is also meritless. (Op. Br. at 47.) Apotex produced its aBLAs and supporting documents such as batch records to Amgen prior to sending its pre-litigation letters. (Appx7382; Appx7427.) As discussed above, there is no dispute that Apotex's aBLAs' specifications speak directly to the issue of infringement, and it would be legal error for the district court to have considered evidence beyond Apotex's aBLAs and batch records. *See Abbott*, 300 F.3d at 1373 (stating that the relevant inquiry is whether the specifications set forth in an applicant's FDA regulatory filings define a drug product that falls within the scope of an issued patent); *see also Ferring*, 764 F.3d at 1408-09.

[3] Under Amgen's theory, the logical conclusion would be that all pre-litigation letters are binding, including Amgen's statements. Notably, in its pre-litigation letters to Apotex, Amgen did not assert that the term "refold mixture" had a 1 g/L limitation, and likewise did not assert that Apotex infringed claim 1 of the '138 Patent because it had a protein concentration above 1 g/L in Apotex's refold mixture. (Appx11222-11229; Appx11267-11273.)

For these reasons, the district court was correct to rely upon this Court's precedent in *Takeda* in finding that Apotex's pre-litigation letters are not controlling of the infringement inquiry because they were not part of Apotex's aBLAs, were never filed with FDA, and do not impact Apotex's process that will be approved by FDA. (*See* Appx34-35.) Apotex respectfully submits that this holding should be affirmed. For these same reasons, Amgen's request that Apotex's pre-litigation letters be given probative weight as a matter of law should be denied.

II. The District Court's Non-Infringement Findings Based on Apotex's Use of a Non-Infringing Protein Concentration Should Be Affirmed

The district court concluded that Apotex's process for protein refolding, both as defined by Apotex's aBLAs and as used in practice (based on Apotex's batch records), does not infringe claim 1 of the '138 Patent. After a bench trial, this Court reviews a finding of non-infringement for clear error. *See Alza*, 464 F.3d at 1289; *see also Amgen v. Hoechst*, 314 F.3d at 1339. Under clear-error review, this Court defers to the district court's factual findings unless there is a "definite and firm conviction that a mistake has been made." *See Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1303 (Fed. Cir. 2015) (citing *U.S. Gypsum Co.*, 333 U.S. at 395); *see also Polaroid*, 789 F.2d at 1559 ("The burden of overcoming the district court's factual findings is, as it should be, a heavy one.").

A. The District Court Did Not Clearly Err in Holding That Apotex's aBLAs Define a Non-Infringing Protein Refolding Process

Apotex showed that its aBLAs' specifications allow a maximum total protein concentration in Apotex's refold mixture of 0.708 g/L. (Appx20; *see* Appx3619-3620; Appx5902.) Because Apotex is statutorily bound by its aBLAs' specifications, *see, e.g., Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc.*, 731 F.3d 1271, 1279 (Fed. Cir. 2013), there is no question that Apotex's aBLAs define a process that does not infringe claim 1 of the '138 Patent. *See also Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1186 (Fed. Cir. 2014); *In re Brimonidine Patent Litig.*, 643 F.3d 1366, 1377 (Fed. Cir. 2011); *Abbott*, 300 F.3d at 1373. Apotex is therefore entitled to judgment of non-infringement as a matter of law because its aBLAs include specifications that limit Apotex's protein refolding process "in a way that directly addresses the question of infringement." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1249 (Fed. Cir. 2000). The district court thus properly concluded that Apotex's aBLAs' specifications define a process that does not infringe any claim of the '138 Patent. (Appx22; Appx31.)

In response, Amgen argues that Apotex's aBLAs' specifications are not limiting. (Op. Br. at 17-19, 61-64.) That is, Amgen argues that Apotex *could* violate the '138 Patent based on its aBLAs' specifications because its filgrastim concentration of 4.24-11.80 mg/mL in the solubilization buffer is merely a "Key Process Parameter" that *may* be exceeded. (*See id.* at 18-19, 63.) Under Amgen's

theory, because Apotex's aBLAs include no limiting specification for protein concentration—in effect, no specification at all—a finding of infringement is required under *Sunovion* because it *might* happen. (*See id.* at 63 ("For example, if Apotex ran its process with a filgrastim concentration . . . above the KPP range specified . . ." then infringement could occur).)

Amgen's infringement theory under *Sunovion*—which was not presented in Amgen's case-in-chief, but only in reply to Apotex—is contradicted by Apotex's aBLA documents, witness testimony, and this Court's precedent, and therefore should be rejected. (*Id.*) Specifically, in the section regarding the KPP parameters, Apotex's aBLA documents plainly state that the upper limit for filgrastim concentration cannot be exceeded, stating that: "*[b]ased on the ranging studies that were carried out using a Design of Experiments (DoE) approach, the qualified upper limit for the concentration of protein entering the refolding unit operation is 11.8 mg/mL." (Appx5595; Appx5902 (note to Table S.2.2-27).) Further, Dr. Dowd testified that KPP is "a specification upon which we [Apotex] need to maintain the process within for the batch to be acceptable." (Appx3622 at 39:9-15; *see* Appx3623 at 40:16-24; Appx3632 at 49:5-10; Appx3646 at 63:4-15.) Thus, there is no basis for Amgen's assertion that Apotex's aBLAs permit the specified filgrastim concentration of 11.8 mg/mL to be exceeded. Therefore, Amgen's argument that the district court clearly erred in finding that Apotex's aBLAs define

a non-infringing protein refolding process is contradicted by the record and should be rejected. Moreover, there is ample support in the record for the district court's finding that "[i]f Apotex's manufacturing process was to deviate from the amount and quantity of Filgrastim specified in the Apotex aBLAs submitted to the FDA, Apotex would be required to discard that batch." (Appx26 (crediting Dr. Dowd).)

Finally, Amgen points to no specification in the aBLAs for *protein concentration* other than the 4.24-11.80 mg/mL discussed above that could define an infringing process. (Op. Br. at 62-63.) Instead, in response to Apotex's affirmative proof of non-infringement, Amgen attempts to ground its infringement claims under *Sunovion* based on a mere possibility that this specification *may* be exceeded, a legal argument that this Court has expressly rejected. (Op. Br. at 63-34); *see, e.g., Ferring B.V. v. Watson Labs., Inc.-Fla*., 764 F.3d 1382, 1387-88 (Fed. Cir. 2014) ("The district court concluded that under *Sunovion*, Apotex was infringing because Apotex *could* violate the patents-in-suit based on the 2010 ANDA, and Ferring makes the same argument on appeal. We disagree." (emphasis in original)); *see also Glaxo*, 110 F.3d at 1570. Here, if the specification for protein concentration in Apotex's aBLAs can be exceeded, which Apotex asserts that it cannot, then Apotex's aBLAs are, at best, silent as to the protein concentration in Apotex's refold mixture. When a FDA regulatory document (such as an ANDA or aBLA) "is silent with respect to infringement, . . .

the correct analysis is under *Glaxo, Inc. v. Novopharm, Ltd*., 110 F.3d 1562, 1570 (Fed. Cir. 1997), not *Sunovion*." *Ferring*, 764 F.3d at 1387-88 (citing *Sunovion*, 731 F.3d at 1279-80). Therefore, even assuming *arguendo* that Apotex's protein concentration in the refold mixture could exceed 0.708 g/L, such a result would merely take the infringement analysis outside the purview of *Sunovion*.

Where a proposed drug product's specification does not directly address the question of infringement, then it is proper to expand the infringement inquiry to consider evidence beyond the application submitted to FDA, such as testing of actual drug product samples. *See Ferring*, 764 F.3d at 1409 (citing *Glaxo*, 110 F.3d at 1569). Thus, even if the Court were to accept Amgen's argument that the protein concentration in Apotex's refold mixture can theoretically exceed 0.708 g/L, the fact remains that Amgen has failed to offer any evidence that the protein concentration in Apotex's refold mixture not only exceeds 0.708 g/L, but, in fact, meets the "at or above about 1g/L" limitation.

For at least these reasons, the district court did not clearly err in concluding that Apotex's aBLAs' specifications effectively limit the protein concentration in Apotex's refold mixture to a maximum of 0.708 g/L, and therefore define a process for protein refolding that does not infringe claim 1 of the '138 Patent. The judgment of the district court should therefore be affirmed.

B. If Apotex's aBLAs Do Not Speak to Infringement, the District Court Did Not Clearly Err in Holding That Apotex's Batch Records Show That Apotex Is Not Likely to Infringe the '138 Patent

The district court also did not clearly err in finding that Apotex's batch records show that the drug products Apotex intends to market are manufactured by a non-infringing process. (*See* Appx27-28; Appx35.) Therefore, should this Court find that Apotex's aBLAs do not specify a protein concentration during protein refolding, then the district court's non-infringement findings based on Apotex's batch records should be affirmed. Specifically, if Apotex's aBLAs' specifications do not directly address the question of infringement, then it was proper for the district court to expand its infringement inquiry and consider evidence beyond the aBLAs, such as testing of actual drug product samples and other relevant documents such as batch records. *See* Appx35-36 (citing *Glaxo*, 110 F.3d at 1568-70). Amgen argues that the district court committed legal error in considering Apotex's batch records because there was no evidence: (i) that the batch records followed Apotex's aBLAs' specifications; (ii) that the two batch records were in any way representative of the process Apotex actually uses; and (iii) that the batch records accurately represent the process Apotex intends to use upon FDA-approval of its aBLAs. (Op. Br. at 65-66; *see* Appx27-28; Appx35-36.) Ample evidence supports the district court's findings and refutes each of Amgen's assertions.

Dr. Dowd, the project technical lead for Apotex, was responsible for designing and implementing Apotex's manufacturing process in collaboration with Apotex's manufacturing partner, Intas Pharmaceuticals, Ltd., and testified that Apotex's batch records reflect the specifications set forth in Apotex's aBLAs. (Appx3603-3605; Appx3634 at 51:9-11 (discussing Appx4250); Appx3643 at 60:15-22 (discussing Appx4511); Appx3654 at 71:14-20.) Indeed, the batch records introduced at trial were submitted to FDA as supporting documents for Apotex's aBLAs. (*See, e.g.,* Appx36; Appx3643 at 60:8-14 (discussing Appx4250).) Further, as technical lead for Apotex's manufacturing process, Dr. Dowd had personal knowledge of and reviewed additional records from the other 89 production batches that were manufactured according to the specifications set forth in Apotex's aBLAs. (*See* Appx3634 at 51:9-11 (discussing Appx4250); Appx3643 at 60:15-22 (discussing Appx4511); Appx3644-3646.) Therefore, Dr. Dowd's testimony that the highest protein concentration Apotex had observed in the refold mixture was 0.56 g/L (Appx3645-3646 at 62:23-63:3), which the district court relied upon, was based on his personal knowledge. (Appx27-28; Appx35-36.)

Further, FDA requires Apotex to follow the manufacturing processes specified by the aBLAs (and batch records), and FDA has not requested Apotex to modify its manufacturing process that is set forth in its aBLA documents.

(Appx36; Appx3632 at 49:5-18.) Moreover, Apotex has used the specifications in its aBLAs to commercially manufacture filgrastim for the European and Canadian markets, and if Apotex were to modify its manufacturing process prior to commercialization in the United States, at this point it would require prior FDA-approval in order to do so. (Appx3632-3633 at 49:19-50:14.) Therefore, there is ample support for the district court's finding that "even if Apotex's aBLAs had been silent on the issue of protein concentration, Apotex's batch records show that the drug products it intends to market are manufactured by a non-infringing process." (Appx35.)

Finally, it should be noted that Apotex, not Amgen, presented this evidence to the Court. As discussed in the following section, in its case-in-chief, Amgen chose instead to rely upon documents reflective of inclusion body concentration, which the district court rejected as not probative on the question of Apotex's protein concentration relevant to infringement. (Appx34.) Therefore, Amgen can hardly fault the district court for considering the only evidence presented that directly addressed the issue of infringement. For at least the reasons discussed above, the district court's consideration of Apotex's aBLAs' specifications and batch records, as well as testimony regarding the same, cannot have been legal error, and therefore, the districts court's findings and entry of judgment should be affirmed.

C. Amgen's Request to Further Litigate Whether Apotex's Inclusion Bodies Are Wholly Protein Should Be Denied

Recognizing the heavy burden it faces in overturning any of the district court's factual findings as clearly erroneous, Amgen's Opening Brief frames its failure to prove infringement as a legal error in the district court's claim construction, even after the district court adopted each of Amgen's proposed claim constructions related to protein concentration. (Op. Br. at 49-59.) Amgen argues that Apotex's "water theory" deprived it of advancing claim construction arguments earlier in the case because Apotex withheld this contention until its rebuttal case was presented at trial. (*Id.* at 56.)

Amgen's request should denied for at least two separate reasons. First, the district court conducted a proper infringement analysis by first construing the claims and then applying the construed claims to the accused process. Thus, whether Apotex's inclusion bodies are wholly protein, or instead constitute a considerable amount of water, is a question of fact, and Amgen should have been aware of this issue before trial. Second, judicial estoppel precludes Amgen from arguing for a construction of "protein" different from that which it successfully advanced at the district court. This Court should therefore summarily reject Amgen's attempts to re-litigate issues that were properly resolved by the district court, and deny Amgen's attempts to gain a second bite at the apple by asking this Court to remand the case.

1. The District Court's Finding Concerning Apotex's Inclusion Bodies Is a Question of Fact, Not Claim Construction

Amgen's argument that Apotex's "water theory" deprived Amgen of the ability to argue for a different claim construction goes against this Court's long-standing precedent. (*Id.*) It is fundamental that the question of patent infringement is a two-step analysis: first, "the court determines the scope and meaning of the patent claims asserted," and then compares the claims "to the allegedly infringing device". *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998).

Here, the district court followed this Court's guidance by construing the claims, and then applying the construed claims to Apotex's accused process. Amgen's proposed construction for "protein" was "any chain of at least five naturally or non-naturally occurring amino acids linked by peptide bonds," which was the construction the district court adopted based on the definition for this term that is set forth in the specification of the '138 Patent. (Appx2330; Appx2466-2469.) In its case-in-chief, Amgen asserted that Apotex's aBLAs' specifications for inclusion body concentration are the same as protein concentration in the refold mixture in claim 1 of the '138 Patent. (Appx24.) The district court found that Amgen failed to meet its burden to prove that Apotex's process infringed (Appx25), which is a factual finding this Court reviews for clear error. *See Amgen v. Hoechst*, 314 F.3d at 1339.

Amgen can feign no surprise at the fact that water is present in Apotex's inclusion bodies considering the evidence from Apotex's aBLAs, Apotex's batch records, Dr. Willson's testimony, and Dr. Robinson's deposition that the inclusion bodies are a wet pellet after centrifugation. (Appx24; Appx3473-3474; Appx3638-3639; Appx3643-3644; Appx4250-4510; Appx4511-4776; Appx5586-5588; Appx5895-5897.) Further, Amgen's expert, Dr. Willson, testified that he was aware of the water present in Apotex's inclusion bodies at the time they are weighed and was worried about it, yet he failed to account for it in his calculations. (Appx24; Appx3192; Appx3551-3552.) Therefore, the district court did not err in finding that Amgen knew or should have known that Apotex's inclusion bodies contained water. (Appx24.)

In support of its argument that it should be entitled to a new claim construction, Amgen alleges that, prior to trial, the parties had a common understanding of the term "total protein concentration" as it relates to the refold mixture. (Op. Br. at 50.) This is untrue. Instead, only during claim construction proceedings did Apotex learn that Amgen's construction of the term "refold mixture" in claim 1 of the '138 Patent included the additional language that "the refold mixture has a high protein concentration, where 'high protein concentration' is at or above about 1g/L protein." (Appx532; Appx11222-11229; Appx11267-11273.) After the district court adopted Amgen's construction, Apotex's expert,

Dr. Robinson, opined that Apotex did not infringe the asserted claims of the '138 Patent because the concentration of the protein-of-interest, filgrastim, in Apotex's refold mixture was less than 1 g/L. (Appx10372-10375.) Further, Apotex filed a motion for summary judgment based on this very premise, which led to additional court-ordered claim construction briefing on the term "protein." (Appx1609-1611.) Therefore, Amgen's assertions that it should be entitled to re-try its case-in-chief would require this Court to ignore the record and disregard the district court's findings of fact concerning Amgen's case-in-chief on infringement. There is no precedent for this, and Amgen's request should be denied.

2. Amgen Is Judicially Estopped From Re-Litigating Claim Construction Issues That It Won at the District Court

Further, Amgen successfully argued its construction for "protein" at the district court, and applying the doctrine of judicial estoppel, Amgen is precluded from now changing its claim construction position on appeal. *See Interactive Gift Express, Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1345, 1349 (Fed. Cir. 2001) (citing *Key Pharm. v. Hercon Labs. Corp*., 161 F.3d 709, 715 (Fed. Cir. 1998)) (applying to constructions adopted at Appx4-5; Appx9; Appx2466-2469). In *Key Pharm. v. Hercon Labs. Corp*., the defendant won its claim construction at the district court, but subsequently lost its invalidity case. 161 F.3d 709, 711-13 (Fed. Cir. 1998). On appeal, the defendant changed its claim construction position, which this Court noted was "an obvious attempt to salvage its invalidity case" and

that there could be "no [other] reason for [defendant's] claim construction reversal . . . ." *Id*. at 715. Such an obvious reversal of position justifies an estoppel because, as this Court noted:

> Allowing parties in a patent suit to assert "error" in such situations would open the door to mischief and judicial inefficiency. For example, a party could advocate a certain claim construction at trial believing that that claim construction will result in favorable resolution of infringement or validity issues. If the trial court adopts that claim construction but resolves the infringement or validity issues unfavorably, the party could thereafter assert a new claim construction to get the proverbial "second-bite," possibly necessitating a retrial.

Id.

Here, the district court adopted each of Amgen's proposed constructions for claim terms related to protein concentration. (Appx4-5; Appx9; Appx2466-2469.) Amgen was then fully heard on its infringement case. Now, unhappy with the outcome, Amgen seeks to re-try its infringement case under a claim construction other than that which it successfully advocated earlier. (Op. Br. at 56.) Apotex submits this is precisely the behavior this Court warned against in *Key Pharm*. and *Interactive Gift Express*, and for the reasons discussed above, Amgen should be precluded from advancing these arguments on appeal because it is judicially estopped from doing so.

In sum, Amgen should not be allowed to re-try its infringement case in the guise of a new claim construction argument. For all of the above reasons,

Amgen's arguments for this Court to reconsider the district court's claim construction for terms relating to protein concentration should be denied.

D. If This Court Construes the Claim Terms Related to Protein Concentration, Then the Correct Constructions Require "a protein . . . present in a volume at a concentration of 2.0 g/L or greater" in the "refold mixture"

Nonetheless, if this Court reconsiders the district court's construction of the term "protein," then Apotex submits that the related terms "2 g/L or higher" and "refold mixture" should also be considered. These claim terms are interrelated and the ultimate question is whether the "2.0 g/L or greater" protein concentration recited in claim 1 is required in the refold mixture (where protein refolding occurs), or in some other volume prior to protein refolding. Under the district court's constructions for these terms, the only protein concentration recited in claim 1—i.e., 2.0 g/L or greater—was construed such that it is irrelevant to the protein concentration in the refold mixture. Instead, the district court found that the concentration of "2.0 g/L or greater" refers to a protein concentration in a volume prior to refolding, and then inserted an additional protein concentration of "at or above about 1.0 g/L" into the refold mixture limitation. (Appx9; Appx17.) Apotex submits that the district court's constructions are unsupported by the intrinsic record, and that the correct constructions for these terms should require a protein concentration of 2.0 g/L during protein refolding, which can only be in the refold mixture.

This Court reviews claim-construction rulings *de novo* where, as here, the intrinsic record fully determines the proper constructions. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015).

1. "A protein . . . present in a volume at a concentration of 2.0 g/L or greater" Refers to the Protein Concentration During Refolding

Contrary to the district court's construction, the intrinsic record clearly requires "a protein . . . present in a volume at a concentration of 2.0 g/L or greater . . ." to be a protein concentration during protein refolding—that is, *after* dilution in a refold buffer (i.e., in the refold mixture).

To support its conclusion that "2.0 g/L or greater" in claim 1 refers to the protein concentration before contacting the refold buffer, the district court pointed to, *inter alia*, the Background of the Invention. (Appx5.) The district court specifically pointed to the following sentence: "[u]ntil the present disclosure, these types of complex molecules could not be refolded at high concentrations, i.e., concentrations at 2.0g/L and higher . . . ." (*Id.*; *see* Appx57.) The district court's reliance on this sentence highlights the court's misunderstanding of where refolding takes place. Refolding occurs after the protein has been contacted with the refold buffer (i.e., in the refold mixture). (*See*, *e.g.*, Appx5 (construing refold buffer as "[a] preparation that supports the renaturation [i.e., refolding] of protein to a biologically active form.") Thus, the sentence cited by the district court,

which explains that "complex molecules could not be refolded at high concentrations, i.e., concentrations at 2.0g/L and higher . . .", is inapposite to the district court's conclusion that 2.0 g/L is the protein concentration before contact with the refold buffer. (*See id.*) In fact, the cited sentence supports the construction wherein "2.0 g/L or greater" refers to the protein concentration after dilution in the refold buffer—the volume in which refolding occurs.

The district court's construction of this term is also at odds with much of the rest of the '138 Patent's specification. For example, the Abstract and Field of the Invention both refer to protein refolding in concentrations of 2.0 g/L or greater. (*See* Appx48 (Abstract); Appx57 at col. 1, ll. 11-14.) Notably, these passages say nothing about a protein concentration prior to refolding, but instead refer to folding and refolding proteins.

The examples and figures of the '138 Patent further highlight the inconsistency of the district court's construction with the intrinsic evidence. Namely, Figures 1a through 1f depict the effect of thiol-pair ratio and thiol-pair buffer strength on the distribution of product-related species, where the protein concentration in the refold mixture is kept at a constant 6.0 g/L concentration. (*See* Appx60-61.) Similarly, Examples 3 and 4 disclose protein refolding performed at concentrations of "approximately 12 g/L" and 6 g/L, respectively. (*See* Appx63 at col. 14, ll. 53-58; Appx64 at col. 15, ll. 34-40.) Example 4 further discloses that

"[a]fter the inclusion bodies were dissolved, denatured and reduced, they were diluted into a refold buffer . . . . The level of dilution was chosen to . . . maintain the highest possible protein concentration in the refold mixture." (Appx64 at col. 15, ll. 47-58.) Thus, the specification clearly discloses that the '138 Patent uses the term "a protein . . . present in a volume at a concentration of 2.0 g/L or greater" to mean protein present at concentrations of 2.0 g/L or greater after dilution in a refold buffer—the volume in which folding and refolding takes place. (*See id*.) These statements in the specification are supported by an inventor's testimony, Dr. Keener, that the "2.0 g/L or greater" concentration recited in claim 1 refers to the protein concentration during oxidation (i.e., during protein refolding). (*See* Appx4825-4826; *see also* Appx4817 at 80:15-19.)

The prosecution history also refutes the district court's construction and supports Apotex's proposed construction. Discussing their claimed invention, applicants argued that "[i]t is the interaction of these properties provided by applicants' disclosure that facilitate the ability to *refold proteins at concentration of 2.0 g/L and greater.*" (Appx5210 (emphasis added).) Subsequently, Amgen again distinguished the pending claims from the prior art by emphasizing that "the [prior art] does not teach each and every element of the claimed invention, notably *refolding proteins at concentrations of 2.0 g/L or greater* . . . ." (Appx5232 (emphasis added).) The district court's claim construction ignored these clear

statements from the prosecution history of the '138 Patent, and impermissibly negates Amgen's statements to the Patent Office. *See, e.g.*, *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995) ("Claims may not be construed one way in order to obtain their allowance and in a different way against accused infringers.").

In sum, the district court's construction is inconsistent with the disclosures in the specification, the prosecution history, and the testimony of Dr. Keener, an inventor of the '138 Patent. Accordingly, the district court's construction of this term should be vacated, and this Court should adopt Apotex's construction, "a protein . . . present in a volume at a concentration of 2.0 g/L or greater after dilution in a refold buffer," which accords with both the intrinsic and extrinsic evidence of record. *See Renishaw plc v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998) ("The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.").

2. The Term "refold mixture" Refers to "a mixture formed from contacting the protein and the refold buffer"

The term "refold mixture" in claim 1 of the '138 Patent would have been readily understood by a person of ordinary skill in the art to mean "a mixture formed from contacting the protein and the refold buffer." Support for this construction is in the words of the claims themselves as well as the specification of

the ’138 Patent. Element (a) of claim 1 makes clear that the term “refold mixture” means the mixture that is formed after “contacting the protein with a refold buffer.” (Appx65.) Further, the specification discloses in Example 4, “[a]fter the inclusion bodies were dissolved, denatured and reduced, they were diluted into a refold buffer . . . . The level of dilution was chosen to . . . maintain the highest possible protein concentration in the refold mixture.” (Appx64.)

In its Claim Construction Order, the district court stated: “[t]he language of the claim, the specification and the state of the prior art support the conclusion that the refold mixture of claim 1 of the ’138 Patent would be interpreted . . . to have a minimum or ‘floor’ concentration at or above about 1g/L.” (Appx9.) Notably, however, the district court cited nothing in the claims or specification that would require a “minimum or ‘floor’ [protein] concentration at or above about 1g/L” in the refold mixture. (*See id*.) A review of the ’138 Patent specification reveals that Amgen never used the phrase “minimum protein concentration” or “floor protein concentration” when discussing the refold mixture, much less a specific “‘floor’ concentration at or above about 1g/L.” (*See* Appx48-65.) To the contrary, and as discussed above, the ’138 Patent specification consistently refers to refolding proteins at concentrations of 2 g/L and above. Further, the specification does not link or associate “high concentrations” or “high protein concentrations” with “at or above about 1g/L protein.” (*See id.*) Tellingly, the specification only uses the

phrases "high concentrations" or "high protein concentrations" when describing refolding of proteins at concentrations of 2.0 g/L or greater. (*See, e.g.*, Appx57 at col. 2, ll. 17-20; Appx58 at col. 4, ll. 15-23.)

Further, much as with the term "a protein . . . present in a volume at a concentration of 2.0 g/L or greater," the prosecution history likewise refutes the district court's construction of "refold mixture." As explained above, Amgen clearly distinguished its invention from the prior art by arguing that a key element of the invention is refolding proteins at concentrations of 2.0 g/L or greater after dilution in the refold buffer (i.e., in the refold mixture), not "at or above about 1 g/L" as construed by the district court. (*See e.g.*, Appx5210; Appx5232.)

Further, the district court's construction of "refold mixture" cannot be correct because it impermissibly rewrites the claims. *See, e.g., Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1349 (Fed. Cir. 2002); *see also K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1364 (Fed. Cir. 1999) ("Courts do not rewrite claims; instead, we give effect to the terms chosen by the patentee."); *Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1171 (Fed. Cir. 1993). Here, the patentee plainly did not incorporate a protein concentration of 1.0 g/L anywhere in claim 1, and the district court improperly rewrote claim 1 by inserting this limitation.

Finally, the district court improperly credited extrinsic evidence submitted by Amgen concerning the state of the prior art (*see* Appx9), which is contradicted by the specification of the '138 Patent that refers to high protein concentrations as 2.0 g/L or greater. (*See* Appx57 at col. 1, ll. 11-14, col. 2, ll. 17-20.) Legal error arises when a court relies on extrinsic evidence that contradicts the intrinsic record. *See Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 790 F.3d 1329, 1338 (Fed. Cir. 2015). There is no justification—in either the intrinsic or the extrinsic record—to broaden the term "refold mixture" to include protein concentrations less than 2.0 g/L.

3. Amgen's New Proposed Construction for "Protein" Is Unsupported by the Intrinsic Record and Should Be Rejected

Even if Amgen was not judicially estopped from asking this Court for a second bite at the apple, any attempt to equate total protein concentration with inclusion body concentration is contradicted by the intrinsic record and cannot be correct.

Here, the district court further construed "protein" in order to clarify its earlier claim construction, and adopted Amgen's proposed construction that was based on a definition set forth in the specification of the '138 Patent. (*See* Appx2466-2469.) The term Amgen now seeks to construe—"total protein concentration"—does not appear in any claim of the '138 Patent (*see* Appx65), and

therefore would "not ordinarily" require construction. *See Edwards Lifesciences LLC v. Cook Inc.*, 582 F.3d 1322, 1334 (Fed. Cir. 2009) (citing *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002)). Thus, there is no basis for Amgen's request for further claim construction.

Nonetheless, Amgen's proposed further construction is contradicted by the words of claims, which do not limit or equate "proteins" to inclusion bodies. Instead, the claims also include protein concentrations in, for example, non-native soluble protein form captured from cell lysate (which is not an inclusion body). (*See* Appx63-64.) Therefore, any construction that equates "protein" to "inclusion body" would exclude a preferred embodiment from the claims, which "is rarely, if ever correct." *See SanDisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1285 (Fed. Cir. 2005) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996)). Further, dependent claims 4 and 5 further limit the "protein" of claim 1 by requiring that the protein is "an inclusion body." (Appx65.) Thus, the plain language of claims 4 and 5 makes clear that "protein" has a different meaning than "inclusion body" because both terms appear in the same claim. *See Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1119 (Fed. Cir. 2004) ("[W]hen an applicant uses different terms in a claim it is permissible to infer that he intended his choice of different terms to reflect a differentiation in the meaning of those terms.").

Amgen's proposal is also contradicted by the prosecution history of the '138 Patent, in which Amgen asserted that: "the Patent Office has misinterpreted the disclosure of the '370 patent [prior art] and *is equating the inclusion bodies of the '370 patent with protein, which is inappropriate.*" (Appx5231 (emphasis added).) In comparing the prior art with the claims of the '138 Patent, Amgen argued that "[a]pplicants submit that all of these dilution steps are relative to inclusion body concentration, *not* protein concentration as applicants' claims recite." (*Id*. (emphasis in original).) Having relied on the distinction between protein and inclusion bodies to obtain allowance of the '138 Patent, Amgen is now precluded from arguing that proteins and inclusion bodies are the same here. *See Southwall*, 54 F.3d at 1576 ("Claims may not be construed one way in order to obtain their allowance and in a different way against accused infringers.").

4. Under the Correct Construction of the Claim Terms "a protein . . . present in a volume at a concentration of 2.0 g/L or greater" and "refold mixture," Amgen Cannot Prove Infringement

Amgen cannot prove infringement, either literally or under the doctrine of equivalents, under the correct construction of the claim terms "a protein . . . present in a volume at a concentration of 2.0 g/L or greater" and "refold mixture." Amgen cites the 0.9 to 1.4 g/L inclusion body concentration in Apotex's refolding process as its proof of infringement, which the district court properly denied as a measure of protein. (Appx25.) Even assuming *arguendo* that such a comparison could be

made, the maximum inclusion body concentration of 1.4 g/L is well under a protein concentration of 2.0 g/L or greater in the refold mixture, which is required by claim 1 of the '138 Patent. Thus, Amgen cannot prove literal infringement. Indeed, in its expert reports, Amgen did not allege literal infringement of the 2.0 g/L limitation if the district court had construed the term as in the refold mixture. (Appx4133-4135.)

Nor can Amgen prove infringement under the doctrine of equivalents. The '138 Patent recognizes that the prior art refolded complex molecules at less than 2.0 g/L. (Appx57.) The scope of equivalents cannot be taken in a vacuum, free from the prior art. *Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 684 (Fed. Cir. 1990). The Federal Circuit "has consistently limited the doctrine of equivalents to prevent its application to ensnare prior art." *Gemalto S.A. v. HTC Corp.*, 754 F.3d 1364, 1374 (Fed. Cir. 2014) (quoting *Marquip, Inc. v. Fosber Am., Inc.*, 198 F.3d 1363, 1367 (Fed. Cir. 1999)). "[B]ecause prior art limits the exclusive right available to an inventor, it also limits the range of permissible equivalents of a claim." *Id.* at 1375 (quoting *Marquip*, 198 F.3d at 1367). Allowing Amgen to claim that 1.4 g/L is equivalent to 2.0 g/L or greater would ensnare the prior art, and is thus improper.

III. The District Court Did Not Clearly Err in Holding That Amgen Failed to Prove That Apotex's Redox Component Infringes Under the Doctrine of Equivalents

The district court properly construed the term "2mM or greater" as "2mM or greater, wherein the redox buffer strength is effectively bounded at a maximum of 100 mM." (Appx10; Appx17.) Further, the district court's findings of fact regarding the redox buffer strength used in Apotex's refolding process were not clearly erroneous, and the district court did not misapply the law of the doctrine of equivalents in determining Amgen did not meet its burden of proving infringement. (Appx28-31; Appx36-38.)

A. The District Court Correctly Construed "2mM or greater" as Being "effectively bounded at a maximum 100 mM"

The district court correctly construed the term "2mM or greater" as being "effectively bounded at a maximum of 100 mM" in view of the specification of the '138 Patent. (Appx10; Appx17.) "The patentee is free to choose a broad term and expect the full scope of its plain and ordinary meaning unless the patentee explicitly redefines the term or disavows claim scope." *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1367 (Fed. Cir. 2012). Here, Amgen expressly limited the redox buffer strength through statements made in the patent specification.

As the district court correctly recognized, "the specification [of the '138 Patent] does, indeed, impose an upper limit of 100mM on the thiol-pair buffer

strength." (Appx10.) Specifically, where the specification sets forth possible ranges for the thiol-pair buffer strength (i.e., redox buffer strength), each and every time it states that "the thiol-pair buffer strength is effectively bounded at a maximum of 100 mM." (*See* Appx58; Appx61; Appx62.) Further, exemplary embodiments of the '138 Patent show that "in terms of ranges, the thiol buffer strength [i.e., redox buffer strength] is between 2 and 20 mM" (*see* Appx57; Appx61-62), which is further exemplified in the figures. (*See* Appx49-54 (Figs. 1a–1f (disclosing redox buffer strengths of 5 to 20 mM)).) Thus, similar to this Court's holding in *SciMed Life Sys. v. Advanced Cardiovascular Sys., Inc*., here, the summary of the invention, detailed description, and figures of the '138 Patent limit the scope of the claims to a redox buffer strength of 2 to 100 mM. 242 F.3d 1337, 1342-45 (Fed. Cir. 2001). Therefore, the district court correctly construed the term "2 mM or greater" as describing a redox buffer strength between 2 mM and 100 mM.

B. Amgen Did Not Meet Its Burden of Showing That Apotex Has a Redox Buffer Strength That Is Equivalent to the Redox Buffer Strength of Claim 1 of the '138 Patent

The district court did not err in determining that Amgen did not meet its burden of showing that Apotex has a redox buffer strength that is equivalent to the redox buffer strength of claim 1 of the '138 Patent for a least three reasons: (1) Amgen's equivalence theory requires an equivalent of an equivalent, and is thus

incorrect as a matter of law; (2) Amgen failed to perform the correct analysis when it focused on equivalence in the refold mixture, not the redox component; and (3) Amgen's equivalence theory has no boundary and would require Apotex to change its process and specifications, which Apotex is not allowed to do. (Appx36-38.)

1. Amgen's Equivalence Theory Is Incorrect as a Matter of Law

The district court's claim construction of redox buffer strength in claim 1 of the '138 Patent requires that the redox buffer strength be calculated in the redox component, not the refold mixture. (Appx7-8; Appx17.) First, Amgen's equivalence analysis requires it to establish that Apotex has the claimed redox component of claim 1 of the '138 Patent. At trial, Amgen alleged that Apotex had an equivalent to the claimed redox component. (Appx29.) Because no redox component exists in Apotex's refolding process, Amgen formed a hypothetical redox component (the combined volume of Apotex's Cystine and Cysteine Solutions (i.e., 476.32 mL)). (*Id.*) The district court assumed without deciding that Apotex's hypothetical redox buffer strength is equivalent to the claimed redox buffer strength. (*Id.*; Appx37.)

Even assuming that it was proper for Amgen to change Apotex's process and form this hypothetical redox component (and the district court to assume it is equivalent), which to be clear it was not, the redox buffer strength of this

hypothetical redox component is 214 to 340 mM. (Appx20; Appx30; Appx37.) This value is more than 2 to 3 times greater than the maximum redox buffer strength of 100 mM mandated by this Court. (Appx37; *see* Appx3176-3177.) Given that a redox buffer strength of 214 to 340 mM falls outside the claimed range, Amgen was forced to conduct an additional equivalency analysis on the hypothetical redox component formed under the doctrine of equivalents—meaning a doctrine of equivalents analysis on top of a doctrine of equivalents analysis. There is no precedent for Amgen to conduct such an analysis. Thus, Amgen's equivalence analysis is incorrect as a matter of law.

2. Amgen Failed to Perform the Correct Analysis When It Focused on Equivalence in the Refold Mixture, Not the Redox Component

Amgen's equivalency analysis improperly focused on the amount of oxidant (Cystine) and reductant (Cysteine) molecules in the refold mixture, not the redox component. (Appx30-31.) Asking this Court to find equivalency based on the number of molecules that ultimately end up in the "refold mixture" is improper because a patentee "cannot merely point to other claim limitations to satisfy the doctrine of equivalents." *See Advanced Steel Recovery, LLC v. X-Body Equip., Inc.*, 808 F.3d 1313, 1320 (Fed. Cir. 2015). As the Supreme Court stated, the doctrine of equivalents "must be applied to individual elements of the claim, not to

the invention as a whole." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29, 39-40 (1997).

Under the district court's claim construction of "redox buffer strength," the proper equivalency analysis necessarily has to take place in the redox component. (Appx17; Appx37-38.) The district court adopted Amgen's construction of "redox buffer strength," which requires that the concentrations of the oxidant and reductant are based on the concentrations "in the redox component[,]" not the refold mixture. (Appx8-9; Appx17.) As Amgen's expert, Dr. Willson, testified, "it would be very impractical" to calculate the redox buffer strength in the refold mixture. (Appx3173-3174.) Thus, the district court did not err in determining that the relevant inquiry for Amgen under the doctrine of equivalents is whether a redox buffer strength of 214 to 340 mM is equivalent to a redox buffer strength of 2 to 100 mM in the redox component. (Appx37.)

Amgen did not conduct this analysis. Amgen did not determine whether 214 to 340 mM is insubstantially different from the claimed redox buffer strength of 2 to 100 mM in the redox component, nor did Amgen determine whether a redox buffer strength of 214 to 340 mM performs substantially the same function, in substantially the same way, to yield substantially the same result as the claimed redox buffer strength in the redox component. (Appx30-31; Appx37.)

Thus, the district court did not err in finding that the redox buffer strength of Apotex's hypothetical redox component of 214 to 340 mM is more than 2 to 3 times greater than the maximum redox buffer strength of 100 mM. (Appx30; Appx37.) Further, the district court did not err in finding Amgen failed to establish that this is an insubstantial difference or that a redox buffer strength of 214 to 340 mM performs substantially the same function, in substantially the same way, to yield substantially the same result as the claimed redox buffer strength in the redox component. (Appx30; Appx37.)

3. Amgen's Equivalency Analysis Would Require a Change to Apotex's Process, Which Is Prohibited by the FDA

Amgen's equivalency analysis arbitrarily adjusted the volume of the hypothetical redox component from 472 mL to 1.0 – 1.6 L in an effort to make the redox buffer strength of Apotex's hypothetical redox component meet the claimed redox buffer strength limitation. (Appx30.) Amgen attempts to show equivalence by changing Apotex's process. This cannot be done. (Appx20-21; Appx31; Appx38; Appx3622-3623; Appx5600; Appx5906.) Apotex is bound by the specifications in its aBLAs. *See Ferring*, 764 F.3d at 1408. Indeed, as Dr. Dowd testified, Apotex is required to obtain prior approval from the FDA prior to making any changes to its manufacturing process, including changing the amounts and quantities of the Cystine and Cysteine Solutions. (Appx3623; Appx3632-3633; Appx3682.) Here, according to Apotex's aBLAs' specifications, the maximum

possible combined volume of Apotex's Cystine and Cysteine Solutions is 476.32 mL (444 mL of Apotex's Cystine Solution and 32.32 mL of Apotex's Cysteine Solution). (Appx20-21; Appx29; Appx38; Appx3622-3623; Appx5600; Appx5906.) Thus, the combined volume of Apotex's Cystine and Cysteine Solutions cannot be arbitrarily increased to 1 to 1.6 L as suggested by Amgen. (*See* Appx29-31; Appx38; Appx3622-3623.)

Further, under Amgen's theory, there is no boundary to its equivalence analysis. Indeed, under Amgen's analysis, one would just need to adjust the volume of Apotex's hypothetical redox component further to reach a redox buffer strength of 25 mM or 50 mM, as opposed to 100 mM. (Appx30; Appx3180-3181.) Amgen's analysis renders this claim limitation meaningless because one could simply adjust the volume of any redox component with a redox buffer strength greater to any desired mM amount in order to make it fall within the claimed limitation. (Appx38.) This is improper. *See Warner-Jenkinson*, 520 U.S. at 29 ("It is important to ensure that the application of the doctrine [of equivalents], even as to an individual element, is not allowed such broad play as to effectively eliminate that element in its entirety."); *see also Akzo Nobel Coatings, Inc. v. Dow Chem. Co.*, 811 F.3d 1334, 1342-43 (Fed. Cir. 2016).

C. If This Court Construes the Claim Term "2 mM or greater" as Not Effectively Bounded, Then "redox buffer strength" Should Be Construed as Being Calculated in the Refold Mixture

The district court construed the term "redox buffer strength" as "also called 'buffer thiol strength,' 'thiol-pair buffer strength,' or 'thiol-pair strength,' defined by the following equation: 2[oxidant] + [reductant] where the concentrations are the concentrations in the redox component." (Appx8-9; Appx17.) This Court reviews claim-construction rulings *de novo* when based solely on the intrinsic record. *See Teva Pharm.*, 135 S. Ct. at 841. For this term, the intrinsic record fully determines the proper construction, and thus this Court should review the district court's construction *de novo*.

The error in the district court's construction lies with the volume in which the redox buffer strength is calculated. The '138 Patent clearly states that the redox buffer strength must factor in the entire refold mixture. (*See* Appx58; Appx60; Appx63.) Indeed, the only volume in which all components necessary for refolding are present is the refold mixture. To calculate the concentration of the redox buffer strength in any other volume (i.e., the redox component as adopted by the district court) would not result in a final concentration.

What is more, the specification discloses:

> The optimal refold chemistry for a given protein represents a careful balance that maximizes the folded/oxidized state while minimizing undesirable product species . . . . One factor that is important in

> achieving this balance is the redox-state of the refold system. The redox-state is affected by many factors, including . . . the ratio and concentration of the redox couple chemicals in the refold solution . . . .

(*See* Appx60.) The specification further discloses, "by controlling the thiol-pair buffer strength, in conjunction with thiol-pair ratio and protein concentration, the efficiency of protein folding operations can be optimized and enhanced and the refolding at high concentrations, for example 2g/L or greater, can be achieved." (Appx58.) Likewise the specification discloses "in addition to demonstrating that buffer thiol strength interacts with the thiol-pair ratio, it has also been shown that the buffer thiol strength relates to the protein concentration in the total reaction as well." (*Id*.) Notably, the only volume in which the thiol-pairs and the protein are found concurrently is the refold mixture. Thus to "control" the redox buffer strength (also known as thiol-pair buffer strength) in conjunction with the thiol-pair ratio and protein concentration, the redox buffer strength must be calculated in the refold mixture.

In Example 2 of the '138 Patent, the inventors disclose a method for identifying refold conditions and redox components. (Appx63.) The specification states "[t]he thiol-pair ratio and redox buffer strength were determined using an experimental matrix of thiol-pair ratio (0.1 to 100, more typically 1 to 25) versus buffer strength (typically 2 mM to 20 mM, depending on the protein concentration, the number of cysteine residues in the protein, and the concentration of reductant

used to solubilize the inclusion bodies)." (*Id.*) This passage further demonstrates to a person of ordinary skill in the art that the volume used to calculate the redox buffer strength would account for both the volume of protein and refold buffer (i.e., the refold mixture). In fact, Dr. Hart, an inventor of the '138 Patent, testified at trial that the only disclosed calculation of the final redox buffer strength in the figures of the patent were calculated in the refold mixture, not the redox component. (Appx3033.)

In light of these disclosures, a person of ordinary skill in the art would understand that the only volume in which the protein and redox components "interact" to facilitate refolding is the refold mixture. Thus, the "redox buffer strength" would necessarily be calculated in the refold mixture to ensure a "balanced relationship" and "interaction" between the thiol-pair ratio, thiol-pair buffer strength and protein concentration. (*See* Appx5210.)

CONCLUSION

For the reasons set forth above, Apotex respectfully requests that the Court affirm the district court's September 6, 2016 final judgment of no infringement of the '138 Patent. In the alternative, Apotex respectfully requests this Court to reverse the district court's constructions of the terms "a protein . . . present in a volume at a concentration of 2.0 g/L or greater," "refold mixture," and "redox buffer strength," and find no infringement of the '138 Patent.

Dated: January 17, 2017

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on this 17th day of January, 2017, 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 Court's CM/ECF system.

January 17, 2017

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CERTIFICATE OF COMPLIANCE WITH FED. R. APP. P. 32(a)(7)

This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B). This brief contains approximately 13,802 words, excluding the part of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii) and Fed. Cir. R. 32(b).

The brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a proportionally-spaced typeface using Microsoft Word 2013 in 14-point Times New Roman type.

January 17, 2017

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