Appeal No. 2017-1010

United States Court of Appeals

for the

Federal Circuit

AMGEN INC., AMGEN MANUFACTURING LIMITED,

Plaintiffs-Appellants,

– v. –

APOTEX INC., APOTEX CORP.,

Defendants-Appellees.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF FLORIDA IN CASE NO. 0:15-CV-61631-JIC (CONSOLIDATED WITH 0:15-CV-62081-JIC), JUDGE JAMES I. COHN

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

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January 31, 2017

CERTIFICATE OF INTEREST

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

   AMGEN INC. and AMGEN MANUFACTURING LIMITED

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

   AMGEN INC. and AMGEN MANUFACTURING LIMITED

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

   AMGEN INC.

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

   HOGAN LOVELLS US LLP: John F. O'Sullivan, Allen P. Pegg, Jason D. Sternberg

   PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP: Nicholas Groombridge, Catherine Nyarady, Eric Alan Stone, Jennifer H. Wu, Jennifer Gordon, Peter Sandel, Conor McDonough, Ana J. Friedman, Arielle K. Linsey, Stephen A. Maniscalco, Michael Wu*

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INTRODUCTION

The district court committed four errors of law, each of which independently requires reversal and/or remand of the district court's judgment of no infringement. Apotex's Red Brief, however, suggests that this is an appeal from the district court's factual findings that are reviewed for clear error. This is incorrect. The issues that Amgen appeals are:

Whether the district court erred in construing the term "2mM or greater" in claim 1 of '138 Patent to be "effectively bounded at a maximum of 100 mM." The district court erred by imposing an effective maximum boundary on this claim term. If this claim construction is incorrect, then reversal is required because Apotex's process meets this limitation. This Court reviews claim-construction rulings de novo when based solely on the intrinsic record, as is the case here. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). In the alternative, if this Court affirms the district court's construction of "2 mM or greater," the district court clearly erred in finding that Apotex's manufacturing process does not meet this limitation equivalently. *See Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed. Cir. 2004) (infringement determinations are reviewed for clear error following a bench trial).

Whether the district court's finding that Apotex's refold mixture does not have a protein concentration at or above about 1 g/L is legal error;

specifically, this finding is premised on three separate errors of law, each of which requires reversal and/or remand. First, the district court found no infringement by ignoring Apotex's statements pursuant to subparagraph 262(*l*)(3)(B) of the BPCIA that this claim limitation is met. The question of law is: given that the BPCIA dictates an orderly disclosure of information by the aBLA Applicant (here, Apotex) about its proposed biosimilar product to the Reference Product Sponsor (here, Amgen) in reliance on which the Sponsor may be required to file a 42 U.S.C. § 262(*l*)(6) infringement lawsuit, can the Applicant subsequently simply repudiate these statements and have the district court accord them zero evidentiary weight? This is an issue of first impression. Amgen submits that ignoring Apotex's statements made during its BPCIA exchanges during the infringement analysis flouts the very purpose of the statutory exchanges. As a matter of law, the district court should have considered Apotex's statements during the BPCIA exchanges, especially where, as here, Apotex provided no explanation for the purported error in the statements.

Second, the district court erred as a matter of law by not construing the claimed 1 g/L protein concentration to be interchangeable with washed-inclusion-body concentration. The intrinsic evidence supports a construction that the two concentrations are interchangeable. Thus, reversal and/or remand is required.

Third, the district court erred by determining that the claim limitation is not met even though the specifications of Apotex's aBLAs expressly permit the proposed biosimilar product to be made by a process in which the refold mixture has a protein concentration at or above about 1 g/L, as the claims require. The district court committed legal error by crediting self-serving testimony from Apotex's witnesses about what Apotex had done in the past in its batch records, rather than considering the correct inquiry under the precedent of this Court: what Apotex would be permitted to do under its aBLA specifications. The proper focus for infringement in these circumstances where Apotex is seeking FDA approval for its biosimilar product is to compare the aBLA specification—what Apotex is seeking FDA approval to do—with the claims. Otherwise, a clever Applicant could avoid infringement by choosing operating parameters for its manufacturing batch records that fall outside the patent claims prior to FDA approval, and then switching to different, infringing parameters within the scope of the aBLA specification after FDA approval. As this Court has already held in the Hatch-Waxman context with respect to ANDA lawsuits, because Apotex's aBLA specifications "directly address[] the infringement question," if the specifications "would allow" Apotex to practice an infringing refolding process, "a judgment of infringement must necessarily ensue." *Sunovion Pharm., Inc. v. Teva Pharm.*

USA, Inc., 731 F.3d 1271, 1278 (Fed. Cir. 2013). Thus, the district court erred in finding that the protein-concentration limitation is not met.

ARGUMENT

I. Apotex's Refolding Process Satisfies the "2 mM or Greater" Limitation

A. "2 mM or Greater" Means 2 mM or Greater With No Maximum Boundary

It is undisputed that the redox buffer strength of Apotex's equivalent redox component is greater than 2 mM. (Apotex Red Br. at 12.) Thus, under a straight-forward reading of the claim language, this limitation is met in Apotex's process. The district court erred in finding that this limitation was not met in Apotex's process by construing this claim term to have an effective maximum boundary, i.e., to mean 2 mM to 100 mM. (Appx10.) The claim language supports Amgen's construction because it does not contain an upper boundary of 100 mM. (Amgen Blue Brief at 28.) Contrary to Apotex's suggestion, this claim language cannot be ignored. *See Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1344 (Fed. Cir. 1998) ("The actual words of the claim are the controlling focus.").

The only place in the patent that discusses a maximum boundary is the specification: as Apotex concedes, the "effectively bounded" language is used "where the specification sets forth possible ranges for the thiol-pair buffer strength (i.e., redox buffer strength)." (Apotex Red Brief at 53 (emphasis added).) This description, however, does not justify importing an effective maximum boundary

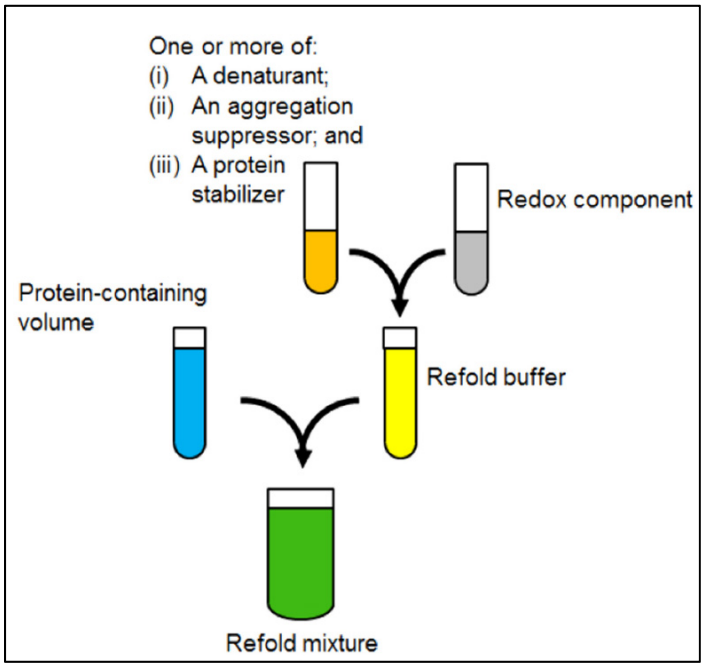
limitation into the claims. While some embodiments are described as having an "effective" maximum boundary of 100 mM, this is not true for all embodiments. When the specification first introduces the "2 mM or greater" limitation, it includes no mention of an effective maximum boundary. ('138 Patent at col. 2:57.) Further, Apotex does not dispute the district court's finding that the 100 mM "effective" maximum boundary mentioned in the specification refers to solubility limits of certain redox chemicals in certain solvents. (*See* Appx29.) Therefore, the reference to effective boundaries applies only to certain redox chemicals of limited solubility, and should not limit the claim. (*See* Amgen Blue Br. at 31-32.)

B. Apotex's "Redox Buffer Strength" Claim-Construction Argument Should Be Rejected

Apotex argues that if this Court construes "2 mM or greater" as having no effective maximum boundary, then it should construe the term "redox buffer strength" as being calculated in the refold mixture. (Apotex Red Br. at 59.) This construction of "redox buffer strength" should be rejected.

A review of the claim's terminology is instructive. As construed by the district court, the claim requires contacting a protein-containing "volume" (the blue solution in the diagram below) with a "refold buffer" (yellow) to form a "refold mixture" (green). ('138 Patent at claim 1; *see* Appx9832.) The "refold buffer" comprises (1) one or more of a denaturant, aggregation suppressor, and protein

stabilizer (orange) and (2) a "redox component" (gray) having a "redox buffer strength" of "2 mM or greater." (Appx65.)



(Appx9832.)

Apotex proposes that the redox buffer strength should be construed to be calculated in the refold mixture, not in the redox component as the district court correctly found. Apotex's proposal is incorrect and also an improper argument because it is not an alternative ground for affirmance.

1. The Court Need Not Consider Apotex's Alternative Claim-Construction Argument Because It Does Not Support Affirmance

The Court need not address the district court's construction of the term "redox buffer strength" because Apotex's argument is not an alternative ground for affirmance. (Apotex Red Br. at 59.) An appellee can challenge the district court's

determinations only where arguments are "in support of the judgment of noninfringement." *Bailey v. Dart Container Corp. of Mich.*, 292 F.3d 1360, 1362 (Fed. Cir. 2002). Here, Apotex fails to explain why reversal of the district court's construction of the term "redox buffer strength" supports a finding of no infringement (*see* Apotex Red Br. at 59-61), nor could it. The record does not support the conclusion that the redox buffer strength of Apotex's refold mixture is less than 2 mM. On the contrary, in Amgen's expert's opening report that was prepared before the claim-construction order, Amgen's expert calculated the redox buffer strength of Apotex's refold mixture to be greater than 2 mM. (Appx4136-4137.)

2. In Any Event, Apotex's Proposed Construction of "Redox Buffer Strength" Is Wrong

Even if the Court were to consider Apotex's challenge to the construction of "redox buffer strength," Apotex's proposed construction is wrong. In the district court, the parties disputed whether the volume in which the redox buffer strength is measured is the redox component (Amgen) or the refold mixture (Apotex). As the district court correctly found, the claim language resolves the dispute: "a redox component comprising . . . a redox buffer strength." ('138 Patent at claim 1 (emphasis added).) The redox component, not the refold mixture, "compris[es]" the redox buffer strength. Apotex's proposed construction ignores this claim language. Indeed, as the district court found, "[a]dopting Apotex's proposed

construction [of redox buffer strength] would require the Court to re-write the claim." (Appx8.) *See 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.").

Moreover, the redox buffer strength should not be construed as being measured in the refold mixture because the plain language of claim 1 recites a redox component that is not initially part of the refold mixture; rather, the redox buffer strength is a characteristic of the redox component. (*See* Appx9832.) Indeed, "the claim language is careful to say which value is measured at which stage." (Appx8.) Further, the specification recites the redox component, not the refold mixture, as having the redox buffer strength. (*See, e.g.*, '138 Patent at col. 10:22-30, col. 11:11-17, 40-46, 64-67.)

C. Even if "2 mM or Greater" Is Construed To Have an Effective Maximum Boundary of 100 mM, Apotex's Process Satisfies This Limitation Equivalently

1. Amgen Properly Analyzed Equivalents on an Element-by-Element Basis

Apotex faults Amgen's doctrine-of-equivalents theory as an "equivalent of an equivalent." (Apotex Red Br. at 54-55.) This is incorrect. Amgen's doctrine-of-equivalents analysis is in accordance with the well-settled law that equivalence is determined on an "element-by-element basis." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997). At trial, Amgen presented sufficient

evidence of infringement, either literal or under the doctrine of equivalents, on an element-by-element basis. Specifically, Apotex's process meets the redox-component element and the "2 mM or greater" element—two distinct elements—equivalently.

Redox component. Apotex introduces its oxidant and reductant into the refold mixture in a stepwise manner rather than first premixing the oxidant and reductant into a single redox component and then adding the premixed solution to the refold buffer, as literally called for by the claim. (Appx3124-3125; Appx5597-5599; Appx5904-5905.) As Amgen showed at trial, Apotex's stepwise addition is insubstantially different from using the premixed redox component of the asserted claims. (*See* Appx3135-3138; Appx3886-3889.) The district court assumed without deciding in its opinion that Apotex's redox component is an equivalent of the claimed redox component. (Appx29.)

2 mM or greater. Apotex's redox buffer strength is 214-340 mM (Appx30). Although this exceeds the effective maximum boundary of 100 mM imposed by the district court, Amgen showed at trial that a redox component with a redox buffer strength of 214-340 mM is insubstantially different from a redox component within the scope of the claim as construed by the court, namely a 1.0-1.6 L redox component having a redox buffer strength of 100 mM. (Amgen Blue Br. at 35-37.)

2. Apotex Seeks Improperly to Narrow the Equivalency Determination

Apotex argues that the proper equivalency analysis "has to take place in the redox component," with no consideration for the interrelationship among the redox component and other claim elements. (Apotex Red Br. at 55-57.) The district court similarly determined no equivalency by comparing the numerical values of the redox buffer strength of Apotex's redox component and the claimed redox component. (Appx30, Appx37.) This is incorrect because it conducts a literal-infringement rather than an equivalency analysis, and also because it ignores the role that the redox buffer strength plays in the claimed and accused processes. Equivalency is not determined in a vacuum. Rather, "[w]hat constitutes equivalency must be determined against the context of the patent, the prior art, and the particular circumstances of the case." *Graver Tank & Mfg. Co. v. Linde Air Products Co.*, 339 U.S. 605, 609 (1950). "An analysis of the role played by each element in the context of the specific patent claim will thus inform the inquiry." *Warner-Jenkinson*, 520 U.S. at 40.

Here, in both Apotex's and the claimed processes, the redox buffer strength is a measure of the dissolved oxidants and reductants in the redox component that are delivered to the refold mixture to facilitate protein refolding. (*See* Appx3149.) Amgen presented ample evidence at trial that Apotex's 472 mL redox component with a redox buffer strength of 214-340 mM is equivalent to a 1.0-1.6 L redox

component with a redox buffer strength of 100 mM because the two redox components would deliver the same mass of dissolved oxidant and reductant to a 160 L refold mixture, the volume of Apotex's refold mixture. (Amgen Blue Br. at 35-37; Appx3150, Appx3154; *see* Appx9974-9975.) Because the claim specifies neither a volume for the redox component nor a volume for the refold mixture, both 1.0-1.6 L and 160 L, respectively, fall within the claim. Furthermore, each redox-component volume is less than 1% of the 160 L refold-mixture volume. (Appx3154; *see* Appx9976) In other words, the redox component of the accused process creates substantially the same redox-chemical environment as a redox component within the scope of the claim when added into the refold mixture.[1]

3. Apotex's Equivalency Analysis Erroneously Focuses on FDA Law

Apotex argues that "Amgen attempts to show equivalence by changing Apotex's process," which cannot be done because "Apotex is bound [by FDA] by the specifications in its aBLAs." (Apotex Red Br. at 57.) But the doctrine of equivalents is assessed under patent law and not FDA law. That Apotex's aBLAs were submitted under FDA law does not mean the processes described within them cannot infringe Amgen's claims under the doctrine of equivalents. And the

[1] There may be a volume at which equivalence is lost, but a 1% change is not it. (Appx3151-3155.) And Amgen need not specify a precise boundary at which equivalence is lost to prove equivalence. (Amgen Blue Br. at 39.)

question of whether Apotex's process could be changed to something within the literal scope of the claim as a matter of FDA law is inapposite. (*See* Amgen Blue Br. at 40.)

Apotex appears to suggest that processes described in aBLAs under FDA law can infringe a claim only literally, and not equivalently. (*See* Apotex Red Br. at 57-58.) This is incorrect because infringement under the doctrine of equivalents is strictly a matter of patent law, as confirmed by this Court's precedent in the Hatch-Waxman context. Even though drug manufacturers are bound by FDA law to the specifications in an ANDA, *see Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002), this Court has affirmed findings of infringement under the doctrine of equivalents without considering whether FDA law would have allowed the drug manufacturers to change their processes or products to also literally infringe. *See, e.g.*, *Cadence Pharm. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1370-71 (Fed. Cir. 2015) (affirming infringement under the doctrine of equivalents where the order of steps specified in an ANDA was insubstantially different from the order of steps in the claimed process).

II. Three Legal Errors Warrant Reversal of the District Court's Conclusion that Apotex's Refolding Process Does Not Include a Refold Mixture Having a High Protein Concentration, at or Above About 1 g/L

A. It Was Legal Error for the District Court to Ignore Apotex's Subparagraph 262(*l*)(3)(B) Statements

As this Court is well-aware, the BPCIA established "a unique and elaborate process for information exchange" between the Applicant and the Sponsor to resolve patent disputes. *Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347, 1352 (Fed. Cir. 2015), *cert. granted*, No. 15-1039, No. 15-1195 (U.S. Jan. 13, 2017); *see Amgen Inc. v. Apotex Inc.*, 827 F.3d 1052, 1055-56 (Fed. Cir. 2016), *cert. denied*, 137 S. Ct. 591 (2016). In reliance on the information exchange, including the subparagraph 262(*l*)(3)(B) statements, the Sponsor, in certain circumstances, is legally required to commence an infringement lawsuit. *See* 42 U.S.C. § 262(*l*)(6). Indeed, that is exactly what happened here: because Apotex wished to litigate all of the patents that were the subject of the subparagraph 262(*l*)(3) exchanges, Amgen was required to file the infringement action that resulted in this appeal. (Appx160-161; Appx180.)

The question of law presented here is whether, having made statements about its biosimilar product to the Sponsor during the BPCIA exchanges, an Applicant is permitted simply to repudiate those statements at any time and have the district court accord them zero evidentiary weight in the subsequent BPCIA lawsuit. This is an issue of first impression. Amgen submits that it is incorrect to

hold, as the district court did here, that the statements cease to matter after the BPCIA lawsuit is commenced. (*See* Appx34-35.) Here, Apotex twice represented to Amgen during the BPCIA exchanges that the protein concentration of its refold mixture is 0.9-1.4 g/L filgrastim, which falls within the protein-concentration limitation of the "refold mixture" of claim 1, as construed by the district court, i.e., "at or above about 1 g/L protein." (Appx7396; Appx7447.) About this, there is no dispute.

Instead, Apotex takes the position that the subparagraph 262(*l*)(3)(B) statements "don't matter." (Appx3784.) Ignoring Apotex's statements made during its BPCIA exchanges during the infringement analysis flouts the very purpose of the statutory exchanges. As a matter of law, the district court should have considered Apotex's statements during the BPCIA exchanges, especially where, as here, Apotex provided no explanation for the purported error in the statements. Otherwise, Applicants would be free to say anything during the BPCIA exchanges—exchanges on which a Sponsor relies in deciding which patents to include in an infringement action—and then later repudiate what was said without any consequence. Indeed, rendering the information exchanges meaningless, as a matter of policy, will incentivize sloppy, incomplete, and, even, misleading subparagraph 262(*l*)(3)(B) statements. The ability to retract factual representations with impunity will harm Sponsors and the courts, as ill-informed

lawsuits waste time and resources. Perhaps worse yet, an inaccurate subparagraph 262(*l*)(3)(B) statement may result in the Sponsor deciding not to assert a patent that is actually being infringed by the Applicant's aBLA submission.

Apotex does not dispute that the 0.9-1.4 g/L concentration identified in its subparagraph 262(*l*)(3)(B) factual representations was subsequently confirmed by Apotex's expert at her deposition to be the protein concentration of Apotex's refold mixture. (*See* Appx3517-3519; Appx9606.) Apotex also does not dispute that it did not seek to retract its factual representations until its rebuttal case at trial, nor that Apotex has provided no explanation for its retraction. To be clear, Amgen is not suggesting that if an Applicant makes a good-faith mistake in a subparagraph 262(*l*)(3)(B) statement (which is not something Apotex has asserted), it is necessarily bound by that mistake. Naturally, good-faith mistakes should be correctable if done at a time that is not tantamount to an ambush. This does not mean, however, that factual representations have no probative value.[2]

Apotex, like the district court, relies on Hatch-Waxman case law for the proposition that ANDA applicants may, during the litigation, modify claims and defenses made in the paragraph IV letter. (Apotex Red Br. at 25.) But there is no authority that an ANDA applicant may change facts (in contrast to legal theories) disclosed in its paragraph IV letter. Apotex also fails to explain how or why it

[2] Amgen argued this at the close of trial, and thus there is no waiver. (Appx3807.)

would have reported a different protein concentration in its refold mixture—a fact that should remain constant—if Apotex had "the benefit of any disclosure from Amgen concerning its bases for infringement, its proposed claim constructions, or any discovery" prior to drafting its subparagraph 262(*l*)(3)(B) statements. (*See* Apotex Red Br. at 26.)[3]

Apotex then attempts to distinguish paragraph IV letters from subparagraph 262(*l*)(3)(B) statements by arguing that subparagraph 262(*l*)(3)(B) statements are merely "optional," citing *Amgen Inc. v. Sandoz Inc.*. (Apotex Red Br. at 26.) *Sandoz*, however, does not hold that subparagraph 262(*l*)(3)(B) is optional. *Sandoz* says that the BPCIA contemplates that the Applicant might fail to comply with subparagraph 262(*l*)(2)(A)—a step that occurs before provision of the subparagraph 262(*l*)(3)(B) statement. *Sandoz*, 794 F.3d at 1355. *Sandoz* does not answer the question of whether subparagraph 262(*l*)(3)(B) statements are mandatory if there has been compliance with the predicate steps of the Applicant's disclosure and the Sponsor's patent list. 42 U.S.C § 262(*l*)(2)(A), (*l*)(3)(A). Indeed, where, as here, Apotex has complied with subparagraph 262(*l*)(2)(A), this Court has suggested that subsequent steps—including subparagraph 262(*l*)(3)(B)—

[3] Apotex incorrectly faults Amgen for not presenting the "same infringement theory" in its subparagraph 262(*l*)(3)(C) statements as at trial. (Apotex Red Br. at 23.) Because the district court construed "2 mM or greater" to have an effective maximum of 100 mM, Amgen necessarily presented proofs of infringement under the doctrine of equivalents rather than literal infringement. (*See* Appx3138-3155.)

are then mandatory. *See Apotex*, 827 F.3d at 1061. In that appeal, Apotex argued that a different step—subparagraph 262(*l*)(8)(A)—was optional if the Applicant complies with subparagraph 262(*l*)(2)(A). *Id.* at 1054-55. The Court rejected that argument, holding that subparagraph 262(*l*)(8)(A) was mandatory in all cases. *Id.* The Court held that "(8)(A) differs materially from (2)(A)" because 35 U.S.C. § 271(e)(2) & (4) provide the "exclusive remedy" for the filing of an aBLA "coupled to a failure to give the (2)(A) notice." *Id.* at 1061. In contrast, "no comparable textual source of [ ] contradiction" would be created by interpreting the "shall" in subparagraph 262(*l*)(8)(A) to be mandatory. *Id.* The same is true for the "shall" in subparagraph 262(*l*)(3)(B). Further, even if subparagraph 262(*l*)(3)(B) statements were optional, that does not mean that they need not be accurate when the option is exercised (as Apotex did here).

Apotex next argues that the Court must choose between two extremes—either the statements have no value or they are binding. (Apotex Red Br. at 22.) This is a false dichotomy. The statements can be both probative, indeed, highly probative, and not binding. For instance, many district courts have adopted patent local rules that require the parties, during an early stage of the litigation, to make certain disclosures regarding infringement and invalidity of the asserted patent claims. *See, e.g.*, N.D. Cal. Patent Local Rule 3 (Revised Jan. 17, 2017), *available at* http://www.cand.uscourts.gov/localrules/patent. Typically, these contentions are

not binding because they may be amended "upon a timely showing of good cause," such as an adverse claim construction or the recent discovery of information that was not found during an earlier diligent search. *See id.* But even though they are not binding, such contentions play a vital role in framing the issues to be litigated. The BPCIA exchanges should be given at least the same weight.

Apotex also argues that the subparagraph 262(*l*)(3)(B) statements are irrelevant "because it is Apotex's aBLA documents and batch records that are relevant to this inquiry." (Apotex Red Br. at 20.) This misses the point. The subparagraph 262(*l*)(3)(B) statements represent Apotex's interpretation of its aBLAs and batch records, which is precisely the factual issue that the parties asked the district court to decide. Finally, Apotex incorrectly relies on Federal Rule of Evidence 104(e) as prohibiting "affording any evidence weight as a matter of law." (Apotex Red Br. at 24.) The rule simply states that it "does not limit a party's right to introduce before the jury evidence that is relevant to the weight or credibility of other evidence." If anything, the sentiment of the rule supports Amgen.

B. Protein Concentration, as a Matter of Claim Construction, Is Interchangeable With Washed-Inclusion-Body Concentration

After the district court construed "refold mixture," a further claim-construction dispute arose at trial as to whether the protein concentration that is part of the district court's construction is interchangeable with washed-inclusion-

body concentration. Amgen submits that it is, and that this is a claim-construction issue that should be resolved as a matter of law.

Prior to trial, the district court construed "refold mixture" to have "a high protein concentration, where 'high protein concentration' is at or above about 1 g/L protein." (Appx9.) Amgen believed that this claim limitation as construed was met in Apotex's process because Apotex had told Amgen, both before and after the claim construction, that the 0.9-1.4 g/L washed-inclusion-body concentration in its refold mixture is the protein concentration: before claim construction in its subparagraph 262(*l*)(3)(B) statements (Appx7396; Appx7447; *see supra* Part II.A) and after claim construction at the deposition of its expert (Appx9606; *see* Appx3517-3519). (Amgen Blue Br. at 12-16.)

Further, it is uncontested that, before trial, Apotex never repudiated that the protein concentration in its refold mixture is the 0.9-1.4 g/L washed-inclusion-body concentration. It is also uncontested that in its rebuttal case at trial, Apotex for the first time asserted a total protein concentration in its refold mixture other than the 0.9-1.4 g/L washed-inclusion-body concentration—Apotex asserted that two-thirds of its 0.9-1.4 g/L washed-inclusion-body concentration is water, leaving a total protein concentration in its refold mixture of about 0.3-0.5 g/L (Apotex's "water theory"), and, if measured by chromatography, its refold mixture has a maximum total protein concentration of 0.708 g/L. (*See* Amgen Blue Br. at 16-

17.) This new theory, first unveiled at trial, gave rise to the present claim-construction dispute as to whether protein concentration is interchangeable with washed-inclusion-body concentration. Had Apotex disclosed this noninfringement theory in a timely fashion, the issue of whether the protein concentration in the refold mixture and washed-inclusion-body concentration are interchangeable could have been resolved by the district court in its claim-construction order. But because Apotex waited until trial to reveal its theory, that did not happen. And although Amgen raised the issue in its post-trial briefing (Appx3871), it was never decided by the district court.

The intrinsic record of the '138 Patent fully supports Amgen's proposed claim construction that the protein in the refold mixture, which was construed by the district court to have a concentration "at or above about 1 g/L," may be in the form of inclusion bodies. (Amgen Blue Brief at 51-53.) Because protein concentration and washed-inclusion-body concentration are interchangeable, a washed-inclusion-body concentration of about 1 g/L, in fact, is sufficient to meet the protein-concentration limitation. The district court erred in declining to address this claim-construction argument. (Appx23-25.)

1. Amgen's Construction is Supported by the Intrinsic Record

The specification supports a construction that the protein concentration "at or above about 1 g/L protein" in the refold mixture of claim 1 of the '138 Patent is

interchangeable with washed-inclusion-body concentration. (Amgen Blue Br. at 51-53.) Apotex addresses none of this intrinsic evidence. Instead, Apotex incorrectly argues that Amgen's proposed construction is contradicted by certain dependent claims, which specify that the protein may be in a non-native soluble form captured from cell lysate. (Apotex Red Br. at 49.) But Amgen never suggested that the protein in the refold mixture of claim 1 is limited to only inclusion bodies. Rather, as stated in Amgen's Blue Brief, "a person of ordinary skill in the art would have understood that the minimum about 1 g/L concentration in the refold mixture can be either about 1 g/L protein or about 1 g/L inclusion bodies." (Amgen Blue Br. at 53.) Simply because the specification of the '138 Patent makes clear that protein concentration and washed-inclusion-body concentration are interchangeable in the context of the "at or above about 1 g/L protein" limitation does not mean this limitation excludes from its meaning the concentration of a protein in non-native soluble form captured from cell lysate.

Dependent claims 4 and 5 further clarify that protein concentration and washed-inclusion-body concentration are interchangeable by making clear that inclusion bodies are one possible form of "protein":

> 4. The method of claim 1, wherein the protein is present in the volume in a non-native limited solubility form.
>
> 5. The method of claim 4, wherein the non-native limited solubility form is an inclusion body.

(Appx65 (emphasis added); *see* Amgen Blue Br. at 51-53.) Amgen's construction is not limited to the refolding of only protein expressed as inclusion bodies. However, where the protein is in the form of inclusion bodies, protein concentration and washed-inclusion-body concentration are interchangeable.

Apotex's argument that Amgen is "precluded from arguing that proteins and inclusion bodies are the same here" based on Amgen's statements to the Patent Office during prosecution is a red herring. (*See* Apotex Red Br. at 50.) During prosecution, Amgen never asserted that the "protein" concentration in claim 1 of the '138 Patent could not be based on washed-inclusion-body concentration. Rather, Amgen asserted that the Patent Office's reading of an entirely different patent, U.S. Patent No. 7,138,370, was incorrect—that the never-washed inclusion bodies in one example of that patent could not be equated with protein: "Applicants submit that the Patent Office has misrepresented the disclosure of the '370 patent and is equating the inclusion bodies of the '370 patent with protein, which is inappropriate." (Appx5231 (emphasis added).) Unlike the washed inclusion bodies described in the '138 Patent (*see* Amgen Blue Br. at 51-52), the prior-art inclusion bodies that were the subject of the rejection were not reported to have been washed prior to solubilization (Appx5231-5232), and without washing, inclusion bodies contain materials other than protein (*see, e.g.*, Appx3197). The issue is not how the '370 Patent defines protein concentration in the refold mixture,

but rather how the patent-in-suit defines it. By ignoring the totality of the intrinsic evidence cited in Amgen's Blue Brief, Apotex has failed to counter it. The intrinsic evidence fully supports Amgen's position that the protein concentration in the refold mixture of claim 1 of the '138 Patent is interchangeable with the washed-inclusion-body concentration.

2. Judicial Estoppel Does Not Apply Because the District Court Never Construed the Relationship Between Protein Concentration and Washed-Inclusion-Body Concentration

Apotex argues that Amgen is precluded by judicial estoppel from arguing that protein concentration and washed-inclusion-body concentration should be construed as interchangeable. (Apotex Red Br. at 39.) This is incorrect. This issue was not decided by the district court in its construction of the term "protein" prior to trial. Nor could it have been because the present dispute between the parties did not arise until trial. Prior to trial, the district court construed "refold mixture" to have a protein concentration "at or above about 1 g/L protein." (Appx9.) Subsequently during the summary-judgment proceedings, but still before trial, the parties disputed whether "protein" is limited to protein of interest or inclusive of all protein in the refold mixture. (Amgen Blue Br. at 15-16.) After a round of supplemental claim-construction briefing, the district court adopted Amgen's proposed construction of "protein" which was inclusive of all protein in accordance with the definition provided in the patent. (Appx2468.) Contrary to

Apotex's present assertion, the disputed issue now was not presented during the construction of "protein." Indeed, when the meaning of "protein" was being construed by the district court, both parties had taken various positions to the effect that protein concentration and inclusion-body concentration are interchangeable (Amgen Blue Br. at 53-56). And Apotex had not yet disclosed the noninfringement positions it unveiled at trial. Thus, the district court's construction of the term "protein" did not address the relationship in the '138 Patent between protein concentration and washed-inclusion-body concentration.

Contrary to Apotex's assertion (Apotex Red Br. at 40), Amgen is not seeking to re-litigate the district court's construction of the term "protein" as inclusive of any protein. Rather, Amgen seeks to clarify, as a matter of claim construction, the relationship between protein concentration and washed-inclusion-body concentration. Amgen is not estopped from making this argument because the district court's construction of "protein" is entirely consistent with Amgen's proposed construction.[4]

3. Apotex's Alternative Claim-Construction Argument Fails

Apotex argues that if the Court construes protein concentration and washed-inclusion-body concentration as interchangeable, then the Court should also

[4] This appeal is unlike *Key Pharm. v. Hercon Labs. Corp.*, where the appellant had prevailed on a claim construction at trial and was seeking reconsideration of that same construction. 161 F.3d 709, 715 (Fed. Cir. 1998).

construe the "2.0 g/L or greater" protein concentration of claim 1 to be measured in the "refold mixture," and not, as the district court correctly found, in the protein-containing "volume." (Apotex Red Br. at 41.) Apotex's proposed construction is incorrect. The district court properly construed "a protein . . . present in a volume at a concentration of 2.0 g/L or greater" to mean "[a] protein as it existed in a volume before contacting the volume with a refold buffer. The protein concentration in the volume is 2.0 g/L or greater." (Appx4-5.) The plain language of the claim makes two things clear. First, the "2 g/L or greater" refers to the concentration of the protein that is present in the "volume." Second, the "volume" containing the protein is necessarily different than the "refold mixture." Otherwise, the "volume" would not need to be "contact[ed]" with the "refold buffer" to form the "refold mixture." The district court properly came to the only logical conclusion: The concentration of 2 g/L or greater is that of the "volume" not of the "refold mixture." The court also found that the specification describes a "volume" having a protein concentration of 2.0 g/L or greater prior to being contacted with the refold buffer to form the refold mixture, consistent with the language of the claim. (Appx5; *see, e.g.*, '138 Patent at col. 11:6-9.)

After the protein-containing volume is contacted with the refold buffer, the resulting mixture, i.e. "refold mixture," necessarily has a more dilute protein concentration than the initial protein-containing volume. Accordingly, the district

court construed the term "refold mixture" as "a mixture formed from contacting (1) the volume in which the concentration of protein is 2.0 g/L or greater with (2) the refold buffer. The refold mixture has a high protein concentration, where 'high protein concentration' is at or above about 1 g/L protein." (Appx9.) As Amgen explained during the *Markman* phase, the specification twice discloses that after diluting the initial protein-containing volume with the refold buffer, the protein concentration in the resulting refold mixture can be as low as 1 g/L. (Appx966; *see* '138 Patent at col. 10:12-16, col. 12:46-48.) Apotex never attempts to explain how the 1 g/L refold-mixture protein concentrations disclosed in the specification can be reconciled with its proposed construction.

Apotex also asserts that the patentees distinguished the claimed invention from "prior art by arguing that a key element of the invention is refolding proteins at concentrations of 2.0 g/L or greater" in the refold mixture. (Apotex Red Br. at 47.) Apotex's characterization of the prosecution history is incorrect and incomplete. The applicants characterized the refold mixture as having a "high" protein concentration (Appx5210), which, as Amgen's expert opined, was understood to mean a protein concentration of about 1 g/L or greater. (Appx987-989.) Contrary to what Apotex suggests, the basis for allowance was not an argument that the refold mixture of claim 1 had a protein concentration of 2 g/L or

greater. Rather, it was the substantiation that the prior art was refolded at a dilute, not a high, protein concentration that allowed the claim. (*See* Appx5304.)

C. Apotex's aBLA Specifications Expressly Allow Apotex's Refold Mixture To Have a Protein Concentration Within the Scope of the Claim

The district court erred in finding that Apotex's process does not meet the protein-concentration limitation even though Apotex's aBLA specifications permit Apotex to use a process that would meet this limitation. (*See* Appx34-36.) Apotex argues that its aBLAs define a process that does not infringe claim 1. (Apotex Red Br. at 29.) This is incorrect. The parties agree that Apotex's aBLA specifications are not "silent" with respect to protein concentration. (*See* Amgen Blue Br. at 61; Apotex Red Br. at 29.) Consequently, *Ferring B.V. v. Watson Labs., Inc.-Fla.*, where the ANDA was "silent" with respect to the dissolution rate at the times claimed in the patent-in-suit, is inapposite. *See* 764 F.3d 1382, 1385-86 (Fed. Cir. 2014).

The parties dispute, however, whether Apotex's aBLA specifications "would allow" infringement. Under *Sunovion*, because Apotex's aBLA specifications "directly address[] the infringement question," if the specifications "would allow" Apotex to practice an infringing refolding process, "a judgment of infringement must necessarily ensue." 731 F.3d at 1278. The question is whether the aBLA specifications would allow Apotex to practice an infringing refolding process. By

comparing the claim to the disclosures in the aBLA specifications, the answer is yes. Although Apotex seems to agree that, under *Sunovion*, the district court may rely on only the aBLA specifications (*see* Apotex Red Br. at 29), Apotex (and the district court) answer the question in the negative by relying on evidence outside the aBLAs, such as fact-witness testimony. The dispute, thus, boils down to what types of evidence the district court may properly consider in its infringement analysis under the BPCIA, which is an issue of law.

1. Apotex's aBLAs Permit a Refold Mixture With a Protein Concentration Greater Than 0.708 g/L

Apotex's aBLAs expressly allow Apotex's refold mixture to have a protein concentration greater than 0.708 g/L because the aBLAs designate the protein-concentration range as a Key Process Parameter (KPP) which may be exceeded in the practice of the process without affecting product quality (albeit potentially affecting the process, e.g., yield). (Appx4790; Appx5595; Appx5902; Appx6724-6725; Appx7353; *see* Appx2471.)[5] Nevertheless, Apotex argues that there is "no basis for Amgen's assertion that Apotex's aBLAs permit the specified filgrastim concentration of 11.8 mg/mL [and, thus, the 0.708 g/L protein concentration in the 160 L refold mixture] to be exceeded." (Apotex Red Br. at 30.) This incorrectly ignores the aBLAs' definition of a KPP, and instead improperly credits

[5] In contrast, Critical Process Parameters (CPPs) require strict compliance. (Appx6724-6725; Appx7353.)

contradictory fact testimony from Dr. Dowd that a KPP cannot be exceeded for a batch to be acceptable. (Apotex Red. Br. at 30; Appx26.) The proper focus for infringement is what Apotex would be permitted to manufacture under the aBLAs, and not what Dr. Dowd predicts Apotex would find acceptable. *See Sunovion*, 731 F.3d at 1278.[6]

2. Apotex's Inclusion Bodies May Have a Concentration at or Above About 1 g/L Protein Because the aBLAs Do Not Specify a Water Content

Apotex's aBLA specifications allow an inclusion-body concentration of 0.9-1.4 g/L with about 1 g/L or greater of such inclusion-body concentration being protein. (*See, e.g.*, Appx5592-5594; Appx5900-5902.) The district court relied on evidence outside the aBLAs to conclude otherwise, namely Dr. Dowd's testimony that Apotex's inclusion bodies are allegedly two-thirds water. (Appx24, Appx34; Apotex Red Br. at 17.) This is error because evidence outside the aBLA specifications is legally irrelevant to the infringement inquiry. *See Sunovion*, 731 F.3d at 1278.

Apotex now argues that the particular aBLA specifications "that Amgen chose to rely upon [i.e., inclusion-body concentration] include no requirement for

[6] The portion of the aBLA relied on by Apotex does not say that the 0.708 g/L protein concentration cannot be exceeded. (*See* Apotex Red Br. at 30.) It says that the 11.8 g/L concentration of the protein-containing volume is a "qualified upper limit," not a binding upper limit. (Appx5595, Appx5902 (emphasis added).) It also designates the 4.24-11.80 g/L range as a KPP.

any amount of protein or water to be present in the inclusion bodies." (Apotex Red Br. at 19.) As an initial matter, Amgen relied on inclusion-body concentration because Apotex pointed Amgen to this as interchangeable with protein concentration, both in its subparagraph 262(*l*)(3)(B) statements and in the testimony of its expert. (*See supra* Part II.A.) In any event, the aBLA specifications are not silent as to whether water is present in inclusion bodies. No water is present in the 0.9-1.4 g/L inclusion-body concentration in Apotex's refold mixture because the concentration is not based on a "wet weight." (*See, e.g.*, Appx5592-5594; Appx5900-5902.) And, as Amgen showed in its opening brief, when Apotex's aBLA specifications mean "wet weight," they say "wet weight." (Amgen Blue Br. at 17-18.) Specifically, after the process step of washing the inclusion bodies, the aBLAs identify a performance parameter called "inclusion body wet weight" with an expected range of 2.8-4.0 g/L. (Appx5588; Appx5896 (emphasis added).) Significantly, the aBLAs do not describe the inclusion-body concentration in Apotex's refold mixture—i.e., 0.9-1.4 g/L—as a wet weight. (*See, e.g.*, Appx5592-5594; Appx5900-5902.) In fact, the choice of words at the refolding step is that an amount of inclusion bodies "equivalent to" 0.9-1.4 g/L in the refold mixture is to be used, suggesting water content was accounted for. (Appx5592; Appx5900.) Thus, Apotex's aBLA specifications permit inclusion

bodies consisting of pure protein (or at least about 1 g/L protein); Apotex "has asked the FDA to approve" an infringing process. *See Sunovion*, 731 F.3d at 1278.

Lastly, Apotex relies on certain testimony by Amgen's expert, Dr. Willson, that he was "worried" about the presence of water in the inclusion bodies. (Apotex Red Br. at 19-20.) This testimony—on which the district court did not rely—represents nothing more than a turn of phrase by Dr. Willson as he explained how he had taken the water issue into account. He noted that the aBLAs had information on water with respect to some parameters and not others, and concluded that the 0.9-1.4 g/L concentration is not a wet weight because it is not designated as such. (*See* Appx3191-3193.)

CONCLUSION

Amgen respectfully requests that this Court reverse and/or remand the district court's judgment of no infringement.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on this 31st of January, 2017, I caused the foregoing REPLY BRIEF OF PLAINTIFFS-APPELLANTS AMGEN INC. AND AMGEN MANUFACTURING LIMITED to be filed with the Clerk of the Court using the CM/ECF system. I also caused a true and correct copy of the foregoing REPLY BRIEF OF PLAINTIFFS-APPELLANTS AMGEN INC. AND AMGEN MANUFACTURING LIMITED to be electronically served on Defendants-Appellees Apotex Inc. and Apotex Corp.'s counsel of record, as follows:

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This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B) because it contains 6,971 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b). The word count includes the words counted by the Microsoft Word 2010 function and the words included in images within this brief. This brief also complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6) because the brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 with 14-point Times New Roman font.

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