Nos. 2019-1650, 2019-1770

United States Court of Appeals for the Federal Circuit

AMGEN INC.,
Plaintiff-Appellant,

v.

WATSON LABORATORIES, INC., ACTAVIS PHARMA, INC.,
Defendants-Appellees,

AMNEAL PHARMACEUTICALS LLC, AMNEAL PHARMACEUTICALS OF NEW YORK LLC, CADILA HEALTHCARE LTD., DBA ZYDUS CADILA, CIPLA LIMITED, CIPLA USA INC., PIRAMAL HEALTHCARE UK LIMITED, SUN PHARMA GLOBAL FZE, SUN PHARMACEUTICAL INDUSTRIES, INC., SUN PHARMACEUTICAL INDUSTRIES, LTD., ZYDUS PHARMACEUTICALS (USA) INC.,
Defendants.

On appeal from the United States District Court for the District of Delaware,
Case No. 1:16-cv-00853-MSG

NON-CONFIDENTIAL OPENING BRIEF FOR PLAINTIFF-APPELLANT AMGEN INC.

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CERTIFICATE OF INTEREST

Counsel for Plaintiff-Appellant Amgen Inc. certifies the following:

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

Amgen Inc.

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

See response to number 1.

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

None.

4. The names of all law firms, and the partners or associates, that appeared for the party represented by me in the trial court or are expected to appear in this Court and who are not already listed on the docket for the current case are:

Venable LLP (formerly, Fitzpatrick, Cella, Harper & Scinto)
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5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal is:

See Statement of Related Cases, *infra*, at vii.

/s/ Bradford J. Badke
Bradford J. Badke

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CONFIDENTIAL MATERIAL OMITTED

The material omitted on pages 11, 22, 29, 36, 40, 46, 47, 48, 50 and in the addendum to this brief at ADD-1 through ADD-42 contains information filed under seal or subject to a protective order.

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STATEMENT OF RELATED CASES

Counsel for Amgen is aware of two pending consolidated cases before this Court that may be directly affected by the decision here: *Amgen Inc. v. Amneal Pharmaceuticals LLC,* No. 18-2414, docketed September 25, 2018, and No. 19-1086, docketed October 16, 2018. Those appeals concern the same district court case and the same patent, U.S. Patent No. 9,375,405 (the '405 patent) at issue here.

Counsel for Amgen is aware of a case before the U.S. Court of Appeals for the Third Circuit that may be directly affected by the Court's decision here: *Cipla Ltd. and Cipla USA, Inc. v. Amgen Inc.*, No. 19-2017, docketed May 3, 2019. The underlying lawsuit is proceeding in the district court during its appeal: *Cipla Ltd. v. Amgen Inc.*, C.A. No. 19-cv-44, filed January 8, 2019, in the United States District Court for the District of Delaware. Sun has also filed a motion to enforce its settlement agreement in the consolidated district court case underlying this appeal, which filing Amgen disputes. These actions concern settlement agreements regarding the '405 patent.

Counsel for Amgen is aware of another pending district court case that may be directly affected by the Court's decision here: *Amgen Inc. v. Accord Healthcare, Inc.*, C.A. No. 18-cv-956, filed June 28, 2018, in the United States District Court for the District of Delaware. Amgen has asserted the '405 patent against the defendant in that action.

Counsel for Amgen is unaware of any other related case(s) pending in this or any other court that will directly affect or be affected by the decision on appeal.

INTRODUCTION

The parties' agreement to settle should have ended this case. Immediately after Watson launched its generic cinacalcet HCl product at-risk, Watson and Amgen signed an agreement in which Watson "*admitted* … that the manufacture, use, sale, offer to sell, and distribution of [its] Products in the United States and importation of [its] Product into the United States, *would infringe* [Amgen's '405] Patent." APPX2 (first emphasis added) (quoting agreement). This agreement also had a critical premise—the parties had to seek vacatur of the district court's now-contradictory judgment of *non*-infringement and secure entry of their agreed-upon consent judgment. That provision is crucial; the agreement is not fully effective until it is satisfied. But two interloping generics, Sun and Cipla, who had long ago settled their own cases and admitted infringement, opposed Amgen and Watson's submission of their consent judgment to the district court. Urged on by these non-parties, the district court refused Amgen and Watson's joint request to effectuate their agreement.

This Court can right this wrong by vacating the district court's non-infringement judgment, remanding for entry of the parties' consent judgment, and putting an end to a case that neither party wants to litigate. The Court has two separate means for doing so given the agreed-upon settlement. It can exercise its authority to vacate independent of anything the district court did, under 28 U.S.C.

§ 2106. Or it can vacate based on errors in the district court's rejection of Amgen and Watson's consent judgment.

Section 2106 generally vests this Court with broad power to vacate as long as it is "just under the circumstances." It is. Vacatur is warranted because Watson, the party that won in the district court, has now recognized that the non-infringement judgment was in "error" through its infringement admission. *See, e.g.*, *Aqua Marine Supply v. AIM Machining, Inc.*, 247 F.3d 1216, 1221 & n.1 (Fed. Cir. 2001). Vacatur is also warranted because Watson wants this result at least as much as Amgen does—to remove the specter of damages from Watson's at-risk launch.

Honoring such agreements in multi-party Hatch-Waxman litigations such as this, moreover, serves the public interest. Whereas vacatur will impact only a Watson-specific non-infringement judgment that binds no future litigant, leaving that judgment in place multiplies the burden on courts and companies. Not only does it force this Watson litigation onwards against the wishes of the parties, but it inspires generics who have settled and admitted infringement, like Sun and Cipla, to try to litigate whether the Amgen-Watson events allow them to escape their agreements and launch their own admittedly infringing products. Especially in that context, there is no good reason to keep a judgment in place that both parties have since agreed should be replaced with a judgment reaching the opposite conclusion.

Alternatively, the Court should vacate because the district court's indicative ruling decision was replete with errors. The court used the wrong legal standard—that reserved for appellate review instead of Rule 60—to deny Amgen and Watson's joint motion to set aside the non-infringement judgement. Rule 60 allows district courts to relieve parties from a final judgment when it is no longer "equitable" or for "any other reason that justifies relief." The business and litigation certainty to be gained by honoring the parties' agreement to settle, plus Watson's admitted infringement, justify such relief. And the district court was simply wrong to conclude that *U.S. Bancorp Mortgage Co. v. Bonner Mall Partnership*, 513 U.S. 18 (1994) controls the outcome here when, in truth, the need to vacate and enter the consent judgment to effectuate any settlement makes this Hatch-Waxman case decidedly "[u]nlike *Bancorp*." *Major League Baseball Props., Inc. v. Pac. Trading Cards, Inc*, 150 F.3d 149, 152 (2d Cir. 1998).

If the Court does not vacate the judgment based on the agreement to settle, it should do so on the merits. The district court analyzed infringement under the doctrine of equivalents based on Watson's substitution of a different disintegrant than those claimed. But the district court erroneously focused on details about Watson's disintegrant that do not concern what is claimed, and ignored Watson's ANDA admissions that confirm equivalents. Such insubstantial differences are precisely what the doctrine was designed to capture.

Either way, the Watson non-infringement judgement cannot stand.

JURISDICTIONAL STATEMENT

The district court had subject-matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a) over Amgen's patent infringement lawsuit and entered judgment of non-infringement in favor of Watson on August 24, 2018. Amgen filed a timely notice of appeal on September 20, 2018, and this Court has jurisdiction over that appeal under 28 U.S.C. § 1295(a)(1).

After that appeal was docketed, and Amgen filed its opening brief, Amgen and Watson executed an agreement to settle. Because this Court had jurisdiction over the appeal, the parties jointly filed (1) a motion in the district court under Federal Rule of Civil Procedure 62.1 for an indicative ruling that it would vacate its judgment of non-infringement, and (2) a motion in this Court under Federal Rule of Appellate Procedure 12.1 for a stay pending the district court's decision. The district court denied the parties' motion on March 26, 2019. Amgen filed a timely notice of appeal from that denial on April 10, 2019, and this Court has jurisdiction over the appeal under 28 U.S.C. § 1295. *See, e.g.*, *LFoundry Rousset, SAS v. Atmel Corp.*, 690 F. App'x 748, 750-51 (2d Cir. 2017); *Dice Corp. v. Bold Techs.*, 556 F. App'x 378, 382-83 (6th Cir. 2014); *U.S. ex rel. Lockey v. City of Dallas*, 576 F. App'x 431, 434 (5th Cir. 2014) (per curiam); *Ray v. Pinnacle Health Hosps., Inc.*, 416 F. App'x 157, 160-61& n.3 (3d Cir. 2010).

STATEMENT OF ISSUES

1. Whether the Court should vacate the district court's judgment of non-infringement by Watson and direct entry of the consent judgment necessary to effectuate the parties' agreement to settle, because:

a. It is "just under the circumstances," 28 U.S.C. § 2106, to vacate and remand when, during an at-risk generic launch and ongoing multi-party litigation, Watson admitted infringement, and both parties need vacatur and entry of a consent judgment to dispense with their claims and thus premised their agreement on that outcome; or

b. the district court, in its denial of Amgen and Watson's motion for an indicative ruling, committed several errors and applied the wrong legal standards for determining circumstances warranting vacatur.

2. If the Court does not vacate in light of the parties' agreement, whether the judgment of non-infringement should also be vacated because:

a. the ruling on the doctrine of equivalents failed to apply the proper legal standard, and credited immaterial distinctions between Watson's accused ANDA products and claimed elements, when the equivalents analysis "should not be the prisoner of a rigid formula," *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1579 (Fed. Cir. 1984); and

b. Amgen's trial presentation was belatedly upended by an erroneous construction of independent claim 1 that violates this Court's Markush group and claim construction case law.

STATEMENT OF THE CASE

I. FACTUAL BACKGROUND

A. Technical Background And Sensipar®

The technology at the heart of these appeals is embodied in Sensipar®, which is Amgen's first-in-class drug that is FDA approved to treat hypercalcemia (above-normal calcium levels) in patients with parathyroid cancer, primary hyperparathyroidism, or secondary hyperparathyroidism with chronic kidney disease. APPX11459; APPX11791; APPX3352-3353. Sensipar®'s active ingredient is cinacalcet HCl, a calcimimetic, which means that it mimics a function of calcium in the body.

As two of defendants' experts conceded, cinacalcet HCl is a "really poorly soluble drug" and a "formulator's worst nightmare." APPX3203; APPX4006. After having chosen to pursue cinacalcet HCl, the Amgen inventors thus faced the challenging task of developing a cinacalcet HCl formulation that effectively dissolves and delivers the medicine. APPX3203-3204. They ultimately made a unique composition with a distinctive dissolution profile that solved the problem and proved highly effective for the treatment of parathyroid diseases.

The composition requires certain amounts of cinacalcet HCl and certain percentages of excipients—inactive substances that serve as the vehicle for the active ingredient. The relevant excipients for these purposes are diluents, binders, and disintegrants. Generally speaking, diluents are fillers that add bulk to the tablet, binders hold the ingredients together as a tablet, and disintegrants break up the tablet after ingestion to release the medicine. APPX11-12. Amgen's invention uses hardening binders, meaning they harden upon drying after a manufacturing process known as "wet granulation," and superdisintegrants, meaning they disintegrate rapidly. APPX3342; APPX3347-3348.

Amgen submitted its New Drug Application (NDA) on Sensipar® to the FDA in September 2003, and it was promptly approved in March 2004. APPX11791.

B. Amgen's Patent And Prosecution History

Amgen's U.S. Patent No. 9,375,405 (the '405 patent) is listed in the FDA's Orange Book and covers the essential composition embodied in Sensipar®. The specification describes the active ingredient and exemplary excipients, as well as their respective amounts. The patent also informs the skilled artisan which excipients can be categorized as diluents, binders, and disintegrants for purposes of determining their percentage weight in the inventive compositions, and it identifies

hardening binders and superdisintegrants as examples. APPX8061-8062 at 6:57-7:9, 7:32-41.

The originally-examined claims recited weight percentages of cinacalcet HCl as well as weight percentages of binders and disintegrants generally. APPX9737. Only pending dependent claims recited specific binder or disintegrant species. *Id.* Over the course of prosecution, Amgen amended the claims to require a specified amount of cinacalcet HCl and noted the invention's unique dissolution profile. *Id.* Pulling from dependent claims that had also been subject to an earlier rejection, the Examiner included Markush language in the binder and disintegrant elements of independent claim 1, and added a treatment limitation that he acknowledged was related to the amount of cinacalcet HCl and the dissolution profile. APPX10018-10034.

The patent issued on June 28, 2016. APPX8054. As the Examiner recognized, the claimed compositions provide effective and rapid dissolution of the tablet and thus good bioavailability of cinacalcet HCl necessary for treatment. APPX11283. Independent claim 1, the broadest claim, recites the inventive formulation:

> A pharmaceutical composition ***comprising***:
>
> (a) from about 10% to about 40% by weight of cinacalcet HCl in an amount of from about 20 mg to about 100 mg;
>
> (b) from about 45% to about 85% by weight of a diluent selected from the group consisting of microcrystalline cellulose, starch,

dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof,

(c) ***from about 1% to about 5% by weight of at least one binder selected from the group consisting of*** povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof; and

(d) ***from about 1% to 10% by weight of at least one disintegrant selected from the group consisting of*** crospovid[o]ne, sodium starch glycolate, croscarmellose sodium, and mixtures thereof,

wherein the percentage by weight is relative to the total weight of the composition, and wherein the composition is for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

APPX8065 at 13:18-39 (emphases added). The Markush groups of elements (c) and (d) recite the hardening binders and superdisintegrants, respectively, described in the specification. Dependent claims 5 and 6 limit the binder and disintegrant to particular recited members of elements (c) and (d).

II. PROCEDURAL BACKGROUND

A. Multi-Defendant Hatch-Waxman Litigation

Watson and some 20 other defendant groups submitted ANDAs to the FDA seeking to sell generic versions of Amgen's Sensipar® product. APPX3184. Amgen promptly filed suit under 35 U.S.C. § 271(e)(2), asserting that these ANDA products all infringe Amgen's '405 patent by using the claimed amounts of cinacalcet HCl as well as the claimed excipients or their equivalents, thus achieving the same desired dissolution profile to treat the same diseases.

APPX3206. In the lead-up to trial, Amgen reached settlement with multiple defendants groups, nine of which led to consent judgments.

The district court held a bench trial on only the issue of infringement by certain defendant groups' ANDA products, including Watson. After a last-minute claim construction decision that altered the course of trial, the district court held that Watson, Amneal, and Piramal did not infringe, while Zydus did. Amgen timely appealed the non-infringement judgments, and Zydus cross-appealed the infringement judgment. APPX136-137. Those appeals are docketed and consolidated under Case No. 18-2414.

B. Amgen And Watson's Negotiated Settlement

Amgen submitted its opening appeal brief against Amneal, Piramal, and Watson in Case No. 18-2414 on December 11, 2018. A couple of weeks later, on December 27, 2018, the FDA approved Watson's ANDA. The next day, Watson shipped approximately 400,000 bottles of its generic cinacalcet product to wholesalers. *Cipla Ltd. v. Amgen Inc.*, No. 1:19-cv-00044-LPS (D. Del. May 2, 2019), ECF No. 186, at 4. Watson estimated that the shipment would bring about $200 million in revenue. *Id.*

Once Amgen learned of the launch, the parties quickly came to the bargaining table. On January 2, 2019, Amgen and Watson executed a Litigation Settlement Agreement that, once effective, fully resolves their respective

infringement and invalidity claims. Both Amgen and Watson made significant concessions to get a deal done. On Watson's side, it stipulated that its ANDA products infringe the '405 patent and that the '405 patent is valid and enforceable. [redacted][1] Based on its admitted infringement, Watson also agreed to pay Amgen up to $40 million dollars in damages, and agreed to stop selling its ANDA products before a negotiated entry date. *See* [redacted]; *see also Cipla Ltd. v. Amgen Inc.*, No. 1:19-cv-00044-LPS (D. Del. May 2, 2019), ECF No. 186, at 5. For its part, Amgen agreed to withdraw its pending appeal from the Watson non-infringement judgment, and to release any further damages claims that Amgen could have otherwise made in connection with the $200 million worth of Watson ANDA products that had already launched. [redacted]. Under the terms of the Agreement, the parties were required to ask the district court to enter a consent judgment, and the provisions on payment and release of claims do not take effect until that consent judgment is entered.

[1] Although the consent judgment was attached as an exhibit to the motion for an indicative ruling, the Amgen-Watson Agreement was not entered on the district court docket. That agreement, however, has been entered on the docket in *Cipla Ltd. v. Amgen Inc.*, No. 1:19-cv-00044-LPS (D. Del.), ECF No. 73-1, Ex. 3. Because that filing is under seal, Amgen has included the agreement here for the Court's convenience.

The terms of the Amgen-Watson Agreement were effectively identical to numerous other consent judgments the district court had already approved and entered in the case.

C. Amgen And Watson's Motions Directed To Their Consent Judgment

Pursuant to their agreement, Amgen and Watson sought entry of their consent judgment. Because Amgen's appeal of the Watson non-infringement judgment was pending in this Court, Amgen and Watson employed Federal Rule of Civil Procedure 62.1, which explicitly allows a district court that "lacks authority to grant [a motion] because of an appeal" to state that it would do so "if the court of appeals remands for that purpose." Fed. R. Civ. P. 62.1(a). On January 9, 2019, Amgen and Watson jointly asked the district court for an indicative ruling that it would vacate its July 27, 2018 Opinion and Trial Order (APPX7-8, APPX9-51) and August 24, 2018 Final Judgment and Order (APPX79-80, APPX5010-5012) (collectively, "the Orders") as they relate to Watson and, specifically, the provisions stating that Watson's ANDA Products do not infringe the '405 patent. APPX5077-5081, APPX5082-5094. With the non-infringement judgment vacated, the parties would then seek entry of the consent judgment.

The parties' motion explained that vacatur was warranted under Federal Rule of Civil Procedure 60(b)(5) or 60(b)(6). APPX5079, APPX5090-5093. The former authorizes vacatur when "applying [a final judgment] prospectively is no

longer equitable," and the latter does so for "any other reason that justifies relief." Fed. R. Civ. P. 60(b)(5), (6); *see also Kirby Forest Indus., Inc. v. United States*, 467 U.S. 1, 18 (1984); *Stradley v. Cortez*, 518 F.2d 488, 493 (3d Cir. 1975). Under those rules, Amgen and Watson argued that, on remand, the specific context and terms of their agreement warranted vacating the non-infringement judgment and entering a consent judgment like the many others that had preceded it. APPX5077-5079.

In this Court, Amgen and Watson jointly sought to stay the merits appeal with respect to Watson while the district court decided the indicative ruling motion. Unopposed Emergency Joint Motion to Stay Appellate Proceedings as to the Watson Appellees, *Amgen Inc. v. Amneal Pharm., LLC*, No. 18-2414 (Fed. Cir. Jan. 9, 2019), ECF No. 59. This Court granted the unopposed stay request. Order, *Amgen*, No. 18-2414 (Jan. 11, 2019), ECF No. 61. The other parties to the appeal (Amneal, Piramal, and Zydus) moved to deconsolidate the appeal related to Watson from their proceedings. Unopposed Joint Motion for Clarification and Deconsolidation as to the Watson Appellees, *Amgen*, No. 18-2414 (Jan. 15, 2019), ECF No. 63. This Court granted the motion, deconsolidated the Watson appeal, and directed the opening of a new appeal number for Watson. Order at 2, *Amgen*, No. 18-2414 (Jan. 9, 2019), ECF No. 64. The Court then stayed all proceedings in Watson's new case No. 19-1650. *Id.*

D. The District Court's Denial Of Amgen And Watson's Motion For An Indicative Ruling

Two generics who previously had settled their own cases and admitted infringement, Cipla and Sun, sought to inject themselves into the district court's consideration of Amgen's and Watson's joint motion for an indicative ruling. APPX5104-5143. Specifically, Cipla and Sun both filed what purported to be "oppositions" to the joint motion, urging the district court to deny the motion and maintain its non-infringement judgment. *Id.* Apart from the substantive flaws with these filings, Amgen and Watson explained that Cipla and Sun had no right to oppose a motion after their own cases were terminated and in an action to which they are not parties. APPX5144-5157.

On March 26, 2019, the district court denied the parties' joint motion for an indicative ruling. APPX1-6. Largely ignoring Amgen and Watson, the district court cited the unsolicited (and improper) briefing from Cipla and Sun. APPX3-4. The court's reasoning for denying the motion was brief. It held that *U.S. Bancorp Mortgage Co. v. Bonner Mall Partnership*, 513 U.S. 18 (1994), controls the outcome, dismissed in a footnote the parties' explanation that *Bancorp*'s standard was inapplicable, and found this case "similar" to an unpublished decision from outside the Hatch-Waxman context. APPX4-5. As for Rule 60, the district court stated that it would decline to vacate under subparagraph (6), despite the Rule's allowance for relief from a judgment for "any other reason that justifie[s] relief."

APPX4 (citing Rule 60(b)(6)). In a footnote, the district court also dismissed subparagraph (5), which permits vacatur when, among other things, "applying [the judgment] prospectively is no longer equitable" and reasoned that none of the provision's "stated reasons seem to apply." APPX5.

E. The Return To This Court

On April 10, 2019, Amgen notified this Court of the district court's decision on the motion for an indicative ruling and requested that the Court maintain the stay of the merits appeal (No. 19-1650) because this Court's decision on vacatur based on the consent judgment could (and should) dispose of any remaining merits appeal. Notice Regarding Status of Indicative Ruling, ECF No. 25; Order at 2, *Amgen*, No. 18-2414 (Jan. 11, 2019), ECF No. 61. Amgen also stated that Watson would neither join nor oppose an appeal on the vacatur issue. *Id.* On April 29, 2019, the Court lifted the stay on the merits appeal and consolidated all Amgen-Watson appeals under one lead case. ECF No. 26.

SUMMARY OF ARGUMENT

I. There are two separate ways the Court can and should vacate the non-infringement judgment and direct entry of the consent judgment pursuant to the parties' settlement.

A. The Court should vacate and remand pursuant to its own authority under 28 U.S.C. § 2106, independent of the district court, and order that the

parties' proposed consent judgment of infringement be entered for at least three reasons.

First, this Court and others recognize that vacatur is appropriate when the party that won below acknowledges that it should *not* have won. *See, e.g.*, *Aqua Marine Supply*, 247 F.3d at 1221 & n.1. That is what happened here—Watson prevailed in the district court but then admitted infringement in the proposed consent judgment. The contrary district court judgment should be vacated and the agreed-to consent judgment should be entered.

Second, the "victor in the district court wanted a settlement as much as, or more than, the loser did." *Major League Baseball*, 150 F.3d at 152. Given the context of Watson's at-risk launch, the agreement to settle allows *both* parties to "end [their dispute] on a commercial basis satisfactory to both." *Id.* That is why *both* parties jointly moved for vacatur and entry of the consent judgment.

Third, the particular circumstances of multi-party Hatch-Waxman litigation means that the proper way to promote "orderly operation of the federal judicial system," *Bancorp*, 513 U.S. at 27, is to allow brands and generics to agree to settlements that provide for vacatur of non-infringement judgments and entry of consent judgments of infringement. Unlike a judgment of invalidity, the Watson non-infringement judgment has no prospective effect for future parties or litigants. Such non-infringement judgments can, however, have significant collateral

consequences by allowing earlier Hatch-Waxman litigants that settled to try to use the non-infringement judgment as a basis for launching infringing sales of their generic products. That would create chaos and should be rejected.

The Court can vacate on this § 2106 authority alone.

B. On direct appellate review, the Court can vacate based on errors in the district court's indicative ruling decision. First, the district court applied the wrong standard in deciding the motion—a legal error. It used the standard for *appellate* courts under *Bancorp* rather than the framework outlined in Rule 60 that governs district courts. Second, compounding the problem, the district court ignored entirely an on-point provision of Rule 60, under which the non-infringement judgment as to Watson should be vacated because it would be inequitable to apply prospectively given the agreement to settle. Finally, the district court premised its entire analysis on the assumption that this case involves "mootness by settlement" under *Bancorp*, when that is not the case. Amgen and Watson's agreement to settle is premised on entry of their consent judgment after vacatur and, until then, the dispute remains live. For that and other reasons, this case is simply "[u]nlike *Bancorp*." *Major League Baseball*, 150 F.3d at 152. These errors provide another, separate basis for vacatur and remand.

II. If the Court does not vacate the non-infringement judgment and remand based on the parties' agreement to settle, it should do so because the district court's infringement analysis on the merits was incorrect.

First, the district court's analysis of Watson's ANDA products under the doctrine of equivalents applied the wrong test. The district court formulated and imposed a strict standard that this Court has never endorsed, and even faulted Amgen's expert for failing to use magic words like "function," "way," and "result" in his equivalents analysis. The district court then rejected equivalents based on supposed distinctions that had nothing to do with the claimed properties of the excipients, discounting and even declining to consider highly relevant admissions in Watson's ANDA that underscore equivalents. This approach violates this Court's precedent and thwarts the maxim that the doctrine of equivalents "is not the prisoner of a formula and is not an absolute to be considered in a vacuum." *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 609 (1950).

Second, the district court erroneously construed a pharmaceutical composition "comprising" several ingredients, including "at least one binder" and "at least one disintegrant" selected from Markush groups, as requiring "at least one" such binder and "at least one" such disintegrant "*and no unlisted binders [or] disintegrants*." APPX52. That is contrary to this Court's case law. Because trial proceeded under this claim construction error, and because Watson's non-

infringement presentation invoked issues implicated by that construction, the Court can vacate on that basis as well.

ARGUMENT

I. THIS COURT SHOULD VACATE THE DISTRICT COURT'S NON-INFRINGMENT JUDGMENT IN LIGHT OF THE PARTIES' NEGOTIATED AGREEMENT TO SETTLE.

The Court should vacate the district court's non-infringement judgment in light of the parties' agreement to settle for two independent reasons. First, the Court should vacate the non-infringement judgment under its independent and discretionary authority under 28 U.S.C. § 2106. Second, the Court may also vacate under its ordinary appellate jurisdiction to review the district court's misguided indicative ruling decision.

A. The Court Should Vacate The Non-Infringement Judgment Under Its Section 2106 Authority.

This Court has ample authority to vacate the district court's non-infringement judgment on its own: section 2106 allows the Court to "affirm, modify, vacate, set aside or reverse any judgment" when doing so would be "just under the circumstances." That provision gives "broad discretion to grant relief." *United States v. Edwards*, 728 F.3d 1286, 1296-97 (11th Cir. 2013); *GuideOne Specialty Mut. Ins. Co. v. Missionary Church of Disciples of Jesus Christ*, 687 F.3d 676, 682 n.3 (5th Cir. 2012) (§ 2106 gives courts of appeal "broad authority to dispose of district court judgments as they see fit"); *Abdallah v. Scism*, 424 F.

App'x 84, 85 n.1 (3d Cir. 2011) (per curiam) (§ 2106 "empowers [courts of appeal] to choose from a broad range of remedies"); *see also United States v. Martinez*, 606 F.3d 1303, 1304 (11th Cir. 2010) ("[W]e cannot imagine how the appellate court's discretion could be framed more broadly.").

What is "just," of course, depends on "the circumstances." Under Section 2106, the Supreme Court in its *Bancorp* decision observed that appellate courts' "established practice … in dealing with a civil case from a court in the federal system which has become moot while on its way here or pending our decision on the merits is to reverse or vacate the judgment below and remand with a direction to dismiss." 513 U.S. at 22-23. The Court noted, however, that this "established practice" typically does not extend to "mootness by reason of settlement." *Id.* at 29. But the Court quickly added that it was "not say[ing] that vacatur can never be granted" following any agreement to settle—indeed, it recognized that "exceptional circumstances" can lead to vacatur even after settlement. *Id.*

Following *Bancorp*, courts of appeals have found it "just" to vacate in cases like this one. That may include, for example, a settlement that affected no "significant public interests" and created "exceptional circumstances … to warrant vacatur." *See, e.g.*, Mandate, *Mattel, Inc. v. Goldberger Doll Mfg. Co.*, No. 04-6432 (2d Cir. Nov. 20, 2006); *see also Major League Baseball*, 150 F.3d at 152 (vacating judgment in circumstances "[u]nlike *Bancorp*"). Here, Amgen and

Watson agreed to settle—and Watson admitted to infringement—during a multi-defendant Hatch-Waxman litigation that created unique and exceptional economic realities justifying a business-decision end to litigation for both sides. That was nothing like *Bancorp*, in which a two-party settlement about a bankruptcy reorganization plan did not revolve around any market-based incentives or settlement circumstances remotely comparable to those that exist under Hatch-Waxman. *See* § I.B (further distinguishing *Bancorp* and explaining why it does not control).

At least three reasons render the circumstances here both "exceptional" and certainly "just" and thus support vacatur.

1. Vacatur Is Appropriate Because Watson Agrees That It Has Infringed The '405 Patent.

The first is that Watson has admitted infringement, in contradiction of the judgment of non-infringement.

Vacatur of a judgment is appropriate when the party that won below acknowledges that it should *not* have won. In *Aqua Marine Supply*, this Court recognized the importance of such an admission. 247 F.3d at 1221 n.1. The Court noted that vacatur typically is not appropriate following settlement, but highlighted that the outcome would be different if the "opposing party," *i.e.*, the party that won in the district court, acknowledged that the trial court's decision was an "error." *Id*.

In subsequent cases, too, the Court has found vacatur appropriate when the appellee acknowledges that the appellant had the better argument. *See, e.g.*, *Katz-Pueschel v. Merit Sys. Prot. Bd.*, 352 F. App'x 417, 418 (Fed. Cir. 2009) (vacating after one party confessed error); *Durr v. Merit Sys. Prot. Bd.*, 297 F. App'x 966, 969 (Fed. Cir. 2008) (per curiam) (vacating after one party confessed error). Likewise, the Supreme Court's "practice" is to vacate a lower court decision based on only a "plausible confession[] of error." *Lawrence ex rel. Lawrence v. Chater*, 516 U.S. 163, 171 (1996) (per curiam). Such "plausible" confessions need not expressly say that the court "erred." Rather, they can include something as simple as changes in position, like "a new agency interpretation of a statute" entitled to *Chevron* deference. *See id.* Where the winning party's admission undermines the judgment's integrity, the best course is to remove that judgment from the books.

These principles compel vacatur here. Although Watson prevailed below on infringement, it has now "admitted … that the manufacture, use, sale, offer to sell, and distribution of [its] Products in the United States and importation of [its] Products into the United States, would infringe the ['405] Patent." APPX2; [redacted] [redacted] That agreement does not use the term "error" *per se* to describe the non-infringement judgment, but it did not need to: Watson prevailed and then signed an agreement admitting to infringement. The settlement agreement is unequivocal

about Watson's infringement; it contains no standard-issue settlement language in which Watson "neither admits nor denies" infringement.

This Court has recognized, moreover, that it is perfectly appropriate to take Watson at its word in these circumstances. Settlements "can reflect the assessment by interested and adversarial parties of the range of plausible litigation outcomes." *Prism Techs. LLC v. Sprint Spectrum L.P.*, 849 F.3d 1360, 1369 (Fed. Cir. 2017. "[G]iven the necessary premise that discovery and adversarial processes tend to move a legal inquiry toward improved answers, the parties' agreement seems especially probative if reached after the litigation was far enough along that the issue was already well explored and well tested." *Id.* This post-trial litigation was certainly "far enough along"—Watson settled after Amgen filed its opening appellate brief. Watson's admission of infringement, therefore, reflects an "especially probative" view of the merits. In such circumstances, it is prudent to vacate the non-infringement judgment and remand for entry of a judgment that mirrors Watson's settlement position.

If more were needed, Watson's about-face also presents real practical concerns about the underlying appeal. It is elementary that the Court is "dependen[t] … on the adversarial process for sharpening the issues for decision," without which it could issue an "improvident or ill-advised opinion." *Carbino v. West*, 168 F.3d 32, 34-35 (Fed. Cir. 1999). But it is unclear whether Watson will

even participate in these appeals, never mind how Watson will try to navigate its admission of infringement on the merits if it does. Indeed, even though the parties' agreement does not become fully effective until entry of a consent judgment, Watson previously indicated that it would not oppose or participate in Amgen's appeal of the indicative ruling decision. Notice Regarding Status of Indicative Ruling, ECF No. 25. All the more reason to simply vacate the now-compromised non-infringement judgment, wipe the slate clean, and end a case that neither party wants to litigate by entering the consent judgment needed to effectuate their settlement.

2. Vacatur Is Appropriate Because The Deal Benefited Both Parties.

The second reason for vacatur is that the Amgen-Watson agreement is an emphatically two-sided agreement through which both parties seek and want that result.

The remedy of vacatur is appropriate when the "victor in the district court wanted a settlement as much as, or more than, the loser did." *Major League Baseball*, 150 F.3d at 152. That principle underlies the Second Circuit's decision in *Major League Baseball*, a decision that has been cited with approval by this Court. MLB, the plaintiff there, lost a preliminary injunction motion seeking to restrain a baseball card company from selling cards. *Id.* at 150. While MLB's request for expedited appeal (and its motion for an injunction pending appeal) were

pending before the Court of Appeals, the parties reached a settlement conditioned on vacatur of the district court's order. *Id.* at 151.

That agreement reflected each side's unique circumstances. The card company had to sell cards to stay in business but was financially unable to post an appeal bond and could not "test the merits of the favorable lower-court opinion without risking the severe financial consequences." *Id.* at 152. MLB "was agreeable to a settlement but needed a vacatur because, in the course of defending its [trade]marks, it … had to be concerned about the effect of the district court's decision in future litigation with alleged infringers." *Id.* The parties "were thus locked in a dispute that they could end on a commercial basis satisfactory to both." *Id.* That is, the "victor in the district court wanted a settlement as much as, or more than, the loser did," and the loser was amenable to an agreement but needed a vacatur to protect its interests. The Second Circuit vacated the judgment. *See id.*

This Court has cited that decision favorably. In *Aqua Marine Supply*, the Court explicitly recognized that *Major League Baseball* vacated the district court judgment when one party "could not test the merits of the district court's judgment without severe financial risk" and the other party "insisted on vacatur out of concern over future litigation." 247 F.3d at 1221.

This case is much like *Major League Baseball* and *Aqua Marine Supply*'s reference to it. Amgen and Watson agreed to settle during Watson's at-risk launch

of its generic cinacalcet HCl product, a situation in which both sides had significant and time-sensitive exposure. For Watson, it risked, among other things, massive damages flowing from the sale of its products. Like *Major League Baseball*, therefore, "the victor in the district court wanted a settlement as much as, or more than, the loser did," 150 F.3d at 152, and that settlement could spare Watson from "severe financial risk," *Aqua Marine Supply*, 247 F.3d at 1221. Also like *Major League Baseball*, Amgen was "agreeable to settlement" but "needed a vacatur" to effectuate Watson's admitted infringement and to avoid the "effect of the district court's decision" on earlier settlements in this case—and thus on sales of Sensipar®. 150 F.3d at 152.

These dynamics demonstrate the bilateral and reciprocal nature of the deal. Watson put itself in a situation in which it wanted to settle "as much as, or more than" Amgen did, and the parties were able to agree to "end [their dispute] on a commercial basis satisfactory to both." *Id.* The Court should allow the parties to fulfill that agreement by vacating the existing judgment and remanding with instructions to enter the consent judgment so that the parties can go their separate ways. *See Tommy Hilfiger Licensing, Inc. v. Costco Cos.*, No. 99-cv-3894, 2002 WL 31654958, at *2 (S.D.N.Y. Nov. 25, 2002) ("The courts have undeniably been more flexible where vacatur would bring an end to the tortured history of a

litigation, opening a door to settlement by relieving some party from having to fight an undesirable ruling on appeal.").

3. Vacatur Is Appropriate Because It Will Promote The Public Interest In Efficient Hatch-Waxman Litigation.

The third reason supporting vacatur is tied to the unique circumstances that the Hatch-Waxman Act creates. The Supreme Court has counseled that the "equitable" considerations governing vacatur should include evaluating the public interest in preserving "the orderly operation of the federal judicial system" as well as the private interests of the parties. *Bancorp*, 513 U.S. at 26-27. In the Hatch-Waxman context, permitting parties to reach settlements and vacate contrary judgments promotes the "orderly operation of the federal judicial system," while a different result would hinder that system. *Id.* at 27.

Generally speaking, "[t]he law strongly favors settlement of litigation, and there is a compelling public interest and policy in upholding and enforcing settlement agreements voluntarily entered into." *Hemstreet v. Spiegel, Inc.*, 851 F.2d 348, 350 (Fed. Cir. 1988). This Court thus "heartily endorses" the proposition that "courts should favor and enforce settlement agreements." *Hartley v. Mentor Corp.*, 869 F.2d 1469, 1473 n.5 (Fed. Cir. 1989). Such agreements by their nature conserve judicial resources and provide certainty to parties.

These policies are uniquely magnified in Hatch-Waxman litigation, where "orderly operation" of the judiciary often demands that brand-generic settlements

be effectuated through vacatur and entry of consent judgments. The Hatch-Waxman Act established a regulatory framework that is designed both to "'induc[e] pioneering research and development of new drugs and [to] enabl[e] competitors to bring low-cost, generic copies of those drugs to market.'" *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1325 (Fed. Cir. 2003) (per curiam). It sets up a "carefully crafted balance" between brands and generics. *See Closing the Gaps in Hatch-Waxman: Assuring Greater Access to Affordable Pharmaceuticals: Hearing Before the S. Comm. on Health, Educ., Labor, and Pensions*, 107th Cong. 11 (2002) (statement of Sen. Hatch).

Under this system, there can be many different ANDA filers on a given drug and thus many different infringement lawsuits occurring simultaneously. These cases feature a host of generics, with an array of approval dates, which can enter the market, for example, at-risk upon expiration of the 30-month litigation-induced stay under Hatch-Waxman or a non-infringement decision by the district court. This system of overlapping suits, moreover, generates dynamic economic circumstances where settlement often emerges as the most rational option for certain parties. Any generic launch disrupts the status quo for a particular drug's pricing. Generics thus may choose to settle at various times to guard against the financial risks inherent in an at-risk launch. And brands may settle to protect against the potentially irreversible effects of at-risk generic entry. In short, the

circumstances present in Hatch-Waxman litigation often incentivize settlement to create certainty among the multiple participants in the context of a changing market.

The net effect of ANDA settlements, moreover, is usually to facilitate generic entry earlier than it otherwise would occur. The agreement at issue here is a good example, as it allows generic entry before the '405 patent expires. *See* [redacted]. Such settlements are typically submitted to and subject to review by the Federal Trade Commission and the U.S. Department of Justice to ensure that they are beneficial to the public interest. *See, e.g.*, [redacted].

Within this Hatch-Waxman context, courts have recognized that vacatur is appropriate to promote efficiencies and orderly judicial functioning. *See, e.g.*, *Braintree Labs., Inc. v. Lupin Atlantis Holdings SA*, No. 3:11-cv-01341-PGS-LHG, 2016 WL 8814360, at *1-2 (D.N.J. Sept. 20, 2016); *Zeneca Ltd. v. Pharmachemie B.V.*, 37 F. Supp. 2d 85, 90 (D. Mass. Feb. 26, 1999); *Hospira, Inc. v. Sandoz Inc.*, No. 09-4591, 2014 WL 794589, at *5 (D.N.J. Feb. 27, 2014). That is particularly true when the settlement agreement builds in the need for vacatur and entry of a consent judgment. In analogous circumstances, for example, a district court held

that "it would be inequitable … to refuse to modify a judgment preventing the parties from carrying out [their] settlement." *Janssen Prods., L.P. v. Lupin Ltd.*, No. 10-5954 (WHW), 2016 WL 1029269, *3 (D.N.J. Mar. 15, 2016). In addition, the requested modification from a judgment of non-infringement to a judgment of infringement left "intact the Court's findings of fact and law and the injunctive relief ordered against the remaining Defendants," *id.*, and was "suitably tailored to the changed circumstances," *id.*

This case is analogous. Despite admitting infringement, Watson still has a judgment on the books of non-infringement. Allowing that non-infringement judgment to stand therefore risks eliminating altogether the parties' ability to "end [these disputes] on a commercial basis satisfactory to both," *MLB*, 150 F.3d at 152, and creates an inequitable result that has no precedential value. The public interest is therefore squarely aligned with effectuating the terms of the parties' agreement to settle.

All of this demonstrates why the outward-facing effects of a vacatur determination in the Hatch-Waxman context—including in this case—are different in kind from other litigation contexts. On the one hand, the non-infringement judgment against Watson was a fact-specific finding as to Watson's ANDA products. The Amgen-Watson settlement, in turn, is premised on entry of a consent judgment that recognizes the admission that only Watson can make: its

ANDA products infringe. No other companies' products are implicated, and vacating the contrary underlying Watson judgment will have no forward-looking precedential effect.

On the other hand, leaving the Amgen-Watson judgment in place does have an inequitable impact beyond just these two parties—in particular, vis-à-vis prior litigants in this ANDA case which themselves have admitted infringement and are subject to consent judgments. Those consent judgments and settlement agreements, in turn, typically contain provisions connecting a settled generic's right to launch to the existence of another generic's final (post-appeal) judgment of non-infringement. Sun and Cipla, for example, have tried to use the district court's refusal to vacate the Watson non-infringement judgment at their urging to leverage provisions in their own settlement agreements. Entry of Amgen and Watson's consent judgment will put an end to such misplaced arguments.

This is different than seeking vacatur of a judgment tethered to broader determinations, like invalidity, that can impact prospective public rights in the patent beyond the accused infringer in the present case. Even then, some courts have vacated invalidity decisions when the opinion had limited precedential value as "mere persuasive authority." *Hospira*, 2014 WL 794589, at *4. But no such *prospective* public interest lies in Watson's non-infringement judgment, and

vacating the Watson judgment does not foreclose any other company from challenging the validity of the '405 patent claims.[2]

Even if there were a prevailing public interest in preserving a Hatch-Waxman non-infringement judgment, moreover, "the public interest is not served only by the preservation of precedent" but also "by settlements when previously committed judicial resources are made available to deal with other matters, advancing the efficiency of the federal courts." *Hartford Cas. Ins. Co. v. Crum & Forster Specialty Ins. Co.*, 828 F.3d 1331, 1337 (11th Cir. 2016) (overturning a district court's denial of a Rule 60(b) motion where settlement would be impossible without vacatur). Agreements to settle should therefore be evaluated with "proper consideration … given to the interests of the parties, the judicial system, and the public taken together." *Id.* In such instances, "vacatur may still prove an appropriate remedy even if the public's interest in the preservation of precedent is not affirmatively advanced when considered in isolation." *Id.* That is precisely the case here.

In short, Hatch-Waxman dynamics create circumstances that provide yet another reason to vacate the non-infringement judgment and order entry of the proposed consent judgment. *See, e.g.*, *Janssen Prods., L.P.*, 2016 WL 1029269, at

[2] To the extent that the public has an interest in the interpretation of the asserted claims, that claim construction is not anchored exclusively to the Watson judgment and is before this Court in Appeal No. 18-2414.

*3; *Braintree Labs.*, 2016 WL 8814360, at *1-2; *Zeneca Ltd.*, 37 F. Supp. 2d at 90; *Hospira*, 2014 WL 794589, at *5. Watson gambled on a brief at-risk launch, before seeking the certainty of settlement. Amgen, too, was motivated to eliminate any threat from the Watson non-infringement judgment and protect its patent rights on Sensipar®. Enforcing such rationally-minded agreements is the proper—indeed, only—way to ensure "the orderly operation of the federal judicial system." *Bancorp*, 513 U.S. at 27.

The Court should exercise its broad discretion under Section 2106, vacate the non-infringement judgement, and direct entry of the parties' consent judgment.

B. The Court Should Vacate The Non-Infringement Judgment Because The District Court's Analysis Was Critically Flawed.

All of the above is more than sufficient for this Court to hold that the Watson judgment of non-infringement should be vacated with instructions to enter the parties' agreed consent judgment. The Court need not go any further to decide this appeal and end this litigation.

Separate from Section 2106, however, there is another reason to vacate: this Court can and should overturn the district court's erroneous decision denying the joint motion for an indicative ruling. That path of appellate review still rests on equitable considerations, but direct review of the district court's decision brings about distinct standards of review. In particular, a district court's denial of a Rule 62.1 motion for indicative ruling is typically reviewed for abuse of discretion, *Ray*,

416 F. App'x at 160-61 & n.3, while any "legal conclusions" therein are reviewed "*de novo*," *Tanikumi v. Walt Disney Co.*, 616 F. App'x 515, 517 (3d Cir. 2015) (per curiam); *see also Amado v. Microsoft Corp.*, 517 F.3d 1353, 1357 (Fed. Cir. 2008) (issue "is reviewed under the law of the regional circuit").

The district court's denial of the joint motion for an indicative ruling committed at least four fundamental errors that provide additional reasons why it should be overturned.

First, the district court invoked the wrong legal standard—an issue reviewed *de novo*. It applied the "exceptional circumstances" standard from *Bancorp*, APPX4-5, but that standard does not apply to district courts. Rather, *Bancorp* "by its terms, … does not apply to district courts but rather only to the Supreme Court and to courts of appeals." *Dana v. E.S. Originals, Inc.*, 342 F.3d 1320, 1328 (Fed. Cir. 2003) (Dyk, J., concurring). Vacatur in the district court is therefore *not* "cabined by the 'exceptional circumstances' test." *Marseilles Hydro Power LLC v. Marseilles Land & Water Co.*, 481 F.3d 1002, 1003 (7th Cir. 2007).

In a footnote, the district court seemed to suggest either that it need only consider *Bancorp*'s "exceptional circumstances" appellate standard (and not Rule 60(b)), or that it need only consider Rule 60(b) if the case is remanded. APPX4. Neither assertion is correct. Rule 60(b) itself provides the applicable district court standard: whether the non-infringement judgment should be vacated because

applying it "would no longer be equitable," Fed. R. Civ. P. 60(b)(5), or for "any other reason that justifies relief," Fed. R. Civ. P. 60(b)(6). And the fact that an appellate court may "remand the case with instructions that the district court consider the request [to vacate]," *Bancorp*, 513 U.S. at 29, does not mean, contrary to what the district court held, that *Bancorp*'s "exceptional circumstances" test for appellate vacatur of a district court decision applies to a district court's own vacatur decision.

Second, again in a footnote, the district court erroneously dismissed the parties' argument that relief was warranted under Rule 60(b)(5) or 60(b)(6) as inapplicable. According to the district court, "[n]one of the[] stated reasons [in Rule 60(b)(5)] seem to apply here. APPX5. But Rule 60(b)(5) is not limited to a discrete list of specific "reasons"; it applies anytime that it would "no longer [be] equitable" to apply a judgment prospectively, Fed. R. Civ. P. 60(b)(5). As discussed above, application of a non-infringement judgment would "no longer [be] equitable" following a "significant change … in factual conditions" like Watson's admission of infringement here. *Agostini v. Felton*, 521 U.S. 203, 215 (1997). To the extent the district court considered only Rule 60(b)(6)—yet another legal question that this Court considers *de novo*—that too was wrong. And, as explained above, the agreement here meets Rule 60(b)(6) as well.

Third, the premise of the district court's decision was that this case concerns "[m]ootness by reason of settlement" under *Bancorp*. APPX4. But Amgen and Watson never said that the case was in fact moot, and the district court made no actual finding as to why it was. In truth, there is still a live dispute because the "Effective Date" of the Amgen-Watson agreement is tethered to entry of the consent judgment. [redacted] Unless and until that happens, the agreement does not moot the parties' dispute. The not-yet-fully-effective agreement to settle plainly does not strip Article III jurisdiction, and the "mootness by settlement" framework is therefore not squarely on point.

Fourth, the district court was wrong to conclude that this is a case in which "the party seeking relief [on appeal, *i.e.*, Amgen,] voluntarily terminate[d] the controversy." APPX4. When a case settles on appeal, it may be because one party has "voluntarily abandoned review," or "voluntarily forfeited his legal remedy by the ordinary processes of appeal or certiorari, thereby surrendering his claim to the equitable remedy of vacatur." *Bancorp*, 513 U.S. at 25, 28. Facts that "diminish[] the voluntariness" of the forfeiture, however, counsel in favor of vacating the underlying judgment. *Id.* at 29. A settlement for reasons other than the losing party's voluntary decision to relinquish its right to further review would thus put a

thumb on the vacatur side of the scale. *See generally Alvarez v. Smith*, 558 U.S. 87, 97 (2009) (vacating judgment because there was "not present … the kind of 'voluntary forfeit[ure]' of a legal remedy that led the Court in *Bancorp* to find that considerations of 'fairness' and 'equity' tilted against vacatur"); *Hartford Cas. Ins. Co.*, 828 F.3d at 1336.

For reasons explained above, *supra* § I.A.2, nothing about the agreement to settle in this case demonstrates that Amgen "voluntarily forfeited [its] legal remedy by the ordinary process[] of appeal." *Bancorp*, 513 U.S. at 25. The agreement and need for vacatur were mutual, and this case thus does not reflect a one-sided decision by Amgen to give up its appeal rights. Contrary to the district court's decision, therefore, this case is "[u]nlike *Bancorp.*" *Major League Baseball*, 150 F.3d at 152.

In sum, any one of these errors in the district court's indicative ruling decision provide an independent reason to vacate and remand here.

II. IN THE ALTERNATIVE, THE COURT SHOULD VACATE THE DISTRICT COURT'S ERRONEOUS NON-INFRINGEMENT JUDGMENT ON THE MERITS.

If the Court declines to vacate in light of the parties' negotiated settlement, it should still vacate the judgment on the merits because (A) the district court's infringement analysis of Watson's ANDA products applied the wrong legal

standard, and (B) the trial and the resulting judgment were based on an erroneous construction of independent claim 1.

These issues are generally reviewed *de novo*. That is true of the question of whether the district court applied the correct legal standard in assessing equivalents. *E.g.*, *Insituform Techs., Inc. v. Cat Contracting, Inc.*, 99 F.3d 1098, 1105 (Fed. Cir. 1996) ("we must consider *de novo* whether the legal standards applied … are correct as a matter of law"); *Insituform Techs., Inc. v. Cat Contracting, Inc.*, 161 F.3d 688, 693-95 (Fed. Cir. 1998) (reversing because the district court "legally erred in its methodology" through the "legal errors in," among other things, "defining incorrectly the 'way' in its function-way-result analysis"). Factual findings underlying infringement determinations are reviewed for clear error. *See, e.g.*, *Insituform*, 161 F.3d at 692. The "ultimate construction of [a] claim," as well as any claim construction relying only on intrinsic evidence, as the district court did here, are also reviewed *de novo*. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015).

A. The Court Should Vacate Because The District Court's Equivalents Analysis Was Erroneous.

The district court erred in finding that Watson did not infringe because its decision was premised on an unduly narrow legal standard and erroneous equivalents analysis. In significant part, the Court's decision was contrary to

Watson's admissions to the FDA that demonstrated infringement under the doctrine of equivalents.

1. The District Court's Infringement Trial And Written Decision.

A brief recap of the trial and Watson decision illustrates the district court's errors. In March 2018, a newly-assigned judge bifurcated infringement and invalidity and held a four-day infringement trial. APPX10. Despite bifurcation, Amgen urged the district court to hear evidence about the patented invention—including evidence about Sensipar®—before deciding *any* issue. APPX3186-3187; APPX3357-3358; APPX4377-4378; APPX2796-2798. Amgen explained that, among other things, evidence about the patented invention would provide important context, because the district court should "know about the nature of a claimed invention when deciding infringement issues, particularly those that relate to the doctrine of equivalents." APPX2797 (relying on *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997)). At the remaining defendants' request, however, the district court generally refused to hear evidence about the patented invention on the theory that it was relevant only to validity. *See*, *e.g.*, APPX3357-3361 ("agree[ing] with defense counsel").

Within the district court's confines, Amgen presented testimony explaining why each of Watson's ANDA products infringed the claims as construed, including under the doctrine of equivalents. Amgen needed to look no further than

Watson's ANDA itself for much of that evidence. *See, e.g.*, APPX3475. The evidence is summarized here, with the white boxes indicating the focus of the dispute presented at trial:

APPX4499.

As the chart shows, Watson disputed the binder and disintegrant limitations. Watson's expert opined that there was no literal infringement under the court's claim construction by counting the PGS in its ANDA products as a binder instead

[3] "MCC" is microcrystalline cellulose.
[4] "PGS" is pregelatinized starch, which Amgen counted in the weight percentage in element (b) for purposes of literal infringement because it is a listed diluent. PGS can have a fraction (the cold-water soluble portion) that also acts as a hardening binder. *See, e.g.*, APPX3368-3369.
[5] "L-HPC" is low-substituted hydroxypropyl cellulose.

of a diluent to assert that this constitutes an unlisted binder under the district court's Markush group construction. APPX3843-3844. Watson's expert further opined that Watson's ANDA products do not infringe under the doctrine of equivalents because their disintegrant L-HPC is not equivalent to one of the claimed disintegrants, crospovidone, by focusing on irrelevant differences between the accused products and the claims. APPX3853; APPX3856. In so arguing, Watson urged a severely circumscribed view of infringement and equivalents that meshed with its constricted view of claim construction.

On July 27, 2018, the district court issued its opinion that Watson's ANDA products do not infringe the '405 patent. APPX9-51. The district court addressed only the disintegrant element, even though the binder element was also disputed. APPX28-36. Tracking Watson's expert testimony about supposed "distinctions" between L-HPC and element (d)'s crospovidone, the district court considered both the function-way-result test and the insubstantial differences test. On function-way-result, the district court largely repeated Watson's counterintuitive expert testimony that L-HPC is not equivalent because it is a *worse* disintegrant than those listed in claim element (d). APPX30-34. And on insubstantial differences, the court found four "differences" between L-HPC and crospovidone to be dispositive, without explaining why or how these differences impact whether L-

HPC is substantially different from crospovidone as a disintegrant in Watson's formulation. APPX28-30.

2. The Judgment Of Non-Infringement As To Watson Rests On An Unduly Rigid Legal Standard And Product Attributes Irrelevant To The Claimed Disintegrant.

The district court's analysis of infringement under the doctrine of equivalents was wrong as a matter of law because the district court applied an overly stringent and incorrect legal standard for equivalents.

"Equivalence, in the patent law, is not the prisoner of a formula and is not an absolute to be considered in a vacuum." *Graver Tank*, 339 U.S. at 609; *see also Atlas Powder*, 750 F.2d at 1579 (there is no "rigid formula"). There is a constellation of factors to consider, including "the purpose for which an ingredient is used in a patent, the qualities it has when combined with the other ingredients, … the function which it is intended to perform[,] … [and] whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was." *Graver Tank*, 339 U.S. at 609. The inquiry proceeds limitation-by-limitation, taking into account "the context of the patent, the prior art, and the particular circumstances of the case." *Id.*

Consistent with the doctrine's inherent flexibility, there are different ways to get at the "the essential inquiry" of whether "the accused product … contain[s]

elements identical or equivalent to each claimed element of the patented invention." *Warner-Jenkinson*, 520 U.S. at 40. One is the function-way-result test, which asks whether the accused product performs substantially the same function in substantially the same way to achieve substantially the same result as the claimed limitation. *Graver Tank*, 339 U.S. at 608-09. Another asks more simply whether there are only "insubstantial differences" between the claimed element and accused product. *Voda v. Cordis Corp.*, 536 F.3d 1311, 1326 (Fed. Cir. 2008). Ultimately, a "patentee may prove infringement by 'any method of analysis that is probative of the fact of infringement.'" *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009).

Whatever the "particular linguistic framework used," *Warner-Jenkinson*, 520 U.S. at 40, a few additional principles highlight the standard's adaptable nature. First, supposed differences between accused and claimed compounds must "actually affect[] a[] property of the [composition] relevant to the claim at hand" to matter. *Boehringer Ingelheim Vetmedia, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1352 (Fed. Cir. 2003). Second, a single ingredient in an accused pharmaceutical product may do substantially the same thing as more than one element of a claimed pharmaceutical composition. *Intendis GmbH v. Glenmark Pharm. Inc., USA*,, 822 F.3d 1355, 1361-62 (Fed. Cir. 2016); *see also Eagle Comtronics, Inc. v. Arrow Commc'n Labs., Inc.*, 305 F.3d 1307, 1317 (Fed. Cir.

2002) ("when separate claim limitations are combined into a single element of the accused device … the doctrine of equivalents may still apply"). Third, in the ANDA context, the universe of "relevant evidence" includes "the ANDA filing," and statements in those filings may even "control the infringement inquiry," *Abbott Labs. v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002), or prove "[f]atal" to a non-infringement argument, *Intendis*, 822 F.3d at 1362.

Rather than applying these controlling legal standards, the district court imposed a set of rigid rules that defy them. First, misapprehending *AquaTex Industries, Inc. v. Techniche Solutions*, 479 F.3d 1320, 1329 (Fed. Cir. 2007), the district court required "particularized testimony of a person of ordinary skill in the art, typically a qualified expert," and then formalistically faulted Amgen's limitation-by-limitation expert testimony on equivalents as insufficiently "conclusory" or "brief." APPX16-18; APPX23-24. The district court even chided Amgen's expert for failing to use the words "function," "way," and "result." APPX23-24.

The doctrine of equivalents does not require such needless rigidity. *AquaTex* merely stands for the proposition that an infringement analysis should be predicated on a limitation-by-limitation comparison of the claim to the accused product—*that* comparison is what should be "particularized," because "[g]eneralized" evidence about "overall similarity" to the claim as a whole does

"not suffice" for equivalents. 479 F.3d at 1328-29. Amgen provided exactly that kind of "particularized" testimony—covering each of the claimed limitations through its expert—and the district court was wrong to demand more. Nor does a doctrine premised on flexibility have a "magic words" requirement. *See, e.g.*, *Malta v. Schulmerich Carillons, Inc.*, 952 F.2d 1320, 1327 n.5 (Fed. Cir. 1991). Rather, a patentee can use "any method of analysis that is probative," *Martek*, 579 F.3d at 1372, and evidence like ANDA filings may be determinative all by themselves, *e.g.*, *Intendis*, 822 F.3d at 1362.

Second, the district court's equivalents standard incorrectly hinged on hyper-technical but irrelevant distinctions and ignored defendants' on-point statements to the FDA. Members of a Markush group are, by definition, "functionally equivalent," *Ecolochem, Inc. v. S. Cal. Edison Co.*, 91 F.3d 169, 169 (Fed. Cir. 1996), and so the appropriate point of comparison should be the "property in common which is mainly responsible for their function in the claimed invention," MPEP § 706.03(y). Along the same lines, an accused infringer cannot define the "way" chemical compounds work too narrowly when, for example, "the patent specification" and the infringer's arguments "to the FDA" support a broader definition. *Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc.*, 467 F.3d 1370, 1380-81 (Fed. Cir. 2006). Eschewing these and the principles outlined above, the district court's equivalents analyses reveal its reliance on a faulty legal standard.

Function-Way-Result. When an accused product "chang[es] one ingredient of a claimed composition, it is appropriate for a court to consider … whether the changed ingredient has the same purpose, quality, and function as the claimed ingredient." *Atlas Powder*, 750 F.2d at 1579-80. The district court did not do that, or follow any of the guidelines outlined above. Its approach to whether Watson's decision to swap in L-HPC as a disintegrant yielded an equivalent to those claimed in element (d) showcases its errors.

Function. Even though there was no dispute that Watson's L-HPC was a disintegrant, the district court decided that it did not function substantially the same as the claimed "superdisintegrants." APPX30-31. But that "analysis" overlooks [redacted] That should have been "[f]atal," *Intendis*, 822 F.3d at 1362, and had to be considered, *Abbott*, 300 F.3d at 1373, but the district court ignored it.[6]

[6] Watson's expert similarly conceded that, for example, "you can achieve disintegration with L-HPC just like you can with those superdisintegrants." APPX3894; *see also, e.g.*, APPX3851 (explaining her experience of "many instances where we would look at L-HPC and crospovidone or one of the other superdisintegrants head to head and L-HPC was actually superior in this particular application").

Way. The district court found it "undisputed" that L-HPC and two of the three listed disintegrants act in "substantially the same way"—through swelling—but found no equivalents because, in its (mistaken) view, one of the claimed disintegrants (crospovidone) has a different primary mechanism. APPX31-32. The proper comparison to analyze equivalents to element (d) of claim 1 (as distinct from the comparison to be made in analyzing claim 6's specific recitation of crospovidone) is to the disintegrant Markush group as a whole,[7] *supra* __, rather than to crospovidone individually. Plus, crospovidone also swells, and the district court agreed that swelling could "contribute" to the mechanism of action for it. APPX31-32; APPX3479; APPX3878-3879; APPX3927. The district court's critique reflects an incorrect equivalents analysis for claim 1 (as well as an error in failing to find equivalents for claim 6).

The "purpose" behind Watson's L-HPC substitution can also provide important guidance, *Atlas Powder*, 750 F.2d at 1579-80, but the district court disregarded it altogether. APPX29-34; APPX3927-3929. [redacted]

[7] At one point, the district court claimed that Amgen's arguments about comparing an accused product to the entire Markush group was a "new theor[y]." APPX29. But that only highlights the flaw in the district court's analysis—equivalents can be *illustrated* by comparing one member of a Markush group to a feature of an accused product, but equivalence is *determined* by answering the question of whether the relevant feature of the accused product possesses the property embodied by the Markush group.

[redacted]

Result/Quality. Watson's products have the same quality as Sensipar®, which contains the listed disintegrant crospovidone, and achieve the same results as the claimed composition: rapid disintegration and dissolution. Here, too, [redacted] Such evidence was again "[f]atal," *Intendis*, 822 F.3d at 1362, but the district court improperly focused on a L-HPC manufacturer's document describing relative disintegration rates in tablets that do not contain cinacalcet HCl, APPX32-34. The district court's labored efforts to discredit that document were misguided because, among other things, it does not erase [redacted].

Indeed, the district court's statement that "the dissolution profile has not been relevant in this litigation," despite acknowledging that "the inventive feature of the '405 patent was a 'rapid' dissolution profile for a poorly soluble drug," APPX13, once more accentuates the improper lens through which the district court analyzed equivalents. The only difference in excipients between Sensipar® and Watson's ANDA products is Watson's substitute disintegrant. The fact that Sensipar® and Watson's ANDA products have substantially the same dissolution profile is strong—if not conclusive—evidence that Watson's L-HPC achieves substantially the same result as Sensipar®'s crospovidone, a claimed disintegrant. Yet the district court characterized that shared feature as "not … relevant." APPX13.

Insubstantial Differences. The differences between L-HPC and the claimed disintegrants were also plainly "insubstantial," but the district court's back-of-the-hand analysis indulged Watson's comparison of insignificant physical and chemical differences, never mentioned Watson's FDA admissions, and focused exclusively on one claimed disintegrant (crospovidone) from the Markush group. APPX34-36. None of that was correct. The proper inquiry is not simply an exercise in trying to identify any and all possible points of distinction between these disintegrants. Rather, the differences must "actually affect[] a[] property of the [composition] relevant to the claim at hand." *Boehringer*, 320 F.3d at 1352.

The district court's refusal even to conduct that analysis for any of the four identified "differences" again exposes its foundational errors. The first two were "physical shapes" and "chemical structures," but the district court nowhere explained how those have anything to do with the excipients' *distintegrant* properties. APPX35. They do not. The third was that L-HPC is "multi-functional" (because it can act as a binder or a disintegrant), "whereas crospovidone is not" (because it functions only as a disintegrant). *Id.* Again, the district court did not explain why or how that difference impacts whether L-HPC is substantially different from crospovidone *as a disintegrant* in Watson's formulation. It does not. The fourth was that L-HPC is "less potent" than crospovidone. APPX35-36. By that, the district court meant that formulations generally need higher levels of L-HPC than crospovidone to perform the disintegrant function, but the district court again did not explain why that makes any difference so long as the disintegrant level in any given formulation falls within the claimed weight range (about 1% to 10%). *Id.* Watson's [redacted] disintegrant falls squarely in the claimed range.

Contrast this with a proper equivalents analysis, like the one this Court just recently affirmed in *UCB, Inc. v. Watson Laboratories, Inc.*, No. 2018-1397, 2019 WL 2571401 (Fed. Cir. June 24, 2019). There, despite chemical differences and "different properties," between the claims and the accused ANDA product, this

Court *nevertheless affirmed* equivalents, because "these differences do not matter for how the claimed invention works, as evidenced by," among other things, "comparative [test] results" on drug delivery. *Id.* at *10. Recognizing such "interchangeability" meant recognizing "why the similarities matter more than the differences for the claimed system." *Id.* at *11. The district court in this case failed to do this—and thus fundamentally misdirected its equivalents analysis.

The equivalents holding as to Watson should be reversed.

B. The Court Should Vacate Based On The District Court's Erroneous Claim Construction.

In addition to the erroneous equivalents analysis of Watson's disintegrant, the district court also erroneously held that a pharmaceutical composition "comprising" several ingredients, including "at least one" binder or disintegrant selected from a Markush group, required "at least one" such binder and "at least one" such disintegrant "*and no unlisted binders [or] disintegrants*." APPX52 (emphasis added). As explained in the pending merits appeal vis-à-vis other defendants (Case No. 18-2414, D.I. 55, 75), that construction is wrong because, as long as "at least one" binder from the Markush group is present, the claim does not forbid others. The claim language itself compels such a construction and the remainder of the claims and the specification reinforce that reading. The district court's misreading of this intrinsic evidence was compounded because its

construction considers no extrinsic evidence even though the evidence from trial emphatically supports Amgen.

The claim construction requires correction. To begin with, irrespective of the flawed infringement analysis, the Court regularly vacates after an infringement trial based on the wrong construction. *See Va. Innovation Scis., Inc. v. Samsung Elecs. Co.*, 614 F. App'x 503, 511 (Fed. Cir. 2015) (remanding "with instructions to further develop the record and to determine the meaning of" a disputed term); *Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys.*, Inc., 261 F.3d 1329, 1344-45 (Fed. Cir. 2001) (vacating and remanding to consider extrinsic evidence); *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 813-14 (Fed. Cir. 2002) ("vacat[ing] and remand[ing] the holding of no infringement … by equivalents because the trial court should have an opportunity to develop and assess the record under the proper claim construction"); *Insituform*, 99 F.3d at 1109 ("doctrine of equivalents analysis was distorted by its incorrect claim construction"). Here, those errors occurred right before trial, and the district court even acknowledged that the claim construction issue had "caus[ed] some confusion." APPX4261. Although the district court's non-infringement decision as to Watson focused only on the disintegrant limitation and did not involve any unlisted disintegrant, APPX27-36, this case needs—and deserves—a reset on claim construction, and the Court can vacate and remand on that basis alone.

In addition, Watson injected infringement issues into the case based on the district court's erroneous claim construction that would need to be addressed on any remand on the merits. Watson argued, for example, that the PGS in its product acts as an unlisted binder. *See* APPX28. That contention implicates both the claim construction issue and, related, how PGS should be counted for purposes of literal infringement under the '405 patent. If the Watson-Amgen dispute continues despite the parties' agreement to settle, therefore, the claim construction addressed in Appeal No. 18-2414 will also impact this case.

CONCLUSION

For the foregoing reasons, the Court should vacate the district court's non-infringement judgment and direct it to enter the parties' consent judgment of infringement.

Date: June 24, 2019

Respectfully submitted,

By: /s/ Bradford J. Badke

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ADDENDUM

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN, INC.,	:	**CIVIL ACTION**
Plaintiff,	:	
v.	:	**No. 16-cv-0853**
AMNEAL PHARMACEUTICALS, ET AL.,	:	
Defendants.	:	

ORDER

AND NOW, this 26th day of March, 2019, upon consideration of the "Joint Motion for an Indicative Ruling Pursuant to Federal Rule of Civil Procedure 62.1" filed by Plaintiff Amgen, Inc. ("Amgen") and Defendants, Watson Laboratories, Inc. and Actavis Pharma, Inc. (collectively, "Watson") (ECF No. 412), and the responses thereto (ECF Nos. 418, 419, 427), I find as follows:

Background

1. Between September 22, 2016 and June 9, 2017, Amgen filed multiple lawsuits against numerous defendants, including Watson, alleging infringement of United States Patent No. 9,375,405 (the "'405 Patent").
2. On July 27, 2018, following a bench trial, and as it relates to Watson, I issued a Memorandum Opinion and Order, finding that "Watson d[id] not infringe any of the claims asserted against it, which are claims 1-6 and 9-20 of the '405 Patent." (Trial Or. ¶ 3, July 27, 2018, ECF No. 375, 376.) Thereafter, on August 24, 2018, I entered judgment, stating that "[a] judgment of NON-INFRINGEMENT of claims 1-6 and

9-20 of the'405 Patent is hereby entered in favor of Watson and against Amgen." (Or. ¶ 3, Aug. 24, 2018, ECF No. 384.)

3. On September 25, 2018, Amgen appealed my decision to the United States Court of Appeals for the Federal Circuit. (ECF No. 397.) Presently, the appeal remains pending. Amgen, Inc. v. Amneal Pharm., LLC, Nos. 2018-2414, 2019-1086 (Fed. Cir. Sept. 25, 2018).

4. Amgen and Watson have advised that, on January 2, 2019, they executed a Litigation Settlement Agreement (the "Agreement"), which fully resolves their respective infringement claims (and invalidity counterclaims) as to the '405 Patent.

5. Amgen and Watson explain that:

> Under the terms of the Agreement, the parties must ask the Court to enter a consent judgment almost identical to those that this Court has already approved as to several other defendants . . . stating, in pertinent part that: Watson "ha[s] admitted . . . that the manufacture, use, sale, offer to sell, and distribution of [its] Products in the United States and importation of [its] Product into the United States, would infringe the ['405] Patent;" and, except as otherwise provided in the Agreement, Watson, along with its "successors and assigns, [is] enjoined until the date of expiration or lapse of the last to expire claim of the ['405] Patent, including any extension and/or additional periods of exclusivity to which Amgen is or becomes entitled, from infringing the ['405] Patent by making, having made, using, selling, offering to sell, or distributing [its] Products in the United States, or importing [its] Products into the United States."

(Joint Mot. Indicative Ruling ¶ 7, ECF No. 412 (emphasis added).)

6. Amgen and Watson suggest that I should issue an indicative ruling under Federal Rule of Civil Procedure 62.1 stating that I "would grant the parties' motion under Federal Rule of Civil Procedure 60(b) to vacate my Order as to Watson," wherein I found that Watson's Products did not infringe the '405 Patent. FED. R. CIV. P. 62.1(a) ("If a timely motion is made for relief that the court lacks authority to grant because of an appeal

that has been docketed and is pending, the court may . . . state . . . that it would grant the motion if the court of appeals remands for that purpose.").

7. In short, after fully litigating the issue of infringement, Amgen and Watson now request that I completely reverse course and vacate my previous findings and Orders.

8. Defendants Cipla Limited and Cipla USA (collectively, "Cipla") strenuously oppose this Motion, asserting that Amgen and Watson are asking me to issue an unjustified and unexplained "indicative ruling" that would amount to a "collusive judgment." (Def.'s Resp. 4, ECF No. 418.)[1]

Analysis

9. The Committee Notes to Federal Rule of Civil Procedure 62.1 explain the Rule's purpose:

> This new rule adopts for any motion that the district court cannot grant because of a pending appeal the practice that most courts follow when a party makes a Rule 60(b) motion to vacate a judgment that is pending on appeal. After an appeal has been docketed and while it remains pending, the district court cannot grant a Rule 60(b) motion without a remand. But it can entertain the motion and deny it, defer consideration, or state that it would grant the motion if the court of appeals remands for that purpose or state that the motion raises a substantial issue. Experienced lawyers often refer to the suggestion for remand as an "indicative ruling."

10. While Federal Rule of Civil Procedure 62.1 provides jurisdiction to district courts to issue an indicative ruling even when an appeal is pending, "Federal Rule of Civil Procedure 60(b) empowers district courts to vacate judgments for several specified reasons." Dragon Intellectual Prop., LLC v. Apple, Inc., No. CV 13-2058-RGA, 2018 WL 4658208, at *2 (D. Del. Sept. 27, 2018).

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[1] Sun Pharmaceutical Industries, another Defendant in this matter, has also filed a motion in opposition to Amgen and Watson's request under Rule 62.1.

11. Federal Rule of Civil Procedure 60(b)(6) provides that the court "may relieve a party . . . from a final judgment, order, or proceeding" for several reasons, including "any other reason that justified relief." FED. R. CIV. P. 60(b)(6). "[C]ourts are to dispense their broad powers under 60(b)(6) only in 'extraordinary circumstances where, without such relief, an extreme and unexpected hardship would occur.'" Cox v. Horn, 757 F.3d 113, 120 (3d Cir. 2014) (quoting Sawka v. Healtheast, Inc., 989 F.2d 138, 140 (3d Cir. 1993)). Such consideration involves "equitable and case-dependent" analysis. Id. at 115–16.

12. A case becomes moot when the party seeking relief voluntarily terminates the controversy. Aqua Marine Supply v. Aim Machining, Inc., 247 F.3d 1216, 1220 (Fed. Cir. 2001). "When a case is moot due to a settlement agreement entered into by the parties, the party seeking relief from judgment has the burden of demonstrating 'equitable entitlement to the extraordinary remedy of vacatur.'" U.S. Bancorp Mortgage Co. v. Bonner Mall P'ship, 513 U.S. 18, 26 (1994).[2] "Mootness by reason of settlement does not justify vacatur absent 'exceptional circumstances'" because "the party who seeks the relief has 'caused the mootness by voluntary action.'" Polymasc Pharm., PLC. v. Alza Corp., No. CIV.A. 01-228-JJF, 2004 WL 633256, at *1–2 (D. Del. Mar. 26, 2004) (quoting Bancorp, 513 U.S. at 24, 29)).

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[2] Amgen and Watson suggest that Bancorp is not applicable because the Supreme Court only analyzed when an appellate court may grant vacatur. (Reply Br. 5–6, ECF No. 427.) Bancorp held that an appellate court may either (a) determine whether vacatur is appropriate or (b) "remand the case with instructions that the district court consider the request, which it may do pursuant to Federal Rule of Civil Procedure 60(b)." Bancorp, 513 U.S. at 393. Defendant's argument is unavailing because, in the present case, Defendant requests the latter option, whereby the Federal Circuit Court would remand the case to me, and I would consider the parties' motion under Federal Rule of Civil Procedure 60(b).

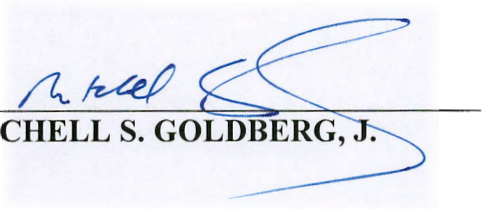
13. A court in this district has found that such an "extraordinary circumstance" existed where the Patent Trial and Appeals Board subsequently invalidated the claims at issue, and the Federal Circuit affirmed that decision. Dragon Intellectual Prop., LLC v. Apple, Inc., No. CV 13-2058-RGA, 2018 WL 4658208, at *2 (D. Del. Sept. 27, 2018). In contrast, another court concluded that the plaintiff did not prove the existence of an "exceptional circumstance" in the context of a settlement, such that vacatur was appropriate. Polymasc Pharm., PLC. v. Alza Corp., No. CIV.A. 01-228-JJF, 2004 WL 633256, at *1–2 (D. Del. Mar. 26, 2004). In Polymasc, the court granted summary judgment to the defendant, finding that it did not infringe the patent. The plaintiff filed an appeal to the Federal Circuit. Id. at *1. However, prior to a decision by the Federal Circuit, the parties entered into a settlement agreement. Id. The court held that this was not an "exceptional circumstance" where the only reason provided was that the parties had settled. Id. at *2.

14. The present case is similar to Polymasc because the parties have settled prior to the appeal decision in the Federal Circuit, but yet seek a vacatur of my Order, wherein I found that the patent was not infringed. Amgen and Watson request vacatur solely based on their settlement agreement, and have provided no other basis whatsoever which would amount to exceptional circumstances permitting my grant of vacatur under Federal Rule of Civil Procedure 60(b).[3]

[3] Amgen and Watson seek relief under both Federal Rule of Civil Procedure 60(b)(5) and 60(b)(6). Rule 60(b)(5) states that relief from a final judgment may be granted where "the judgment has been satisfied, released, or discharged; it is based on an earlier judgment that has been reversed or vacated; or applying it prospectively is no longer equitable." FED. R. CIV. P. 60(b)(5). None of these stated reasons seem to apply here.

WHEREFORE, it is hereby **ORDERED** that the "Joint Motion for an Indicative Ruling Pursuant to Federal Rule of Civil Procedure 62.1" filed by Amgen and Watson (ECF No. 412) is **DENIED**.

BY THE COURT:



MITCHELL S. GOLDBERG, J.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AMGEN INC., Plaintiff, v. AMNEAL PHARMACEUTICALS LLC, et al., Defendants.	Civ. No. 16-853-MSG CONSOLIDATED

TRIAL ORDER

Plaintiff Amgen, Inc. ("Amgen") asserts patent infringement claims against Defendants Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals of New York LLC (collectively, "Amneal"), Piramal Healthcare UK Ltd. ("Piramal"), Watson Laboratories, Inc., Actavis, Inc., and Actavis Pharma, Inc. (collectively, "Watson"), and Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Ltd. (collectively, "Zydus"). The court bifurcated the infringement claims and invalidity counterclaims for trial. A four-day bench trial on infringement was held between March 5, 2018 and March 9, 2018, and the parties submitted post-trial briefs. (D.I. 353, D.I. 354, D.I. 355, D.I. 356, D.I. 359, D.I. 360, D.I. 366, D.I. 367).

After considering the evidence presented at trial and the submissions of the parties, IT IS HEREBY ORDERED and ADJUDGED, consistent with the opinion issued this same date, that:

1. Amneal does not infringe any of the claims asserted against it, which are claims 1, 2-4, 6, 8-12, and 14-18 of United States Patent No. 9,375,405 (the "'405 patent");

2. Piramal does not infringe any of the claims asserted against it, which are claims 1-6 and 8-20 of the '405 patent;

3. Watson does not infringe any of the claims asserted against it, which are claims 1-6

and 8-20 of the ’405 patent; and

4. Zydus does not infringe claims 18 and 20 of the ’405 patent; but

5. Zydus does infringe claims 1-4, 6, 8-9, 15-17, and 19 of the ’405 patent, to the extent each claim is found valid and enforceable.

Dated: July 26, 2018

/s/ Mitchell S. Goldberg

MITCHELL S. GOLDBERG
UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AMGEN INC., Plaintiff, v. AMNEAL PHARMACEUTICALS LLC, et al., Defendants.	Civ. No. 16-853-MSG CONSOLIDATED

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GOLDBERG, M., District Judge **JULY 26, 2018**

OPINION

I. INTRODUCTION

This is a consolidated patent infringement action arising under the Drug Price Competition and Patent Term Restoration Act of 1984, 21 U.S.C. § 355, also known as the Hatch-Waxman Act. United States Patent No. 9,375,405 (the "'405 patent") is assigned to Plaintiff Amgen Inc. ("Amgen") and listed in the Approved Drug Products with Therapeutic Equivalents (the "Orange Book") as covering Sensipar®. Amgen accuses multiple Defendants of infringing the '405 patent by filing Abbreviated New Drug Applications ("ANDAs") seeking FDA approval to manufacture, use and/or sell generic versions of Sensipar®. These Defendants are Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals of New York LLC (collectively, "Amneal"), Piramal Healthcare UK Ltd. ("Piramal"), Watson Laboratories, Inc., Actavis, Inc., and Actavis Pharma, Inc. (collectively, "Watson"), and Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Ltd. (collectively, "Zydus").

I bifurcated the infringement claims and invalidity counterclaims for trial, and held a four-day bench trial on infringement beginning on March 5, 2018. At the time of the pretrial conference, this case involved five additional defendants that have since entered into a consent judgment or stipulation of dismissal. (D.I. 316, D.I. 317, D.I. 320, D.I. 321, D.I. 348). Of those

five defendants, only one participated at trial: Aurobindo Pharma USA Inc. and Aurobindo Pharma USA, Inc., known collectively as "Aurobindo." Presently before me are the parties' post-trial proposed findings of fact and conclusions of law concerning infringement of the '405 patent. (D.I. 359, D.I. 360, D.I. 366, D.I. 367). I have subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this court under 28 U.S.C. §§ 1391 and 1400(b).[1]

II. BACKGROUND

A. The '405 Patent

The '405 patent, entitled "Rapid Dissolution Formulation of Calcium Receptor-Active Compound," was issued by the United States Patent and Trademark Office ("Patent Office") on June 28, 2016. (D.I. 293, Ex. 1 at ¶ 5). The patent issued from U.S. Patent Application No. 12/942,646 (the "'646 application"), filed on November 9, 2010, and claims priority to U.S. Provisional Patent Application No. 60/502,219, filed on September 12, 2003. (*Id*. at ¶¶ 7, 8). The '405 patent has two independent claims (claims 1 and 20) and twenty-one dependent claims. (JTX 2 at 13:18-15:3).

For most of the asserted claims, the parties' stipulated that a finding of infringement would depend on the findings for claim 1 of the '405 patent. (*See* D.I. 336). Claim 1 recites a pharmaceutical composition combining specific excipients in specific amounts with the active ingredient cinacalcet hydrochloride ("cinacalcet HCI"). Excipients are the inert ingredients used in drug formulations to perform specific functions, such as diluent, binder, or disintegrant. (JTX 11 at 2545). Diluents provide bulk to the formulation so that the tablets are of sufficient size for

[1] On May 18, 2017, Chief Judge D. Brooks Smith of the United States Court of Appeals for the Third Circuit designated me as a visiting judge for the District of Delaware, pursuant to 28 U.S.C. § 292(b), to handle this and other Delaware cases.

handling. (PTX 454 at 404; D.I. 356 at 946:13-19). Binders act as the adhesive that holds the drug and excipients together. (D.I. 353 at 186:8-20). Disintegrants ensure the breakup of the tablet upon ingestion thereby promoting absorption of the drug substance. (JTX 11 at 2545; PTX 447 at 105). With that background in mind, claim 1 of the '405 patent specifically states:

> A pharmaceutical composition comprising:
>
> (a) from about 10% to about 40% by weight of cinacalcet HCl in an amount of from about 20 mg to about 100 mg;
>
> (b) from about 45% to about 85% by weight of a diluent selected from the group consisting of microcrystalline cellulose, starch, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof;
>
> (c) from about 1% to about 5% by weight of at least one binder selected from the group consisting of povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof; and
>
> (d) from about 1% to 10% by weight of at least one disintegrant selected from the group consisting of crospovidine (sic), sodium starch glycolate, croscarmellose sodium, and mixtures thereof;
>
> wherein the percentage by weight is relative to the total weight of the composition, and wherein the composition is for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

(JTX 2 at 13:18-39).

For reasons unknown to me, the parties' stipulation did not cover three of the dependent claims Amgen has asserted against various defendants. Those are claims 5, 6, and 18. Claim 5 recites, "The composition according to claim 1, wherein the at least one binder is povidone." (JTX 2 at 13:53-54). Claim 6 recites, "The composition according to claim 1, wherein the at least one disintegrant is crospovidone." (*Id.* at 13:55-56). Claim 18 recites, "The composition according to claim 1, wherein the hyperparathyroidism is primary hyperparathyroidism or secondary hyperparathyroidism." (*Id.* at 14:23-24).

B. Person of Ordinary Skill in the Art ("POSA")

The parties' definitions of a POSA do not meaningfully differ. (*See, e.g.*, D.I. 356 at 907:1-8; D.I. 353 at 183:5-16). A POSA should have an advanced degree with a M.S. or Ph.D. in chemistry, pharmacy and/or pharmacology or a related field, as well as work experience in drug dosage and formulations. (D.I. 356 at 939:17-940:4; *accord* D.I. 353 at 182:10-183:4).

C. Prosecution of the '405 Patent

1. The Original Claim

The '646 application was a continuation of U.S. Patent Application No. 10/937,870 (the "'870 application"). As originally-filed by Amgen, the '646 application contained one broad claim. (JTX 5 at SENS-AMG 47; D.I. 355 at 621:23-622:14). Claim 1 covered a "pharmaceutical composition comprising an effective dosage amount of a calcium receptor active compound and at least one pharmaceutically acceptable excipient." The claim further stated that the composition had a particular dissolution profile. (JTX 5 at SENS-AMG 47). But the dissolution profile has not been relevant in this litigation, except to note that the inventive feature of the '405 patent was a "rapid" dissolution profile for a poorly soluble drug. (*Id*. at SENS-AMG 520).

2. The 2011 Preliminary Amendment

Before the Patent Office took formal action on the original claim, Amgen filed a preliminary amendment on November 15, 2011 (the "2011 Preliminary Amendment") cancelling claim 1 and adding new claims 2 through 24. (JTX 5 at SENS-AMG 257-62). Claim 2 narrowed the scope of the claims by requiring specific amounts of three specific types of excipient—diluents, binders, and disintegrants—and further requiring that the diluent be selected from a Markush group. (*Id.*; D.I. 354 at 393:16-20). A Markush group "lists alternative species

or elements that can be selected as part of the claimed invention." *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1357 (Fed. Cir. 2016). It is typically expressed in the form: "a member selected from the group consisting of A, B and C." *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1280 (Fed. Cir. 2003). New independent claim 2 read:

> A pharmaceutical composition comprising:
>
> (a) from about 10% to about 40% by weight of cinacalcet HCl;
>
> (b) from about 45% to about 85% by weight of a diluent selected from the group consisting of microcrystalline cellulose, starch, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof,
>
> (c) from about 1% to about 5% by weight of at least one binder; and
>
> (d) from about 1% to 10% by weight of at least one disintegrant, wherein the percentage by weight is relative to the total weight of the composition.

(JTX 5 at SENS-AMG 258). Claims 3 through 23 were dependent on claim 2; claim 24 was the same as claim 2 except without the Markush group. (*Id.*).

On September 16, 2014, the Patent Office issued a non-final Office Action rejecting claims 2 through 24 as obvious "over Van Wagenen (US 6,211,244 B1) as evidenced by Kajiyama et al. (US 6,656,492), in view of Creekmore (US 6,316,460 B1) and Hsu et al. (US 2005/0147670)." (JTX 5 at SENS-AMG 291-97). As the Examiner explained, Van Wagenen discloses compounds that "read on cinacalcet HCl" and "can be used to treat diseases such as primary hyperparathyroidism and secondary hyperparathyroidism." (*Id.* at SENS-AMG 293-94). Hsu discloses pharmaceutical formulations where eleven specific binders—including starch and all four binders in claim 1 of the '405 patent—may be present in an amount from about 1% to about 80% by weight. (*Id.*; PTX 11 at ¶¶ 17, 46). Hsu also discloses twelve specific disintegrants—including all three disintegrants in claim 1 of the '405 patent—that may be

present in an amount of about 0.1% to about 10% by weight. (JTX 5 at SENS-AMG 293-97; PTX 11 at ¶ 51). Creekmore discloses pharmaceutical formulations where nineteen binders—including starch, pregelatinized starch, and three of the four binders in claim 1 of the '405 patent—may be present in an amount of 2% to 90% by weight. (JTX 5 at SENS-AMG 295; PTX 7 at 2:32-43). Creekmore also discloses that eight disintegrants—including all three disintegrants in claim 1 of the '405 patent—may be present in an amount of about 2% to 10%. (JTX 5 at SENS-AMG 295; PTX 7 at col. 2-3).

3. The 2014 Amendment

On December 15, 2014, Amgen responded to the September 16, 2014 Office Action by filing an amendment (the "2014 Amendment") that narrowed the claims. (D.I. 354 at 394:20-395:1). Amgen amended independent claim 2 to add that the cinacalcet HCl must be present "in an amount of from about 20 mg to about 100 mg." (JTX 5 at SENS-AMG 308-318). Amgen argued to the Patent Office that the 2014 Amendment overcame the prior art references cited in the Office Action by adding a precise amount of cinacalcet HCI. (*Id.* at SENS-AMG 313-319).

4. The Examiner's Amendment

The Examiner did not allow the 2014 Amendment. (D.I. 354 at 398:2-7). Instead, on March 12, 2015, the Examiner had an interview with Amgen's counsel and proposed an Examiner's Amendment that further narrowed the claims. (JTX 5 at SENS-AMG 340). The Examiner's Amendment canceled dependent claims 6, 8, and 22 and imported those limitations into independent claim 2 (which later issued as claim 1). (*Id*. at SENS-AMG 333-338). Original claim 6 stated, "The composition according to claim 1, wherein the at least one binder is selected from the group consisting of povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof." (*Id.* at SENS-AMG 310). Original

claim 8 stated, "The composition according to claim 1, wherein the at least one disintegrant is selected from the group consisting of crospovidine (sic), sodium starch glycolate, croscarmellose sodium, and mixtures thereof." (*Id.*). Original claim 22 was a treatment limitation. Thus, as proposed by the Examiner, amended claim 2 now read:

> A pharmaceutical composition comprising:
>
> (a) from about 10% to about 40% by weight of cinacalcet HCl in an amount of from about 20 mg to about 100 mg;
>
> (b) from about 45% to about 85% by weight of a diluent selected from the group consisting of microcrystalline cellulose, starch, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof,
>
> (c) from about 1% to about 5% by weight of at least one binder selected from the group consisting of povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof; and
>
> (d) from about 1% to 10% by weight of at least one disintegrant selected from the group consisting of crospovidine, sodium starch glycolate, croscarmellose sodium, and mixtures thereof,
>
> wherein the percentage by weight is relative to the total weight of the composition, and wherein the composition is for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

(*Id.* at SENS-AMG 333-34 (underlining Examiner's amendments)).

After Amgen agreed to the Examiner's Amendment, the Examiner found that the pending claims overcame the obviousness rejection. (JTX 5 at SENS-AMG 338). Thus, on March 25, 2015, the Patent Office issued a Notice of Allowance with three attachments: the Examiner-Initiated Interview Summary, the Examiner's Amendment, and the Examiner's Statement of Reasons for Allowance. (*Id*. at SENS-AMG 332). The Examiner's reasons for allowance stated:

> The closet [sic] prior art was that which was cited in the previous office action filed on 09/16/2014, but fails to specifically disclose or render obvious the combination of components and in the amounts thereof set forth in claim 2.

> The claimed subject matter is not taught or suggested by the cited reference and thus, the claimed subject matter are [sic] considered to be novel and patentably distinct over the prior art of the record.

(*Id.* at 338). Although there was additional prosecution after this first notice of allowance, the claims ultimately issued in the same form. Independent claims 2, 24, and 26 from the patent application issued as independent claims 1, 20, and 21, respectively. (*Id.*).

5. Additional Prosecution and Issuance of the '405 Patent.

After the Examiner allowed Amgen's claims, Amgen filed a series of Requests for Continued Examination ("RCE"). (JTX 5 at SENS-AMG 345-46, SENS-AMG 1092-93, SENS-AMG 1613-14). With each RCE, Amgen submitted Information Disclosure Statements identifying additional prior art and documents Amgen claimed were relevant to the prosecution of the '405 patent. (JTX 5 at SENS-AMG 348-1063, SENS-AMG 1095-1576, SENS-AMG 1611-12). None of Amgen's RCEs amended the claims or made further arguments for patentability. (*Id.*).

On December 1, 2015, while Amgen's second RCE was pending, Amgen submitted a preliminary amendment (the "2015 Preliminary Amendment"). (*Id.* at SENS-AMG 1577-86). In this amendment, Amgen re-submitted the claims as they appeared in the Examiner's Amendment, except Amgen underlined the Examiner's verbatim additions. (Compare JTX 5 at SENS-AMG 1578 (Amgen's Amendment), with *id.* at SENS-AMG 333-34 (Examiner's Amendment); *see also* D.I. 354 at 360:1-14). In the Remarks section of the document, Amgen's counsel stated that the "amendments have not been made in response to a prior art rejection but rather to place the claims in proper format and to better define the claimed subject matter, including equivalents." (*Id.* at SENS-AMG 1583). After each RCE and the 2015 Preliminary Amendment, the Examiner allowed the same claims as originally set forth in the Examiner's Amendment. The Examiner's statement of reasons for allowance identified "the amount of

cinacalcet HCl," "the nature of the excipients," and "their respective combinations." (*See* JTX 5 at SENS-AMG 1064-71, SENS-AMG 1587-95, SENS-AMG 1643-50, and SENS-AMG 1693).

D. Claim Construction

The court has construed three terms in claim 1 of the '405 patent. On July 19, 2017, the Honorable Gregory Sleet, who was first assigned to this matter, construed the term "relative to the total weight of the compositions" in accordance with its plain and ordinary meaning. (D.I. 186). On February 27, 2018, this case having been reassigned to me as a visiting judge, I construed the Markush groups for the binder and disintegrant elements as "closed to unrecited binders and disintegrants." (D.I. 300 at 6). I concluded that "there could be no literal infringement if the Defendants' ANDA product contained an unrecited (or unlisted) binder or disintegrant." (*Id*.). Thus, in order to prove literal infringement, Amgen must prove that all of the binders and disintegrants in a defendant's ANDA product are members of the respective Markush group. (*Id*. at 9).

Amgen opposed the court's construction of the Markush groups by filing a motion for reargument, which was denied. (D.I. 323, D.I. 358). Amgen also elicited testimony from its expert, Dr. Davies, and made arguments in its post-trial brief that were inconsistent with the controlling claim construction. (*See, e.g.*, D.I. 354 at 283:4-18; *Id*. at 297:9-14; *Id*. at 457:8-15; D.I. 355 at 539:8-540:21; D.I. 359 at 25). "Once a district court has construed the relevant claim terms, and unless altered by the district court, then that legal determination governs for purposes of trial." *Exergen Corp. v. Wal-Mart Stores, Inc*., 575 F.3d 1312, 1321 (Fed. Cir. 2009). Thus, Dr. Davies' expert testimony regarding infringement will be disregarded where it was inconsistent with or "based on an incorrect understanding of the claim construction." *Cordis*

Corp. v. Boston Sci. Corp., 658 F.3d 1347, 1357–58 (Fed. Cir. 2011). In addition, I will not address Amgen's arguments that are based on a claim construction I have already rejected.[2]

Finally, I must correct Amgen's assertion in its post-trial brief that my opinion denying the motion for reargument held, as a matter of law, that any pregelatinized starch in a defendant's accused product "count[s]" only as a diluent. (D.I. 359 at 13, 17, 22). That opinion's discussion of pregelatinized starch was limited to the Example in the '405 patent. (*See* D.I. 357 at 9-11). In that opinion, I rejected Amgen's argument that the only way to give meaning to the Example was to construe claim 1 as open to unlisted binders. (*Id*.). As I explained, claim 1 of the '405 patent covers pregelatinized starch that functions as a diluent. (*Id*.). In addition, the '405 patent teaches that the pregelatinized starch in the Example is functioning as a diluent. (*Id*.). So, the '405 patent already covered the Example without having to construe the claim as open to unlisted binders. (*Id*.). What the '405 patent teaches about the Example, however, does not dictate how pregelatinized starch functions in a defendant's formulation. As every expert witness at trial testified, the particular function of pregelatinized starch in any given formulation depends on the context. (JTX 11 at 2548; PTX 438 at 686; D.I. 354 at 268:21-269:3; *Id*. at 309:21-22; *Id*. at 468:1-9; D.I. 355 at 504:14-505:1; *Id*. at 506:15-507:17; *Id*. at 510:2-11; *Id*. at 511:4-512:5; *Id*. at 584:19-585:5; D.I. 356 at 955:14-956:10; *Id*. at 1082:20-1083:15). My memorandum opinion on the motion for reargument was consistent with these scientific principles. Contrary to Amgen's assertion, I did not previously hold that the pregelatinized starch in a defendant's formulation counts only as a diluent.

[2] For example, Amgen argues that Opadry infringes the binder limitation, because the open-ended term "comprising" in claim 1 allows for unlisted excipients such as polyethylene glycol, and Opadry is an excipient made in part with polyethylene glycol. (D.I. 359 at 25).

III. CONCLUSIONS OF LAW

A. Standard

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States ... during the term of the patent." 35 U.S.C. § 271(a). To provide jurisdiction over an infringement dispute before an ANDA applicant has actually made or marketed the proposed product, 35 U.S.C. § 271(e)(2) states that submission of an ANDA is an act infringement "if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent . . . before the expiration of such patent." The filing of an ANDA alone does not prove infringement. *Glaxo, Inc. v. Novopharm, Ltd*., 110 F.3d 1562, 1570 (Fed. Cir. 1997). Rather, the patentee must show, using "traditional patent infringement analysis," that "the alleged infringer will likely market an infringing product." *Id*. at 1569-70; *see also Warner-Lambert Co. v. Apotex Corp*., 316 F.3d 1348, 1365–66 (Fed. Cir. 2003)

A traditional infringement analysis entails two steps. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). First, the court must determine the meaning and scope of the asserted claims. *Id*. Second, the trier of fact must compare the properly construed claims with the product accused of infringement. *Id*. The patent owner must show, by a preponderance of the evidence, that each and every limitation of the asserted patent claim is found in the accused product, either literally or by equivalent. *SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

B. Amneal

Amneal filed Abbreviated New Drug Application No. 204364 ("ANDA") with the FDA seeking approval to market a generic version of cinacalcet hydrochloride in 30, 60, and 90 mg

dosage strengths. (D.I. 293, Ex. 1 at ¶ 35). Amneal included a certification in its ANDA pursuant to 21 U.S.C. §355(j)(2)(A)(vii)(IV) (a "Paragraph IV Certification") stating that the '405 patent is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of Amneal's product. (*Id*. at ¶ 36). Amgen claims that Amneal's product will infringe claims 1-4, 6, 8-12, and 14-18 of the '405 patent. (D.I. 293, Ex. 2 at ¶¶ 25-26). Amneal has stipulated that if its ANDA product infringes claim 1, then its ANDA product will also infringe claims 2-4, 8-12, and 14-17, to the extent each claim is found valid and enforceable. (D.I. 336 at ¶ 1). The stipulation did not cover the asserted claims 6 and 18.

According to the ANDA, Amneal's product has the following composition:[3]

Ingredient	**Function**
Cinacalcet HCl	Active
Mannitol	Diluent
Microcrystalline Cellulose	Diluent
Opadry Clear YS-1-7006	Binder
Crospovidone	Disintegrant
Pregelatinized Starch	Secondary Disintegrant

(PTX 183 at 42).

1. Binder

According to the ANDA, the only binder in Amneal's product is Opadry YS-1-7006 ("Opadry"). But claim 1 of the '405 patent does not list Opadry in the Markush group for binders, which means under my claim construction order, there is not a clear case of literal

[3] As is true for all defendants in this case, Amneal's pharmaceutical composition includes additional excipients not relevant to this litigation and, therefore, not discussed here.

infringement. Amgen nonetheless attempts to prove literal infringement by arguing that Opadry is a pseudonym for hydroxypropyl methylcellulose ("HPMC"), which is a listed binder. (D.I. 359 at 24-25). Alternatively, Amgen argues that infringement is established through the doctrine of equivalents. (*Id*. at 26-27). I disagree with Amgen on both of these arguments.

To start, I find that a POSA would not regard Opadry as a synonym or trade name for HPMC. Authoritative pharmaceutical handbooks relied on in the industry identify synonyms for excipients. (*See* PTX 438 at 326). Opadry is not one of the synonyms given for HPMC. (*Id*.). It was also common practice for the inventors of the '405 patent and Amneal's ANDA to list an excipient followed by its tradename in parenthesis. (*See, e.g.*, JTX 2 at 11:21-42 ("Microcrystalline cellulose (Avicel PH102)," "Povidone (Plasdone K29/32)," etc.); PTX 183 at 42 ("Mannitol, USP (Mannogem EZ)," "Microcrystalline Cellulose, NF (Vivapur Type 101)," etc.)). Whenever HPMC appears in the '405 patent, it is not followed by a reference to Opadry. (JTX 2 at 6:61, 7:30-31). The opposite is also true. Whenever the '405 patent or Amneal's ANDA mention Opadry, it is not linked to HPMC. (JTX 2 at 11:37, 11:39, 12:22, 12:23; PTX 183 at 42).

In addition, I conclude for numerous reasons that Opadry is not literally HPMC. The excipients have different chemical structures, physical characteristics, binding mechanisms, and commercial sources. HPMC is a single molecule, whereas Opadry is a molecular dispersion of three distinct chemical ingredients: HPMC, polyethylene glycol 400, and polyethylene glycol 8000. (D.I. 355 at 796:8-22; DTX-AMN 7 at 8). HPMC is "an off-white poorly flowing powder," whereas the three ingredients in Opadry make a "slurry." (D.I. 355 at 791:4-24). HPMC binds principally through adhesion, while Opadry binds principally through cohesion. (*Id*. at 796:23-797:9). Specifically, HPMC acts as a wet granulation binder by sticking different

types of particles together, forming a granule from the inside, out. (*Id.* at 797:2-5). But Opadry acts as a wet granulation binder by spreading and surrounding the drug and excipient particles, forming a granule from the outside, in. (*Id.* at 797:5-9). Opadry is a product manufactured by a single company, Colorcon, using a proprietary method, whereas HPMC is not. (*Id*. at 788:18-21). Given the above evidence, Amgen has failed to prove by a preponderance of the evidence that Opadry is actually HPMC. Because Opadry is an unlisted binder, Amneal does not literally infringe the binder limitation of claim 1.

Amgen also does not infringe the binder limitation under the doctrine of equivalents. A finding of infringement under the doctrine of equivalents requires a showing that: (1) "the difference between the claimed invention and the accused product or method was insubstantial," or (2) "the accused product or method performs the substantially same function in substantially the same way with substantially the same result as each claim limitation of the patented product or method." *AquaTex Indus., Inc. v. Techniche Solutions*, 479 F.3d 1320, 1326 (Fed. Cir. 2007). Regardless of which test is used, a patentee must "provide particularized testimony and linking argument on a limitation-by-limitation basis." *Id*. at 1328-29. "[W]hile many different forms of evidence may be pertinent, when the patent holder relies on the doctrine of equivalents, as opposed to literal infringement, the difficulties and complexities of the doctrine require that evidence be presented to the jury or other fact-finder through the particularized testimony of a person of ordinary skill in the art, typically a qualified expert." *Id*. at 1329.

Here, Amgen's expert, Dr. Davies, never once used the word "function," "way," "result," or "substantial/insubstantial differences." (*See* D.I. 354 at 263:14-268:11). Nor did he provide

particularized testimony on each point of comparison.[4] (*Id.*). Instead, Dr. Davies opined in conclusory fashion that only the HPMC fraction of Opadry functioned as the binder, and "the polyethylene glycol … in the Opadry doesn't act as a binder." (*Id*. at 267:11-18). The court is not obligated to accept the conclusory assertions of an expert. *Optical Disc Corp. v. Del Mar Avionics*, 208 F.3d 1324, 1336 n. 5 (Fed. Cir. 2000). Thus, Dr. Davies' opinion, given without explanation or corroborating evidence, is not persuasive.

In addition, Amneal presented persuasive evidence refuting Dr. Davies' opinion that polyethylene glycol does not contribute to the binding properties of Opadry. Amneal's expert, Dr. McConville, credibly testified that Opadry is a "co-process excipient," which means that "those excipients work together and can never be separated." (D.I. 355 at 794:2-5). In addition, the presence of the polyethylene glycol in Opadry changes the mechanism by which HPMC binds, because polyethylene glycol, which is a liquid substance, allows the HPMC in Opadry to move freely, spread, and coat the other particles. (*Id*. at 802:13-24). Scientific literature states that, in tablet formulations, polyethylene glycols "can enhance the effectiveness of tablet binders." (PTX 438 at 518). Testing by Amneal demonstrated results consistent with this scientific statement. A series of tests compared formulations using HPMC and Opadry as binders and found a "significant difference" in the rate of release. (PTX 183 at 61-65). From these tests, Amneal concluded that Opadry was "the best choice of binder to achieve enhanced drug release profile."[5] (*Id*. at 65). Dr. Davies admitted that his opinion did not consider or respond to these tests. (D.I. 354 at 484:23-491:5). For all of the reasons stated above, I conclude

[4] It was not until post-trial briefs that Amgen defined the function, way, or result of the purported equivalents. (*See* D.I. 359 at 26-27).

[5] Amneal tested one formulation that compared HPMC to Klucel and found "no significant difference" between the two binders. (PTX 183 at 62-64). Amgen then tested a second formulation that compared Klucel to Opadry and found "faster in drug release" with Opadry as a binder. (PTX 183 at 64-65).

that Amgen has not proven by a preponderance of the evidence that Opadry is equivalent to HPMC.

2. Disintegrant

Amneal's ANDA discloses the use of the listed disintegrant crospovidone and the unlisted disintegrant pregelatinized starch. (PTX 183 at 42). Under my claim construction order, there is no literal infringement if the ANDA formulation contains any unlisted disintegrant. (D.I. 300 at 6). The '405 patent lists "starch" in the Markush groups for diluents, and the parties remaining in this litigation do not dispute that the term "starch" in the '405 patent covers pregelatinized starch. (JTX 2 at 13:21-25). Accordingly, Amgen argues that the pregelatinized starch in Amneal's product is not functioning as a disintegrant, but as a diluent. (D.I. 359 at 28). Amgen's sole support for its argument is Dr. Davies' opinion that crospovidone is a super-disintegrant which destroys the structure of a tablet so quickly that the pregelatinized starch does not have the opportunity to act as a disintegrant. (D.I. 359 at 28; D.I. 354 at 269:4-10). For several reasons, I do not find Dr. Davies' opinion, as applied to Amneal's ANDA product, convincing.

First, as Dr. McConville testified, Amneal's ANDA product does not appear to need another diluent. A diluent is used to increase a tablet's size and weight. (D.I. 353 at 185:20-186:7). Amneal's ANDA product already includes two diluents—microcrystalline cellulose and mannitol—in a large amount; specifically, 67.89% by weight of the accused product. (PTX 183 at 42). Given the presence of two diluents in such a large amount, it does not make sense that Amneal would add a small amount (5.24%) of a third diluent. (D.I. 355 at 821:7-822:2).

Second, Dr. McConville persuasively testified that, with Amneal's manufacturing process, the crospovidone cannot usurp the disintegration function of the pregelatinized starch.

(*Id*. at 809:3-6). In tablet manufacturing, ingredients can be either inside the granule with the active drug (intragranular) or outside the granule (extragranular). (*Id*. at 810:1-5). A disintegrant "can be more effective if used both 'intragranularly' and 'extragranularly,'" because the extragranular disintegrant will rupture the tablet to expose the granules, and the intragranular disintegrant will rupture the granules into fine particles to expose the drug. (DTX 216 at 8; D.I. 355 at 815:13-19, 818:15-819:3). Fine particles dissolve more quickly which helps achieve a rapid rate of dissolution—a required feature of the '405 patent. (D.I. 355 at 819:3-6; D.I. 359 at 6). Here, Amneal uses pregelatinized starch as an intragranular disintegrant and crospovidone as an extragranular disintegrant. (PTX 183 at 74 & 80). Because the crospovidone is only present outside the granules, it cannot accomplish that second disintegration of granules into fine particles. (D.I. 355 at 820:5-10). And because the pregelatinized starch is the only disintegrant inside the granules, it alone acts as a secondary disintegrant.

Third, Amneal's ANDA contains the results of testing which confirm that the pregelatinized starch in its product functions as a secondary disintegrant. (*See* PTX 183 at 70-73). To select a secondary disintegrant, Amneal tested the intragranular use of corn starch, pregelatinized starch, and crospovidone. (*Id*.). Amneal found that tablets with intragranular pregelatinized starch were "comparable" to Sensipar® in drug release, whereas corn starch was "slower in drug release." (*Id*. at 71). Amneal further found that the combination of pregelatinized starch and crospovidone was "better than [a] high amount of Crospovidone alone." (*Id*. at 73). Thus, Amneal concluded that pregelatinized starch was "the best choice for secondary disintegrant to design a robust, immediate release tablet dosage form of Cinacalcet Hydrochloride." (*Id*. at 71). Dr. Davies admits that his opinion does not account for these tests. (D.I. 354 at 466:18-467:24). He also acknowledged that he is not aware of any experiments or

scientific literature showing that, in the presence of crospovidone, pregelatinized starch does not contribute to tablet disintegration. (*Id*. at 527:7-530:24).

For all of these reasons, I find Dr. Davies' opinion regarding the function of pregelatinized starch in Amneal's ANDA product is not well supported. Instead, I conclude, consistent with Dr. McConville's opinion, that the pregelatinized starch in Amneal's product functions as a disintegrant. Because pregelatinized starch is an unlisted disintegrant, Amneal does not infringe the disintegrant limitation of claim 1.

3. Conclusion

To prove infringement, Amgen had the burden to show by a preponderance of the evidence that Amneal's binder Opadry was either a listed member of the binder Markush group or equivalent to a listed member. Amgen has done neither. In addition, Amneal's accused product includes an unlisted disintegrant (pregelatinized starch) that functions as a disintegrant. Thus, Amgen has failed to show by a preponderance of the evidence that Amneal's accused product infringes the binder and disintegrant limitations of the '405 patent. For the foregoing reasons, Amneal does not infringe claim 1 of the '405 patent. This means, pursuant to the parties' stipulation, Amneal does not infringe claims 2-4, 8-12, and 14-17. (D.I. 336 at ¶ 1). This also means that Amgen has not proven by a preponderance of the evidence that Amneal infringed dependent claims 6 and 18. "One who does not infringe an independent claim cannot infringe a claim dependent (and thus containing all the limitations of) that claim." *Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1552 n. 9 (Fed. Cir. 1989).

C. Watson

Watson filed Abbreviated New Drug Application No. 204377 ("ANDA") with the FDA, seeking approval to market a generic version of cinacalcet hydrochloride in 30, 60, and 90 mg

dosage strengths. (D.I. 293, Ex. 1 at ¶ 100). Watson included a Paragraph IV Certification in its ANDA stating that the '405 patent is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of Watson's product. (*Id*. at ¶ 101). Amgen claims that Watson's product will infringe claims 1-6 and 8-20 of the '405 patent. (D.I. 293, Ex. 2 at ¶¶ 39-40). Watson has stipulated that if its ANDA product infringes claim 1, then its ANDA product will also infringe claims 2-4, 8-17, and 19-20, to the extent each claim is found valid and enforceable. (D.I. 336 at ¶ 4). The stipulation did not cover the asserted claims 5, 6, and 18.

According to the ANDA, Watson's product has the following composition:

Ingredient	**Function**
Cinacalcet HCl	Active
Microcrystalline Cellulose	Diluent
Povidone	Binder
Pregelatinized Starch	Binder / Disintegrant
Low Substituted Hydroxypropyl Cellulose (L-HPC)	Disintegrant

(PTX 368 at 27).

The parties dispute whether Watson's ANDA product infringes the binder and disintegrant limitations of claim 1. I need not address the binder limitation, however, because a finding of non-infringement can be based on the disintegrant limitation alone. Watson uses an unlisted disintegrant, low substituted hydroxypropyl cellulose ("L-HPC"), which under my claim construction order means there is no literal infringement. As a result, Amgen argues that L-HPC infringes claim 1 under the doctrine of equivalence. As noted previously, there are two tests for proving equivalence: the function-way-result test or the insubstantial differences test. *Mylan*

Institutional LLC v. Aurobindo Pharma Ltd., 857 F.3d 858, 866 (Fed. Cir. 2017). Amgen's infringement theories under the doctrine of equivalence have shifted since trial.

At trial, Amgen took the position that L-HPC is equivalent only to crospovidone and only under the function-way-result test. (*See* D.I. 353 at 81:2-5 (Amgen's counsel stating in opening arguments that the evidence will show that L-HPC "is the equivalent to crospovidone."); D.I. 356 at 1089:5-7 (Amgen's counsel stating in closing arguments that the evidence has shown that "L-HPC is an equivalent to crospovidone."); D.I. 355 at 552:3-10 (Dr. Davies admitting that his opinions in this case rely only on the function-way-result test.). However, in its post-trial briefs, Amgen takes two new positions: (1) L-HPC is equivalent to all three listed disintegrants of claim 1 under the function-way-result test, and (2) L-HPC is equivalent to crospovidone under the insubstantial differences test.[6] (D.I. 359 at 32-36). Watson correctly points out that Amgen did not fairly present these positions in expert discovery or at trial. (D.I. 360 at 55). For that reason alone, Amgen's new infringement theories should be disregarded as an unfair surprise. Nevertheless, I will address Amgen's new infringement theories as presented in its post-trial briefs. Crospovidone is one of the three listed disintegrants in claim 1. Thus, in explaining why Amgen's new theories under the function-way-result test are not persuasive, I will necessarily explain why Amgen's original theory also would have failed.

1. Function-Way-Result Test

Amgen claims that L-HPC, a disintegrant listed in Watson's ANDA, is equivalent under the function-way-result test to all three listed disintegrants of claim 1. (D.I. 359 at 32-35). The three disintegrants listed in the Markush group of claim 1 are sodium starch glycolate,

[6] Amgen also makes the new argument in its post-trial briefs that L-HPC is "insubstantially different from [all of] the claimed disintegrants." (D.I. 359 at 32). Because Amgen provided no argument on this point besides this one sentence, I will not address it. It was not fairly presented to the court.

croscarmellose sodium, and crospovidone. (JTX 2 at 13:31-34). Under the function-way-result test, the patentee must show that the alleged equivalent "performs substantially the same function, in substantially the same way, to achieve substantially the same result, as disclosed in the claim." *Abbott Labs. v. Sandoz, Inc*., 566 F.3d 1282, 1296 (Fed. Cir. 2009).

The patentee should present its evidence on the doctrine of equivalence through the particularized testimony of an expert or person skilled in the art. *AquaTex*, 479 F.3d at 1329. Thus, Amgen should have presented through its expert, Dr. Davies, particularized testimony regarding the function, way, and result for each disintegrant to be compared. Dr. Davies, however, did not identify at trial what he considered to be the function, way, or result of the disintegrants being compared. (*See* D.I. 354 at 289:20-322:6). Instead, Amgen relies on a brief assertion by Dr. Davies that the disintegrants listed in claim 1 are "superdisintegrants," and L-HPC is "another superdisintegrant" with "similar disintegrant capability to other superdisintegrants." (*Id*. at 295:4-15). This testimony does not satisfy Amgen's burden to present the particularized testimony of an expert regarding the function, way, and result of the disintegrants being compared. Accordingly, Amgen failed to prove at trial that L-HPC is equivalent under the function-way-result test to all three disintegrants listed in claim 1.

Amgen's arguments in its post-trial brief fare no better. Amgen must show that L-HPC, sodium starch glycolate, croscarmellose sodium, and crospovidone perform substantially the same function, in substantially the same way, to achieve substantially the same result. According to Amgen, the function of L-HPC and the three listed disintegrants is to act as "superdisintegrants." (*See* PTX 359 at 9 (stating the disintegrants in claim 1 "function as superdisintegrants"); *Id*. at 32 (stating that "L-HPC functions as a superdisintegrant")). Scientific literature supports Dr. Davies' opinion that the three listed disintegrants are

superdisintegrants, but that same literature disproves Dr. Davies' assertion that L-HPC would be known by a POSA as a "superdisintegrant." According to scientific literature, L-HPC was one of the earliest known disintegrants upon which the new generation of disintegrants, known as superdisintegrants, improved. (JTX 11 at 2546; JTX 12 at 2155; DTX 334 at 235). Thus, the term "superdisintegrants" by its nature is used to distinguish the three disintegrants listed in claim 1 from the L-HPC used in Watson's product. (D.I. 355 at 669:14-670:6). Because L-HPC is not a superdisintegrant, it does not perform substantially the same function as the disintegrants listed in claim 1.

Amgen claims that L-HPC and the three listed disintegrants perform in substantially the same way, because they all use the same mechanism of disintegration: swelling.[7] (D.I. 359 at 32; D.I. 354 at 305:9-12). There is no dispute that the primary mechanism of action for L-HPC is swelling. (D.I. 355 at 671:7-9; DTX 324 at 2). But Amgen has not proven that the primary mechanism of action for each of the three listed disintegrants is swelling. For two of the three disintegrants—sodium starch glycolate and croscarmellose sodium—Amgen presented no evidence to corroborate Dr. Davies' testimony that the primary mechanism of action is swelling. (D.I. 359 at 32-33). In addition, Dr. Davies' testimony on this point was unclear: He also testified that "there are a number of different mechanisms by which [superdisintegrants] work." (D.I. 355 at 517:20-518:1). For the third listed disintegrant—crospovidone—Watson's expert, Dr. Appel, gave persuasive testimony, corroborated by scientific literature, that the primary mechanism of action is not swelling, but the recovery of elastic energy of deformation, also

[7] "Swelling is associated with dimensional amplification where particles enlarge omni-directionally to push apart the adjoining components, thereby initiating the break-up of the tablet matrix." (JTX 11 at 2546).

known as "strain recovery."[8] (*Id*. at 658:8-659:4, 668:3-20). Dr. Appel further testified that if swelling contributed to the disintegration mechanism of crospovidone it would play only a "minor role." (*Id*. at 725:20-726:12).

Scientific literature explains that initially there was no consensus regarding the primary mechanism of action for crospovidone, and researchers initially proposed swelling and wicking.[9] (JTX 11 at 2550). Since then, however, strain recovery has been "proposed and validated" as the "dominating disintegrant mechanism" of crospovidone. (*Id.*). Swelling makes only a "minor contribution." (DTX 334 at 239; *see also* JTX 12 at 2162 ("recovery of strain-energy … is the major mechanism of disintegrant action of crospovidone and not capillarity wicking or swelling")). I accept and credit this updated literature. Accordingly, Amgen has not proven that L-HPC and the three listed disintegrants perform in substantially the same way.

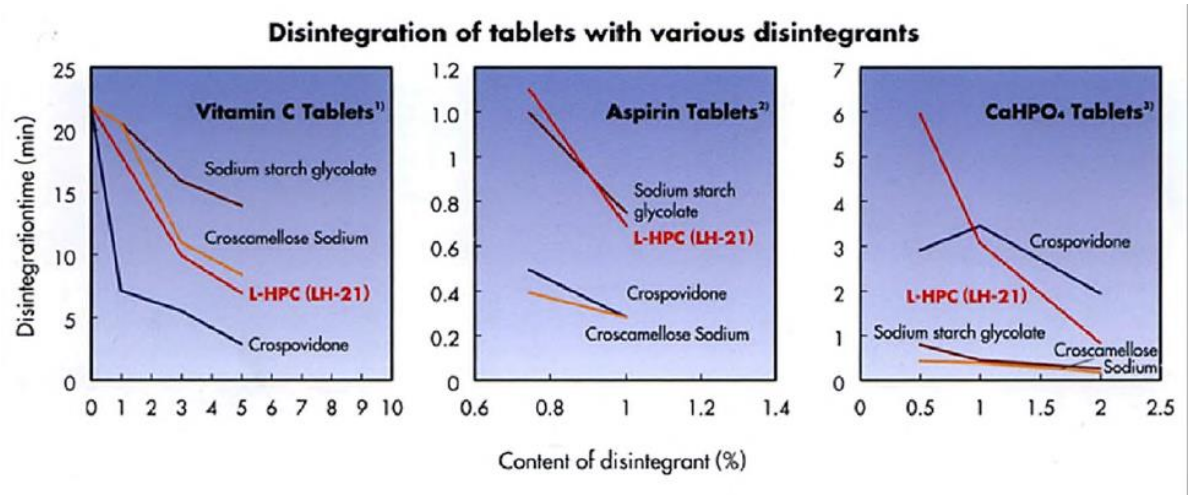
Finally, Amgen asserts that L-HPC and the three listed disintegrants achieve substantially the same result: "rapid tablet disintegration." (D.I. 359 at 32). Amgen's assertion, however, rests on a single sentence in a marketing brochure from the chemical company Shin Etsu stating: "L-HPC has similar disintegration capability to the other 'superdisintegrants.'" (*Id*. at 33; D.I. 354 at 295:4-19; PTX 463 at 12). A marketing brochure is not a peer reviewed scientific article and its goal is to sell a product, in this case L-HPC. (D.I. 355 at 673:24-675:20).

In addition, the marketing brochure itself calls into doubt Amgen's assertion. The brochure includes the caveat that the actual disintegration capability of various disintegrants "is

[8] To describe strain recovery, Dr. Appel used the analogy of a compressed spring returning to its original form. (D.I. 355 at 659:2-13; *see also* JTX 11 at 2548 and JTX 12 at 2155-56 (providing further detail on how the strain recovery mechanism operates in crospovidone)).

[9] Wicking may be defined as a process of liquid entry by capillarity into the microstructured crevices within the compact to displace the air. (JTX 11 at 2547).

dependent on [the] active ingredient and formulation." (PTX 463 at 12). The brochure illustrates its point with several graphs, reproduced below.



(*Id.*). Each graph represents a tablet with a different active ingredient. (D.I. 355 at 685:14-688:10). For each tablet, the graph compares the disintegration rates of L-HPC to the three superdisintegrants. (*Id.*).

Notably, the lines representing the rate of disintegration do not follow the same path and, at least for the CaHPO Tablets, do not even follow the same general direction. (*Id.* at 688:11-693:23). In addition, for Vitamin C tablets, crospovidone disintegrated at the fastest rate and sodium starch glycolate disintegrated at the slowest rate. (*Id.*). But for CaHPO4 tablets, the rankings flipped; sodium starch glycolate disintegrated at a faster rate than crospovidone. (*Id.*). Thus, two conclusions can be drawn from these graphs. One, L-HPC does not necessarily disintegrate at substantially the same rate as the superdisintegrants. (*Id.*). Two, it cannot be shown that L-HPC provides disintegration rates substantially similar to the superdisintegrants without testing involving the active ingredient at issue here, which is cinacalcet HCI. (D.I. 354 at 433:10-19). Amgen, however, did not present any tests or scientific literature that have made

this comparison.[10] Thus, Amgen has not proven that L-HPC achieves substantially the same result as all three listed disintegrants. Given the foregoing, Amgen has not proven by a preponderance of the evidence that L-HPC is equivalent to all three listed disintegrants under the function-way-result test.

2. Insubstantial Differences Test

Amgen argues that L-HPC is equivalent to crospovidone under the insubstantial differences test. (D.I. 359 at 36). The Federal Circuit has recognized that the function-way-result test can obscure important chemical differences and, therefore, advised that "the substantial differences test may be more suitable than [the function-way-result test] for determining equivalence in the chemical arts." *Mylan*, 857 F.3d at 867-69. Under the insubstantial differences test, "[a]n element in the accused product is equivalent to a claimed element if the differences between the two elements are 'insubstantial' to one of ordinary skill in the art." *Wi-Lan, Inc. v. Apple, Inc.*, 811 F.3d 455, 463 (Fed. Cir. 2016). Amgen's expert, Dr. Davies, did not provide an opinion regarding the insubstantial differences between L-HPC and crospovidone. (*See* D.I. 355 at 552:3-10 (Dr. Davies admitting that "[his] opinions in this case are entirely using the function way result test.")). Thus, the only particularized testimony in the trial record regarding the differences between L-HPC and crospovidone was presented by Watson's expert, Dr. Appel. She identified several differences between L-HPC and crospovidone, which were corroborated by scientific literature.

[10] Amgen's comparison of a disintegration test in Watson's Lab Notebook to a disintegration test in Watson's ANDA is not adequate for these purposes, because the formulations used different amounts of each excipient. (D.I. 359 at 33-34; PTX 368 at 27 & 50; PTX 391 at WTS-CNCLT-00173157 & 173159). Most noticeably, the intragranular disintegrant was almost doubled (6.66 mg compared to 10.20 mg) and the extragranular disintegrant was almost halved (16.20 mg compared to 9.75 mg). (PTX 368 at 27; PTX 391 at WTS-CNCLT-00173157). As Dr. Appel testified, a POSA would see these as two different formulations. (D.I. 355 at 740:3-741:14).

First, as Dr. Appel explained, L-HPC and crospovidone have different physical shapes. (D.I. 355 at 655:20-656:11). The physical shape of the particles affects how particles flow. (*Id*.). Particle flow "plays a crucial role" in pharmaceutical manufacturing, because "good flowability" ensures that the tablets' contents are uniform and consistent. (DTX 324 at 4; D.I. 355 at 655:20-656:11). Crospovidone particles are spherical "like marbles," whereas L-HPC particles are long and narrow "like spaghetti noodles." (D.I. 355 at 655:13-656:5; PTX 438 at 209 & 323). "Marbles flow really well," whereas spaghetti noodles "don't really flow well." (D.I. 355 at 655:13-656:5; *see also* DTX 324 at 1 (stating that L-HPC "showed poor flow properties" due to its high aspect ratios)).

Second, crospovidone and L-HPC have different chemical structures. Crospovidone is a five-member ring with four carbons and one nitrogen. (D.I. 355 at 653:1-7; PTX 438 at 208). L-HPC is a six-member ring with five carbons and one oxygen. (D.I. 355 at 653:1-15; PTX 438 at 322). Crospovidone is cross-linked, whereas L-HPC is not. (D.I. 355 at 661:22-662:18, 664:4-5). According to Dr. Appel, these differences mean a POSA would not consider L-HPC and crospovidone "as equivalent chemically." (*Id*. at 652:22-653:15).

Third, L-HPC is multi-functional, whereas crospovidone is not. (*Id*. at 656:15-22, 671:14-16). L-HPC can act as a binder or disintegrant, whereas crospovidone functions only as a disintegrant. (PTX 438 at 208 & 322). A POSA must take into account the multifunctional nature of an excipient, because the specific function such excipient will perform in any given formulation depends on the manufacturing process and the other excipients present. (D.I. 355 at 656:22-658:7; D.I. 354 at 268:21-269:3).

Fourth, when acting as a disintegrant, L-HPC is less potent than crospovidone. (*Id*. at 666:7-23; DTX 334 at 240 (stating that L-HPC "is not as effective as" crospovidone); JTX 12 at

2155 (explaining that crospovidone is "more efficient" than L-HPC)). Crospovidone levels are usually in the 2-5% range, and higher levels may cause problems, whereas L-HPC levels are typically in the 2-10% range, but can be higher. (DTX 334 at 239-40; D.I. 355 at 665:14-666:19). Given all of the foregoing evidence, Dr. Appel has credibly opined that L-HPC and crospovidone have differences that a POSA would find substantial. (D.I. 355 at 647:18-648:6, 653:19-654:7). Therefore, Amgen has not carried its burden of showing that L-HPC is equivalent to crospovidone under the insubstantial differences test.

3. Conclusion

Amgen has failed to prove by a preponderance of the evidence that L-HPC is equivalent to all of the disintegrants listed in claim 1 under the function-way-result test or that L-HPC is equivalent to crospovidone alone under the insubstantial differences test. Therefore, Watson does not infringe claim 1 of the '405 patent. This means, per the parties' stipulation, Watson does not infringe claims 2-4, 8-17, and 19-20. (D.I. 336 at ¶ 4). This also means, per *Wahpeton Canvas*, Watson does not infringe claims 5, 6, and 18. *Wahpeton Canvas*, 870 F.2d at 1552 n. 9 ("One who does not infringe an independent claim cannot infringe a claim dependent (and thus containing all the limitations of) that claim.").

D. Piramal

Piramal filed Abbreviated New Drug Application No. 210207 ("ANDA") with the FDA, seeking approval to market a generic version of cinacalcet hydrochloride in 30, 60, and 90 mg dosage strengths. (D.I. 293, Ex. 1 at ¶ 80). Piramal included a Paragraph IV Certification in its ANDA stating that the '405 patent is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of Piramal's product. (*Id*. at ¶ 81). Amgen claims that Piramal's product will infringe claims 1-6 and 8-20 of the '405 patent. (D.I. 293, Ex. 2 at ¶¶ 35-

36). Piramal has stipulated that if its ANDA product infringes claim 1, then its ANDA product will also infringe claims 2-4, 8-17, and 19-20, to the extent each claim is found valid and enforceable. (D.I. 336 at ¶ 3). The stipulation did not cover the asserted claims 5, 6, and 18.

According to the ANDA, Piramal's product has the following composition:

Ingredient	**Function**
Cinacalcet HCl	Active
Corn / Maize Starch	Diluent
Microcrystalline Cellulose	Diluent
Pregelatinized Starch	Binder
Crospovidone	Disintegrant

(PTX 494 at PIR 229).

The parties dispute whether Piramal's ANDA product infringes the binder and disintegrant limitations of claim 1. A finding of non-infringement, however, can be resolved on the binder limitation alone. Amgen argues that the unlisted binder in Piramal's ANDA product—pregelatinized starch—has two components; a native starch fraction that actually functions as a diluent; and a cold water soluble fraction that functions as a binder. (D.I. 359 at 18-21). Neither pregelatinized starch nor its cold water soluble fraction are listed in the Markush group for binders, which under my claim construction order means there is no literal infringement. Accordingly, Amgen argues that cold water soluble fraction is equivalent to povidone. (*Id.*). For the reasons explained below, however, I find that Amgen is foreclosed by prosecution history estoppel from asserting the doctrine of equivalents against Piramal's use of pregelatinized starch as a binder.

1. Prosecution History Estoppel Applies

Prosecution history estoppel prevents a patent owner from using the doctrine of equivalents to recapture subject matter surrendered to acquire the patent. *Honeywell Int'l v. Hamilton Sunstrand Corp*., 523 F.3d 1304, 1312 (Fed. Cir. 2008). A presumption arises that the patent owner surrendered all equivalents in "the territory between the original claim and the amended claim" where: (1) an amendment narrows the scope of the claims, and (2) the amendment is adopted for a substantial reason related to patentability. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co*., 535 U.S. 722, 740 (2002). Amgen does not dispute that the Examiner's Amendment was a narrowing amendment. (*See* D.I. 359 at 49; D.I. 354 at 400:8-13, 402:19-22). Thus, the only issue here is whether the Examiner's Amendment was adopted for substantial reasons related to patentability. I find that it was.

Amgen tried—and failed—to overcome an obviousness rejection by making only one change to the claims: in the 2014 Amendment, Amgen narrowed the amount of cinacalcet HCl to "about 20 mg to about 100 mg." (JTX 5 at SENS-AMG 309, 316-17). The Examiner did not allow the claims in the 2014 Amendment. Instead, the Examiner proposed the Examiner's Amendment, which added the Markush groups to the binder and disintegrant limitations. (*Id*. at SENS-AMG 328-340). It was only after Amgen agreed to the entry of the Examiner's Amendment that the Examiner allowed the claims over the prior art. (*Id*.). There would have been no need for the Examiner to propose an amendment if Amgen's 2014 Amendment was sufficient. In addition, the Examiner expressly stated that he was allowing the claims as set forth in the Examiner's Amendment because, inter alia, the closest prior art "fails to specifically disclose or render obvious the *combination of components* and in the amounts thereof." (*Id*. at SENS-AMG 338). The Examiner's reliance on the "combination of components" underscores

the fact that the precise amount of cinacalcet HCI proposed in the 2014 Amendment was not enough by itself to overcome the obviousness rejection.

In addition, the Examiner's Amendment employed recognized methods for overcoming an obviousness rejection.[11] Original dependent claims 6 and 8 were canceled and the limitations in those claims—which were the Markush groups for binders and disintegrants respectively—were imported into now independent claim 1. *See, e.g.*, *Ranbaxy Pharm. Inc. v. Apotex, Inc.*, 350 F.3d 1235, 1240 (Fed. Cir. 2003) (where patentee rewrote dependent claims into independent form, amendment was made for a substantial reason related to patentability); *Mycogen Plant Science, Inc. & Agrigenetics, Inc. v. Monsanto Co.*, 261 F.3d 1345, 1350 (Fed. Cir. 2001) (finding that prosecution history estoppel applies where limitations were imported into independent claims from original dependent claims). At the same time, the Markush groups in claim 1 of the '405 patent resulted in fewer combinations of excipients than disclosed in the prior art. Creekmore disclosed 19 binders and 8 disintegrants, resulting in 152 combinations. (PTX 7 at 2:32-43; D.I. 355 at 633:10-21). Hsu disclosed 10 binders and 12 disintegrants, resulting in 120 combinations. (PTX 11 at ¶¶ 17, 46, 51; D.I. 355 at 633:22-634:11). The Examiner's Amendment disclosed a closed group of 4 binders and 3 disintegrants that resulted in 12 combinations. (D.I. 355 at 634:12-635:22). An obviousness rejection can be overcome by narrowing a claim to a smaller set of members within a group. *See, e.g.*, *Ranbaxy*, 350 F.3d at 1240-41 (limiting "highly polar solvent" to a "defined group of solvents" overcame obviousness rejection); *Merck & Co. v. Mylan Pharm. Inc.*, 190 F.3d 1335, 1340-41 (Fed. Cir. 1999) (broad claims to polymers narrowed to specific polymers). For all of these reasons, I find that the

[11] Amgen argues that the Examiner's Amendment did not overcome the obviousness rejection. (D.I. 359 at 60-65). However, a patentee "may not both make the amendment and then challenge its necessity in a subsequent infringement action on the allowed claim." *Bai v. L&L Wings, Inc.*, 160 F.3d 1350, 1356 (Fed. Cir. 1998).

Examiner's Amendment was adopted for substantial reasons related to patentability. Amgen's arguments to the contrary are unpersuasive.

First, Amgen relies heavily on its counsel's remark in the 2015 Preliminary Amendment that the "amendments have not been made in response to a prior art rejection but rather to place the claims in proper format and to better define the claimed subject matter." (D.I. 359 at 58-59; JTX 5 at SENS-AMG 1583). There is no reason to read this statement as describing anything more than the reason behind the 2015 Preliminary Amendment. Amgen itself states that "proper format" means the underlining added to show the changes made to the 2014 Amendment by the Examiner's Amendment, which is exactly what the 2015 Preliminary Amendment did. (D.I. 359 at 46 & 54). Thus, I find that a self-serving remark by Amgen's counsel in the 2015 Preliminary Amendment does not explain the reasons why Amgen agreed to the Examiner's Amendment over eight months earlier.

Second, Amgen relies heavily on the Examiner's statement in the second, third, and fourth notices of allowance that he was allowing the claims due to, inter alia, "the nature of the excipients." (D.I. 359 at 59). It is not clear from the record whether the phrase "nature of the excipients" means the genus of excipients (e.g., binder, diluent, etc.) or the species of excipients (e.g., sucrose, povidone, etc.). Nevertheless, when the Examiner described in the rejection the prior art that the claims failed to overcome, he explicitly pointed to the disclosure of specific excipients in specific functions. (*See, e.g.*, JTX 5 at SENS-AMG 295 (stating that Creekmore discloses "one or more fillers like microcrystalline cellulose," "one or more binders like starch," and "one or more disintegrants like polyvinylpyrrolidone (povidone)"); *Id.* (stating that Hsu discloses "binders like starch," "diluents like microcrystalline cellulose," and "disintegrants such as crospovidone")). When the Examiner first allowed the claims in the '405 patent, he explained

that the "combination of components … was not taught or suggested by" the prior art and is, therefore, "patentably distinct over the prior art." (JTX 5 at SENS-AMG 338). Thus, the Examiner very much had in mind the species of excipients when he decided that adding the Markush groups to claim 1 overcame the prior art. No further amendments or arguments were made after the first notice of allowance. So the later notices of allowance provide no additional insight into the reasons for the Examiner's Amendment.

Third, Amgen argues that if the Examiner's Amendment had been necessary for patentability, the Examiner would have checked one of the boxes in the Interview Summary form under the "Issues Discussed" section. (D.I. 354 at 348:4-349:20; D.I. 359 at 42). Several of the boxes are for common statutory bases used to reject claims: 35 U.S.C. § 101 (patent eligibility), § 112 (enablement), § 102 (novelty), and § 103 (obviousness). (JTX 5 at SENS-AMG 340). One box is for "Others" which, if checked, may have affirmatively indicated that some issue unrelated to patentability was discussed during the interview. (*Id*.). Here, none of the boxes were checked. (*Id*.). Accordingly, the boxes themselves provide no evidence either way regarding whether the amendment was made for reasons of patentability. It is also of no moment that none of the boxes are checked. The Manual of Patent Examining Procedure (the "MPEP") permits the Examiner to state his reasons for allowance in the Examiner's Amendment and not the Interview Summary Form. (*See* MPEP § 713 ("For an examiner-initiated interview, it is the responsibility of the examiner to make the substance of the interview of record either on an Interview Summary form *or*, when the interview results in allowance of the application, by incorporating a complete record of the interview *in an examiner's amendment*." (emphasis added)). Accordingly, I rely on the contents of the Examiner's Amendment to ascertain what was discussed in the interview.

Finally, I am not persuaded by Amgen's argument that the Examiner's Amendment was a clarifying amendment, because the cases on which Amgen relies to illustrate its position are inapposite. (D.I. 359 at 55-58). In those cases, the "clarifying" amendments did not lead to prosecution history estoppel, because the first prong of the *Festo* test was not satisfied: the amendment did not narrow the claims. *See, e.g.*, *Intendis GMBH v. Glenmark Pharma. Inc., USA*, 822 F.3d 1355, 1365 (Fed. Cir. 2016) ("Amendment-based estoppel does not apply because the amendment was not a narrowing amendment made to obtain the patent. Rather, this record demonstrates that the amendment to the dependent claims was a clarifying amendment."); *Interactive Pictures Corp. v. Infinite Pictures, Inc.*, 274 F.3d 1371, 1377 (Fed. Cir. 2001) ("As to the amendment-based estoppel issue, we conclude that the addition of the words 'transform calculation' was not a narrowing amendment because that addition did nothing more than make express what had been implicit in the claim as originally worded."); *TurboCare Div. of Demag Delaval Turbomachinery Corp. v. Gen. Elec. Co.*, 264 F.3d 1111, 1126 (Fed. Cir. 2001) ("Here, the newly added claim only redefined the small clearance position limitation without narrowing the claim. Therefore *Festo* is not applicable."). If anything, these cases suggest that a clarifying amendment is one that by its nature adds additional language without narrowing a claim. Here, the Examiner's Amendment admittedly narrowed the claims, so it is not a clarifying amendment.

2. Scope of Equivalents Surrendered

Because the Examiner's Amendment narrowed the claims and the amendment was made for substantial reasons related to patentability, a presumption arises that Amgen surrendered all equivalents in "the territory between the original claim and the amended claim." *Festo Corp.*, 535 U.S. at 740. Amgen may rebut that presumption by showing that the alleged equivalent (1) "could not reasonably have been described at the time the amendment was made," (2) "was

tangential to the purpose of the amendment," or (3) "was not foreseeable (and thus not claimable) at the time of the amendment." *Research Plastics, Inc. v. Fed. Packaging Corp.*, 421 F.3d 1290, 1298 (Fed. Cir. 2005). Amgen argues that "the tangentiality exception to prosecution history estoppel applies." (D.I. 359 at 66-67).

Amgen has failed to show that the Examiner's Amendment bore no more than a tangential relation to the equivalent in question. "Although there is no hard-and-fast test for what is and what is not a tangential relation, it is clear that an amendment made to avoid prior art that contains the equivalent in question is not tangential." *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1291 (Fed. Cir. 2010). Here, the Examiner's Amendment was able to overcome the prior art by claiming a smaller set of the binders disclosed in the prior art. By agreeing to the Examiner's Amendment, Amgen abandoned the other binders disclosed in the prior art. As the Examiner noted in making his rejection, one of the binders disclosed in both Creekmore and Hsu was "starch." (JTX 5 at SENS-AMG at 295). In fact, Hsu states, "[p]referrably the binder is starch." (PTX 11 at ¶ 46). In this litigation, Amgen has treated the term "starch" as encompassing "pregelatinized starch." Even if Amgen had not done so, Creekmore discloses as a binder the use of "modified starch," which includes pregelatinized starch. (PTX 7 at 2:32-43). The '405 patent does not claim starch or pregelatinized starch as a binder. As a result, prosecution history estoppel bars Amgen from asserting the doctrine of equivalents against Piramal to reclaim pregelatinized starch, or any portion thereof, as a binder. Because Amgen cannot assert the doctrine of equivalents against the binder in Piramal's ANDA product, Amgen cannot prove that Piramal's product infringes claim 1 of the '405 patent.

Finally, all other defendants against whom the doctrine of equivalents was asserted have, like Piramal, raised the defense of prosecution history estoppel. Nevertheless, I have decided for

the sake of expediency to only address the issue as it relates to Piramal.[12] I do not decide, however, that the estoppel defense was not available to these other defendants. Rather, I conclude that even if it was not available, Amgen still could not prove infringement for the reasons stated. In other words, I have not decided the full scope of what Amgen surrendered through prosecution history estoppel, only that it surrendered as an equivalent the use of pregelatinized starch, in whole or in part, as a binder.

3. Conclusion

For the foregoing reasons, Amgen cannot prove that Piramal's product infringes claim 1 of the '405 patent. Per the parties' stipulation, Piramal also does not infringe claims 2-4, 8-17, and 19-20. Finally, under *Wahpeton Canvas*, one who does not infringe an independent claim cannot infringe the dependent claims. 870 F.2d at 1552 n. 9. Therefore, Piramal does not infringe the dependent claims not covered by the stipulation, which are claims 5, 6, and 18.

E. Zydus

Zydus filed Abbreviated New Drug Application No. 20-8971 ("ANDA") with the FDA, seeking approval to market a generic version of cinacalcet hydrochloride in 30, 60, and 90 mg dosage strengths. (D.I. 293, Ex. 1 at ¶ 110). Zydus included a Paragraph IV Certification in its ANDA stating that the '405 patent is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of Zydus' product. (*Id*. at ¶ 111). Amgen, however, claims that Zydus' product will infringe claims 1-4, 6, 8-9, and 15-20 of the '405 patent. (D.I. 293, Ex. 2 at ¶¶ 41-42). Zydus has stipulated that if its ANDA product infringes claim 1, then its ANDA product will also infringe claims 2-4, 8-9, 15-17, and 19 to the extent each claim is found

[12] Amgen has repeatedly indicated that expediency in rendering a decision is important in order to avoid preliminary injunction proceedings. (*See, e.g.*, D.I. 322 at 21:12-16). Only one of the defendants is currently subject to the 30-month stay and Amgen's patent on the active drug cinacalcet HCI expired in March. (*Id*. at 17:22-18:24; 20:8-20).

valid and enforceable. (D.I. 336 at ¶ 5). The stipulation did not cover the asserted claims 6, 18, and 20.

According to the ANDA, Zydus' product has the following composition:

Ingredient	**Function**
Cinacalcet HCl	Active Ingredient
Microcrystalline Cellulose, NF	Diluent
Pregelatinized Starch, NF	Diluent
Hydroxy Propyl Cellulose, NF	Binder
Crospovidone, NF	Disintegrant

(PTX 395 at 27).

Amgen's dispute with Zydus comes down to the function of pregelatinized starch. Amgen takes the position that it functions as a diluent, as stated in Zydus' ANDA. (D.I. 367 at 11). Zydus takes the position that it functions as a binder. (D.I. 360 at 63). Zydus' position adopts an opinion Amgen's expert has asserted against other defendants. (*Id.* at 63-64). Thus, we are in a counterintuitive world where Amgen wins against Zydus only if the opinion of Amgen's expert—which Amgen relies on to prove infringement against the other defendants—is unpersuasive.

1. The Function of Pregelatinized Starch

In tablet formulations, pregelatinized starch can, depending on the context, function as a diluent, binder, or disintegrant. (PTX 438 at 691; PTX 439 at 62). The '405 patent, however,

limited itself by claiming pregelatinized starch only as a diluent.[13] (JTX 2 at 13:21-24). Where a defendant used pregelatinized starch as a binder (like Piramal), or had no binder but used pregelatinized starch as a diluent (like Aurobindo), Amgen's expert, Dr. Davies, opined that pregelatinized starch had two components: a cold water soluble fraction that functioned as a binder and a native starch fraction that functioned as a diluent. (PTX 494 at PIR 229; D.I. 353 at 220:4-221:5; PTX 199 at 30; D.I. 354 at 250:13-251:10). Neither pregelatinized starch nor its cold water soluble fraction are listed in the Markush group for binders. Under my claim construction order, there is no literal infringement if an accused product uses an unlisted binder. (D.I. 300 at 6).

On the face of the ANDA, Zydus' product appears to literally infringe each and every limitation of claim 1. To avoid a finding of literal infringement, Zydus simply adopted Dr. Davies' opinion that the cold water soluble fraction of pregelatinized starch functions as an unlisted binder.[14] (*See* D.I. 354 at 279:7-12). Normally, where literal infringement is unavailable, a patentee can still prove infringement by resorting to the doctrine of equivalents.[15] Here, however, I granted a motion *in limine*, which bars Amgen from asserting the doctrine of equivalents against Zydus. (D.I. 357, D.I. 358). So, if I find Dr. Davies' opinion persuasive, then Amgen cannot prove infringement against Zydus.

---

[13] Actually, the '405 patent claims "starch" not "pregelatinized starch" as a diluent. (JTX 2 at 13:21-24). Nevertheless, the parties have litigated the case as if the term "starch" covers pregelatinized starch. (*See* D.I. 294, Ex. 7.1 at 97-99). Thus, for the purposes of this litigation, I read the term "starch" in the '405 patent as covering pregelatinized starch.

[14] Zydus presented its own expert, Dr. Roth, who gave the same opinion as Dr. Davies. (D.I. 356 at 909:18- 912:12). But the only evidence Zydus relied on to corroborate or explain its expert's opinion was Dr. Davies' opinion. (D.I. 360 at 63 (citing Dr. Davies' testimony as evidence for the opinion)). Accordingly, I do not focus on Dr. Roth's duplicative opinion.

[15] With respect to other defendants, Dr. Davies opined that the cold water soluble fraction was equivalent to povidone. (D.I. 353 at 220:20-221:1; D.I. 354 at 257:3-259:1).

Amgen makes no effort to attack the scientific basis for Zydus' argument as doing so would undermine the very infringement theory Amgen asserts against other defendants. (D.I. 359 at 17-18). Nevertheless, for the following reasons, I am not persuaded that Dr. Davies' opinion regarding pregelatinized starch is scientifically sound. To start, Amgen was not consistent in asserting where Dr. Davies' fractions opinion operates, a practice that does not comport with sound scientific principles. Amgen claims that three defendants literally infringe claim 1, because the fractions opinion applies to Aurobindo and Piramal but not to Zydus. But Dr. Davies could not provide a credible explanation for this variation in treatment. (D.I. 354 at 320:1-321:24). First, he said that the pregelatinized starch in Zydus' product functioned only as a diluent, because that was how Zydus identified the pregelatinized starch in its ANDA. (*Id.*). When it was pointed out that Dr. Davies did not accept how pregelatinized starch was identified in other defendants' ANDAs, he agreed and said that was why he was also asserting his fractions opinion against Zydus. (*Id*.).

This shift in infringement theories does not place Amgen in a better position. The '405 patent limits the weight of binders to "from about 1% to about 5%." (JTX 2 at 13:26-27). As Amgen acknowledges, Zydus already uses 4.98% of hydroxy propyl cellulose as a binder. (PTX 395 at 27). If the cold water soluble fraction in Zydus' product also acts a binder, then that is another 3.97% acting as a binder.[16] Adding 4.98% of hydroxy propyl cellulose to 3.97% of a cold water soluble fraction results in a total 8.95% of binder, which exceeds the "about 5%" weight limitation in the '405 patent. (D.I. 355 at 535:15-22). When Zydus raised this point with Dr. Davies, he shifted infringement theories yet again, stating that Zydus' product literally

[16] Zydus product has 11% of pregelatinized starch. (PTX 395 at 27). Dr. Davies claims that 13.1% of pregelatinized starch is a cold water soluble portion. (D.I. 354 at 253:17-254:20; PTX 202). Therefore, 13.1% x 11% = 3.97%

infringed the binder limitation, because there was "at least one" binder from the Markush group in Zydus' product that was within the about 1% to about 5% weight limitation: the 4.98% of hydroxy propyl cellulose. (*Id*. at 539:4-540:12). This testimony is not consistent with the court's controlling claim construction. (*See* D.I. 300; D.I. 357).

The same problems with Dr. Davies' fractions opinion appeared again when Amgen tried to apply it to the pregelatinized starch in the Example of the '405 patent. Dr. Davies claimed that the cold water soluble fraction of the pregelatinized starch in the Example functions as a binder. (D.I. 354 at 315:22-316:11). The Example has 33.378% of pregelatinized starch, of which 4.373% purportedly acts as a binder.[17] (JTX 2 at 11:22-23). Dr. Davies further testified that the 2.044% of povidone in the Example also functions as a binder. (*Id*. at 315:8-13). Adding these two binder amounts together (4.373% of a cold water soluble fraction and 2.044% of povidone) results in 6.417% of binder total. Thus, under Dr. Davies' fractions opinion, the Example would not meet the "from about 1% to about 5%" weight limitation for binders. This issue is avoided, however, if the court adopts Dr. Davies' prior testimony that the pregelatinized starch in the Example is acting only as a diluent. (D.I. 354 at 312:3-23).

The only evidence Amgen presented to corroborate Dr. Davies' fractions opinion is unpersuasive. Amgen relies on a single sentence in the Handbook of Pharmaceutical Granulation Technology stating: "The water-soluble fraction [of pregelatinized starch] acts as a binder, whereas the remaining fraction facilitates the tablet disintegration process." (PTX 439 at 62; D.I. 359 at 19; D.I. 354 at 471:22-472:12). Reading this sentence in the context of the Handbook and the record as a whole, it appears that Amgen imparts too much meaning to the

[17] As stated previously, Dr. Davies claims that 13.1% of pregelatinized starch is a cold water soluble portion. (D.I. 354 at 253:17-254:20; PTX 202). Therefore, 13.1% x 33.378% = 4.373%.

word "acts" in the phrase "acts as a binder." Nowhere else besides that one word does the Handbooks itself or any other scientific literature in the record suggest that only the cold water soluble fraction of pregelatinized starch is acting as the binder. As Aurobindo's expert pointed out, when that same Handbook advises the percentage amount of binders to use in a formula, it advises using 2-5% of "pregelatinized starch," not 2-5% of "the cold water soluble fraction of pregelatinized starch." (PTX 439 at 61; D.I. 356 at 962:3-963:10). If anything, the sentence on which Amgen relies can be reasonably construed to mean that the cold water soluble fraction of pregelatinized starch imparts properties that improve its binding capabilities. The sentence itself makes this suggestion when it addresses the water soluble fraction and the remaining native starch fraction in parallel: It states that the water soluble fraction "acts" as a binder, and the native starch fraction "facilitates" the disintegration process. (PTX 439 at 62). "Facilitates" means "[t]o make easy or easier." Am. Heritage Dictionary (4th ed. 2009).

Ultimately, Dr. Davies consistently asserted, and other experts agreed, that the particular function of pregelatinized starch in any given formulation "depends on the context," including the amount of pregelatinized starch, the other excipients present, and the manufacturing process. (D.I. 354 at 268:21-269:3; *Id*. at 309:21-22; D.I. 355 at 506:15-507:17; *Id*. at 510:2-11; *Id*. at 511:4-512:5). And yet Amgen did not have its expert give testimony that applied those same contextual factors to each specific defendant. On the defense side, however, Aurobindo's expert, Dr. Fassihi, credibly explained how the amount of pregelatinized starch in a particular formulation will dictate its function.[18] (D.I. 356 at 955:21-960:1). As Dr. Fassihi explained and scientific literature confirmed, the theory of percolation holds that when pregelatinized starch is

[18] Similarly, Amneal's expert, Dr. McConville, explained how the manufacturing process affected the function of the pregelatinized starch in Amneal's product. *See, supra*, Section III(B)(2).

included in a wet granulation formulation in an amount in excess of about 20% by weight, the pregelatinized starch functions as a diluent. (*Id.* at 961:11-18; DTX 228 at 112-14). When, however, the pregelatinized starch in a wet granulation formulation is between 5% and 10%, the pregelatinized starch functions as a tablet binder. (PTX 438 at 692; *see also* PTX 454 at 408 ("[S]olution binders … are included in the formulation at relatively low concentrations, typically 2-10% by weight.")). When evaluating the ANDA products for Amneal, Piramal, and Zydus, the percolation theory provides the consistency lacking in Dr. Davies' opinion. For example, Amneal and Zydus use over 20% by weight of pregelatinized starch which is consistent with the diluent function identified in their ANDAs. (PTX 183 at 42; PTX 395 at 27). Piramal uses 11% of pregelatinized starch which is consistent with the binder function identified in its ANDA. (PTX 494 at PIR 229). Finally, the Example uses 33.378% of pregelatinized starch which is consistent with a diluent function that would result in the '405 patent covering the Example. (JTX 2 at 11:22-23).

Given all of the foregoing, I find that Amgen has not proven by a preponderance of the evidence that pregelatinized starch should be artificially divided into two fractions, with each fraction alone serving a different function. As a result, Zydus cannot defeat Amgen's assertions of literal infringement by adopting Dr. Davies' opinion that the cold water soluble fraction of pregelatinized starch functions as a binder. Zydus' ANDA product literally infringes claim 1 to the extent the claim is found valid and enforceable.

2. Conclusion

Amgen has asserted claims 1-4, 6, 8-9 and 15-20 of the '405 patent against Zydus. (D.I. 293, Ex. 2 at ¶¶ 41-42). Because I found above that Zydus' ANDA product literally infringes claim 1, I also find per the parties' stipulation that Zydus' ANDA product literally infringes

claims 2-4, 8-9, 15-17, and 19, to the extent each claim is found valid and enforceable. (D.I. 336 at ¶ 5). This leaves for resolution claims 6, 18, and 20. Amgen argues that the use of crospovidone in Zydus' ANDA product literally satisfies claim 6. (D.I. 359 at 16 n. 8). I agree, but only to the extent the claim is found valid and enforceable. Finally, Amgen had the burden to prove by a preponderance of the evidence that Zydus infringed asserted claims 18 and 20, yet for reasons unknown to the court, Amgen neither presented argument on these claims nor entered into a stipulation covering these claims. Accordingly, Amgen has not carried its burden as to claims 18 and 20.

IV. CONCLUSION

For the foregoing reasons, I find that Amgen has not proven infringement as to Amneal, Watson, and Piramal. As to Zydus, Amgen has proven infringement of claims 1-4, 6, 8-9, 15-17, and 19 to the extent the claims are valid and enforceable, but Amgen has not proven infringement of claims 18 and 20. Currently pending before the court is Amneal's motion pursuant to Fed. R. Civ. P. 52(c) for judgment and Zydus' motion pursuant to the same rule for partial judgment. (D.I. 325, D.I. 337). A decision on those motions will be forthcoming.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AMGEN INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 16-853-GMS
	)	CONSOLIDATED
AUROBINDO PHARMA LTD., et al.,	)	
	)	
Defendants.	)	

ORDER

IT IS HEREBY ORDERED that:

1. The disputed claim terms in the case are construed as follows:

Claim Term	**Court's Construction**
"at least one binder selected from the group consisting of povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof"	"at least one binder selected from the Markush group and no unlisted binders"
"at least one disintegrant selected from the group consisting of crospovidine (sic), sodium starch glycolate, croscarmellose sodium, and mixtures thereof"	"at least one disintegrant selected from the Markush group and no unlisted disintegrants"

2. Defendant Dr. Reddy's Laboratories shall either produce Movva Snehalatha for a deposition before trial or be prepared to argue at trial why the court should not exclude her as a witness.

/s/ Mitchell S. Goldberg

Dated: February 27, 2018

MITCHELL S. GOLDBERG, J.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AMGEN INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 16-853-GMS
	)	CONSOLIDATED
AUROBINDO PHARMA LTD., et al.,	)	
	)	
Defendants.	)	

MEMORANDUM

Pending before me are several evidentiary issues raised by the parties in connection with a patent infringement trial commencing on March 5, 2018. (D.I. 294-1, Ex. 8 & Ex. 8.1). I will address two of these evidentiary issues below.

I. CLAIM CONSTRUCTION

In the Proposed Joint Pretrial Order, Plaintiff Amgen, Inc. ("Amgen") argues that the Markush groups in the binder and disintegrant limitations should be "open sets." (D.I. 294-1, Ex. 8 at ¶ 2(b)). Amgen also urges that Defendants should be precluded from raising any claim construction issues**,** and that the time to raise this issue was at the Markman hearing. Id. at ¶ 2. Conversely, Defendants urge that the Markush groups are "closed." (D.I. 294-1, Ex. 7.1 at p. 318-19, ¶¶ 32-33).

Claim construction is a "fluid process," *Cadence Pharma., Inc. v. Innopharma Licensing LLC*, 2016 WL 3661751, at *3 n.2 (D. Del. July 8, 2016), and that process is "not final until judgment is entered," *Eaton Corp. v. Parker-Hannifin Corp*., 292 F. Supp. 2d 555, 572 n.2 (D.

Del. 2003). Until then, "[t]he court may re-construe the claims if it finds the original claim construction to be in error based upon a more developed record," and/or "may add claim constructions for terms that become disputed through the course of trial." *Eaton Corp.*, 292 F. Supp. 2d at 572 n.2.

Here, the claim construction issues Defendants now raise appear to have developed after the Markman hearing. Because these issues will substantially effect how the parties present their theories of infringement or non-infringement at trial, I will resolve this dispute now.

Independent claims 1 and 20 of United States Patent No. 9,375,405 ("the '405 patent") contain three Markush groups defining the list of excipients permitted for use as diluents, binders, and disintegrants. (D.I. 294-1, Ex. 7.1 at p. 36, ¶ 21).

Claim 1 states:

> (1) A pharmaceutical composition comprising:
>
> (a) from about 10% to about 40% by weight of cinacalcet HCl in an amount of from about 20 mg to about 100 mg;
>
> (b) from about 45% to about 85% by weight of a diluent selected from the group consisting of microcrystalline cellulose, starch, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof;
>
> (c) from about 1% to about 5% by weight of at least one binder selected from the group consisting of povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof; and
>
> (d) from about 1% to 10% by weight of at least one disintegrant selected from the group consisting of crospovidine (sic), sodium starch glycolate, croscarmellose sodium, and mixtures thereof, wherein the percentage by weight is relative to the total weight of the composition, and wherein the composition is for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

(D.I. 294-1, Ex. 7 at 4).

A Markush group "lists alternative species or elements that can be selected as part of the claimed invention." *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp*., 831 F.3d 1350, 1357 (Fed. Cir. 2016). It is typically expressed in the form: "a member selected from the group consisting of A, B and C." *Abbott Labs. V. Baxter Pharm. Prods., Inc*., 334 F.3d 1274, 1280 (Fed. Cir. 2003). "The members of the Markush group (A, B, and C in the example above) ordinarily must belong to a recognized physical or chemical class or to an art-recognized class." Manual of Patent Examining Procedure § 803.02. By claiming a Markush group, a patentee "has indicated that, for the purpose of claim validity, the members of the claimed group are functionally equivalent." *Ecolochem, Inc. v. S. Cal. Edison Co*., 1996 WL 297601, at *2 (Fed. Cir. June 5, 1996); *see also In re Driscoll*, 562 F.2d 1245, 1249 (CCPA 1977) ("It is generally understood that ... the members of the Markush group ... are alternatively usable for the purposes of the invention.").

As noted above, the parties dispute whether the Markush groups for the binder and disintegrant elements in the '405 patent are closed. (D.I. 294-1, Ex. 8 at ¶ 2(b)). Amgen argues that, even if the Markush groups are closed, it may still rely on the doctrine of equivalents to demonstrate infringement of the binder and disintegrant elements. (D.I. 298).

A. The Markush Groups Are Closed

"Use of the transitional phrase 'consisting of' to set off a patent claim element creates a very strong presumption that that claim element is 'closed' and therefore 'excludes any elements, steps, or ingredients not specified in the claim.'" *Multilayer*, 831 F.3d at 1358 (quoting *AFG Indus., Inc. v. Cardinal IG Co.*, 239 F.3d 1239, 1245 (Fed. Cir. 2001) (internal brackets omitted).

Shire Dev., LLC v. Watson Pharma., Inc., 848 F.3d 981, 986 (Fed. Cir. 2017) (quoting *Multilayer*, 831 F.3d at 1359) ("consisting of" or " consists of" creates a very strong presumption that the claim is closed). "Overcoming this presumption requires 'the specification and prosecution history' to 'unmistakably manifest an alternative meaning,' such as when the patentee acts as its own lexicographer." *Watson*, 848 F.3d at 984 (quoting *Multilayer*, 831 F.3d at 1359).

Amgen argues that the Markush groups for the binder and disintegrant elements are open, because the preamble to claims 1 and 20 use the term "comprising." (*See* D.I. 294-1, Ex. 7 at p. 226 (stating "[a] pharmaceutical composition comprising"); D.I. 298 at 2). The transitional term "'comprising' can create a presumption that the recited elements are only a part of the device, [and] that the claim does not exclude additional, unrecited elements." *Multilayer*, 831 F.3d at 1358 (quoting *Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l, Inc.*, 246 F.3d 1336, 1348 (Fed. Cir. 2001)). Thus, I must determine the effect of the presumably open-ended term "comprising" in the preamble in conjunction with the presumably closed Markush groups in the body of the claim.[1]

[1] Several cases cited by Amgen do not address claims containing both the term "comprising" and a Markush group. *See, e.g.*, *Mannesmann Demag Corp. v. Engineered Metal Prods. Co.*, 793 F.2d 1279, 1282 (Fed. Cir. 1986); *In re Crish*, 393 F.3d 1253 (Fed. Cir. 2004). *Mannesmann* and *Crish* affirmed the basic proposition that, with the term "comprising," a defendant does not defeat infringement by showing that its composition contains additional unrecited elements. *Mannesmann*, 793 F.2d at 1282; *Crish*, 393 F.3d at 1257. But the additional unrecited elements in those cases were not alternatively used for the purposes of the Markush group members. For example, in *Mannesman*, the additional unrecited elements—the "slag-stopping and backbone bars"—were not alternative species of the recited claim element—the cooling pipe coil. 793 F.2d at 1282.

The Federal Circuit recently addressed this issue in *Multilayer,* 831 F.3d 1350. There, the patent claimed a Markush group for resins, stating in relevant part:

> A multi-layer, thermoplastic stretch wrap film containing seven separately identifiable polymeric layers, comprising:
>
> ….
>
> (b) five identifiable inner layers, with each layer being selected from the group consisting of linear low density polyethylene ["LLDPE"], very low density polyethylene ["VLPDE"], ultra low density polyethylene ["ULDPE"], and metallocene-catalyzed linear low density polyethylene ["mLLDPE"] resins; said resins are homopolymers, copolymers, or terpolymers, of ethylene and C3 to C20 alpha-olefins;

Id. at 1353. "The district court construed element (b) as closed to unrecited resins—i.e., types of resin other than LLDPE, VLDPE, ULDPE, and mLLDPE." *Id*. at 1358. Before evaluating whether the plaintiff had overcome the "very strong presumption" that the Markush groups were closed, the court explained what a closed Markush group meant. "[I]f a patent claim recites 'a member selected from the group consisting of A, B, and C,' the 'member' is presumed to be closed to alternative ingredients D, E, and F." *Id*. The court explained, that to construe the Markush group "as open not only to the four recited resins but also to any other polyolefin resin conceivably suitable for use in a stretchable plastic cling film … would render the '055 patent's Markush language—'each layer being selected from the group consisting of'—equivalent to the phrase 'each layer comprising one or more of.'" *Id*.

The claim terms in *Multilayer*,—i.e., use of "comprising" in the preamble and a Markush group with the transitional phrase "consisting of"—are similar to the claim terms before me. And, I am, of course, bound by Federal Circuit precedent. Accordingly, there is a very strong presumption that the binder and disintegrant elements in the '405 patent are closed to unrecited

binders and disintegrants unless Amgen points to sufficient evidence to overcome this presumption.

In *Multilayer*, plaintiff pointed to the specification of the '055 patent as evidence of "an unmistakable intent to open the Markush group of element (b) to unrecited resins." *Id.* at 1359. Several passages of the specification, including three dependent claims and two of the three embodiments, described inner layers with unrecited resins. *Id.* at 1359-60. The court nevertheless concluded that "the specification of the '055 patent, including its dependent claims, [was] insufficient to overcome the very strong presumption, created by the patent's use of the transitional phrase 'consisting of,' that the Markush group of element (b) is closed to resins other than the four recited." *Id*. at 1360-61.

Here, Amgen is unable to point to anything, other than the use of "comprising" in the preamble, to support its argument that the Markush groups for the binder and disintegrant elements are open to unrecited elements. Considering that the evidence in *Multilayer*, which specifically described the use of unrecited resins, was not enough to overcome the presumption, what Amgen offers in comparison cannot be enough, particularly when Multilayer similarly used "comprising" in the preamble. Accordingly, I conclude that Amgen has not overcome the very strong presumption that the Markush groups for the binder and disintegrant elements are closed to unrecited binders and disintegrants.

In reaching the above conclusion, I have considered that, when examining similar language, the court in *Maxma v. ConocoPhillips, Inc*., 2005 WL 1690611 (E.D. Tex. July 19, 2005), took a different tack. In *Maxma*, a Texas district court addressed a Markush group for carrier liquid. The claim stated in relevant part:

> In a fuel additive for a hydrocarbon fuel, the composition comprising:
>
> (a) at least 90 wt. % of a carrier liquid selected from the group consisting of a hydrocarbon fraction in the kerosene boiling range having a flash point of at least 100 F. and an auto-ignition temperature of at least 400 F., a C1–C3 monohydric, dihydric, or polyhydric aliphatic alcohol, and mixtures thereof;

Id. at *4. Based on the open-ended "comprising" in the preamble, the court concluded that "the presence of the recited composition will infringe the claim, even if other structures or ingredients are also present." *Id*. at *5. Thus, the plaintiffs had to "prove the presence of one of the members of the [Markush] group" for carrier liquid. *Id*. But "the [additional] presence of some unlisted ingredient in the accused product that otherwise meets the court's definition of a carrier liquid" would not defeat infringement. *Id*. In other words, the court rejected defendant's argument that the closed Markush group meant the "accused composition may include only one of the recited carrier fluids." *Id*. Under the rules laid out in *Maxma*, if the claim recited "a member selected from a group consisting of A, B, and C," then a defendant's composition met the claim limitation if it included member "A" as well as unlisted member "D." As a result, *Maxma* is not consistent with the rules of construction outlined in *Multilayer*. More importantly, *Maxma* pre-dates *Multilayer* and, therefore, did not apply the "very strong presumption" that Markush groups are closed. *Multilayer*, 831 F.3d at 1358; *see also Watson*, 848 F.3d at 986 (referring to the presumption as "exceptionally strong"). Given the above, I decline to follow *Maxma* on this particular issue.

Finally, I note that there are only a few instances where defendants use as binders or disintegrants both a recited member and unrecited alternative. There are a greater number of instances where defendants use only an unrecited alternative, and Amgen has cited no case showing that even an "open" Markush group would allow it to prove that Defendants'

composition meets the Markush group limitation based on unrecited alternatives only. Indeed, even in *Maxma*, the court was clear that plaintiff could not discharge its burden by "establish[ing] [only] the presence of a substance meeting the court's definition of 'carrier liquid' that is not within the group of listed alternatives." *Id.*; *see also Bristol-Myers Squibb Co. v. Mylan Pharms. Inc*., 2013 U.S. Dist. LEXIS 188207, at *23 (D. Del. Oct. 17, 2013) (allowing the x-ray powder diffraction pattern to include additional 2θ values, but requiring that the x-ray powder diffraction pattern include at least six of the eleven 2θ values, as required by the Markush group language).

B. The Doctrine of Equivalents

Amgen also argues that even if the Markush groups are closed, it may still prove infringement under the doctrine of equivalents. "[T]he [claim] drafter's choice of the phrase 'consisting of' does not foreclose infringement under the doctrine of equivalents." *Vehicular Techs. v. Titan Wheel Int'l*, 212 F.3d 1377, 1383 (Fed. Cir. 2000). Thus, it appears that a patentee may still rely on the doctrine of equivalents to prove infringement of an element containing a closed Markush group. *See, e.g., Intervet Inc. v. Merial Ltd*., 617 F.3d 1282, 1286, 1290-1292 (Fed. Cir. 2010) (holding that a district court "erred in…barring the doctrine of equivalents from its infringement analysis" of a claim covering "[a] vector comprising an isolated DNA molecule comprising a sequence selected from the group consisting of ORFs 1 to 13 of porcine circovirus type II"); *E.I. Du Pont de NeMours & Co. v. Heraeus Precious Metals N. Am. Conshohocken LLC*, 2013 WL 2659533, at *3 (D. Or. June 7, 2013) (rejecting an argument that plaintiff was "foreclosed" from arguing that any compound not listed in a claimed Markush group was an equivalent).

Given the above, Amgen is not precluded from relying on the doctrine of equivalents to prove that a defendant infringed the binder or disintegrant elements, even though the Markush group for those elements are closed.[2]

II. LATE IDENTIFIED WITNESS

In the parties' Proposed Joint Pretrial Order, defendant Dr. Reddy's Laboratories ("DRL") identified Movva Snehalatha ("Snehalatha") as a potential witness that "may be called at trial." (D.I. 293-1, Ex. 4.1). Amgen argues that DRL should either be precluded from calling Snehalatha as witness, because DRL failed to timely identify her or, be ordered to produce Snehalatha for a deposition in advance of trial. (D.I. 294-1, Ex. 8 at ¶ 1(d)).

Fed. R. Civ. P. 26(a)(1) provides that, early in the case, a party must disclose "the name ... of each individual likely to have discoverable information—along with the subjects of that information—that the disclosing party may use to support its claims or defenses." Fed. R. Civ. P. 26(a)(3) provides that a party must "promptly" disclose the name of a witness it may present at trial other than solely for impeachment. Finally, Fed. R. Civ. P. 26(e) states that a party must supplement its disclosures in a "timely manner." If a party fails to timely identify a witness as required by Fed. R. Civ. P. 26(a) or (e), "the party is not allowed to use that … witness to supply evidence … at a trial, unless the failure was substantially justified or is harmless." Fed. R. Civ. P. 37(c)(1). It is left to the trial court's discretion to determine whether a party provides

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[2] The court is aware that Defendants plan to present several arguments as to why Amgen cannot invoke the doctrine of equivalents, including prosecution history estoppel. Nothing herein should be construed as precluding or prejudging those arguments.

substantial justification for their delay or if the delay is harmless. *M. Eagles Tool Warehouse, Inc. v. Fisher Tooling Co.*, 2007 WL 979854, at *12 n. 12 (D.N.J. Mar. 30, 2007). In exercising its discretion, the court should consider: "(1) the prejudice or surprise in fact to the opposing party, (2) the ability of the party to cure the prejudice, (3) the extent of disruption of the orderly and efficient trial of the case, and (4) the bad faith or willfulness of the non-compliance." *Stambler v. RSA Sec., Inc.*, 212 F.R.D. 470, 471 (D. Del. 2003) (quoting *Greate Bay Hotel & Casino v. Tose*, 34 F.3d 1227, 1236 (3d Cir. 1994)).

As no testimony has been taken, I do not yet have the necessary context of Snehalatha's testimony. Nor do I know when Snethalatha was first identified as a witness, or why she was not identified earlier. That said, and in order to avoid further conflict on this issue, Snehalatha shall be produced for deposition before to March 5, 2018. *See Impax Labs. Inc. v. Lannett Holdings Inc.*, 2016 WL 9240617, at *1 (D. Del. Aug. 24, 2016) (allowing late-identified witness to testify at trial where opposing party was amenable to a pre-trial deposition as a remedy).

III. CONCLUSION

An order consistent with this memorandum will be entered.

/s/ Mitchell S. Goldberg

Dated: February 27, 2018

MITCHELL S. GOLDBERG, J.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	**Civ. No. 16-853-MSG**
	:	**CONSOLIDATED**
AMNEAL PHARMACEUTICALS LLC, et al.,	:	
	:	
Defendants.	:	
	:	

Goldberg, J. **April 19, 2018**

MEMORANDUM OPINION

This is a consolidated case for patent infringement brought by Plaintiff Amgen Inc. ("Amgen") against Defendants Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals of New York LLC (together, "Amneal), Piramal Healthcare UK Ltd. ("Piramal"), Watson Laboratories, Inc., Actavis, Inc., and Actavis Pharma, Inc. (together, "Watson"), and Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Ltd. (together, "Zydus," and collectively with all other defendants, "Defendants").[1] Amgen claims that Defendants infringed United States Patent No. 9,375,405 ("the '405 patent") titled "Rapid Dissolution Formulation of a Calcium Receptor-Active Compound." Trial on Amgen's infringement claims was held between March 5, 2018 and March 9, 2018.[2]

[1] On May 18, 2017, Chief Judge D. Brooks Smith of the United States Court of Appeals for the Third Circuit designated me as a visiting judge for the District of Delaware, pursuant to 28 U.S.C. § 292(b), to handle this and other Delaware cases.

[2] All Defendants have filed counterclaims alleging invalidity. For scheduling reasons, trial on the infringement claims proceeded first.

Presently before the court are two motions filed around the start of trial: (i) Amgen's Motion for Reargument of the Court's February 27, 2018 Memorandum and Order which construed the meaning of the Markush groups in the '405 patent; and (ii) Zydus' Motion in Limine to preclude the introduction of a new theory of infringement—the doctrine of equivalents—which was not asserted against it before trial. (D.I. 323, D.I. 307). For the reasons set forth below, Amgen's Motion for Reargument is denied, and Zydus' Motion in Limine is granted.

I. MOTION FOR REARGUMENT

A. Background

In its Motion for Reargument, Amgen contends that the court "misconstrued [its] position on claim construction" and "misapprehended the claim construction issue." (D.I. 323 at 1-2). A brief recitation of the procedural history in this matter and the court's prior rulings on claim construction are necessary to provide the proper context for Amgen's motion.

1. The '405 Patent

The '405 patent issued from U.S. Patent Application No. 12/942,646 (the "'646 application"), filed on November 9, 2010. (D.I. 293-1, Ex. 1 ¶ 7). The parties have agreed that infringement in this case will be decided based on claim 1 of the '405 patent, which states:

> (1) A pharmaceutical composition comprising:
>
> (a) from about 10% to about 40% by weight of cinacalcet HCl in an amount of from about 20 mg to about 100 mg;
>
> (b) from about 45% to about 85% by weight of a diluent selected from the group consisting of microcrystalline cellulose, starch, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof;
>
> (c) from about 1% to about 5% by weight of at least one binder selected from the group consisting of povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof; and

(d) from about 1% to 10% by weight of at least one disintegrant selected from the group consisting of crospovidine (sic), sodium starch glycolate, croscarmellose sodium, and mixtures thereof,

wherein the percentage by weight is relative to the total weight of the composition, and wherein the composition is for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

(D.I. 294-1, Ex. 7 at 4; D.I. 336).

2. Procedural History of Claim Construction

The Honorable Gregory M. Sleet held a Markman hearing in this matter in the spring of 2017. The only claim construction dispute presented to and resolved by Judge Sleet at that time was the meaning of "relative to the total weight of the composition," which appears in claim 1's "wherein clause." (D.I. 186). By the fall of 2017, however, the parties had another claim construction dispute that had not been resolved. That dispute involved the Markush groups for the binder and disintegrant elements in claim 1.[3] (D.I. 356 at 1069:15-17). The parties became aware of the claim construction dispute when they exchanged expert reports. Some of Defendants' experts opined that there was no literal infringement, because the ANDA product contained binders or disintegrants not listed in the Markush groups. (See, e.g., D.I. 355 at 642:13-643:8; Id. at 780:20-782:22). No party, however, sought a further claim construction ruling from the court.

[3] "A Markush group 'lists alternative species or elements that can be selected as part of the claimed invention.'" Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp., 831 F.3d 1350, 1357 (Fed. Cir. 2016)). "It is typically expressed in the form: 'a member selected from the group consisting of A, B and C.'" Abbott Labs. V. Baxter Pharm. Prods., Inc., 334 F.3d 1274, 1280 (Fed. Cir. 2003)).

On January 24, 2018, Amgen's expert, Dr. Davies, was deposed. Dr. Davies testified that Defendants with unlisted binders or disintegrants still literally infringed, because the "comprising language" in the preamble of claim 1 permitted unlisted binders or disintegrants. (D.I. 356 at 1067:16-23). Despite the fact that there was no claim construction to support this opinion, Amgen did not seek a second claim construction from the court or make clear that, for those defendants against whom it had only asserted literal infringement, it would now also assert the doctrine of equivalents in the alternative. (D.I. 354 at 458:18-23).

On February 5, 2018, the parties filed a Proposed Joint Pretrial Order, which made clear that the claim construction dispute over the Markush groups was still in play.[4] (D.I. 293; D.I. 294). In the section setting forth the parties' proposed findings of fact and conclusions of law, Defendants asked the court to construe the Markush groups as closed to unlisted excipients. (D.I. 294-1, Ex. 7.1 at 316-22). Defendants also explained why they thought three arguments they expected Amgen to make should fail. (Id.). Defendants expected Amgen to argue that the Markush groups were not closed due to (1) the term "comprising" in the preamble, (ii) the phrase "at least one" before the Markush group elements, and (iii) the phrase "mixtures thereof" in the Markush group elements. (Id.).

In its part of the Proposed Joint Pretrial Order, Amgen did not make all of the arguments Defendants expected. Instead, Amgen primarily argued that Defendants should be precluded from raising the claim construction dispute, because it was "not raised at the Markman hearing."

[4] On February 6, 2018, the case was reassigned from Judge Sleet to me, due to his pending retirement. I did not reschedule the trial, because Amgen urged that an expeditious ruling was necessary to avoid a launch at risk. (Hr'g Tr. 17-20).

(See D.I. 294-1, Ex. 8 at 1). Amgen also argued that the Markush groups were not closed sets due to the claim term "comprising." (Id.; see also D.I. 294-1, Ex. 7 at 226 (citing Mannesmann Demag Corp. v. Engineered Metal Prods. Co., 793 F.2d 1279, 1282-1283 (Fed. Cir. 1986) and In re Crish, 393 F.3d 1253, 1257 (Fed. Cir. 2004))). Finally, Amgen teed-up the claim construction dispute for the court by identifying it as one of the "Evidentiary Issues [Amgen] Wishes to Raise at the Pre-Trial Conference." (D.I. 294-1, Ex. 8 at 1).

At the pre-trial conference, Amgen argued that the claim construction dispute should not be resolved, because it was untimely. (Hr'g Tr. at 79-80). Amgen also directed the court to the case law it cited in the Proposed Joint Pretrial Order regarding the term "comprising." (Id. at 81-82). Finally, representing that it was not prepared to present argument on the issue, Amgen was given the opportunity to submit a three-page letter on the issue. (Id.). The court granted this request, expecting Amgen to elaborate on the only arguments it had presented so far, i.e., timeliness and the meaning of the term "comprising."

On February 20, 2018, Amgen submitted its letter (the "February Letter"). (D.I. 298). The introduction set forth three arguments: (i) Defendants "waived their right to assert these non-infringement defenses because they failed to raise these issues long ago during claim construction briefing as set forth in the Scheduling Order;" (ii) "the claims at issue—which use the open-ended transitional phrase 'comprising'—do not exclude additional excipients that function as diluents, binders, or disintegrants;" and (iii) even if the Markush groups were not open-ended, Amgen could still assert the doctrine of equivalents. (Id. at 1). The body of the February Letter had two separate sections: one addressing the doctrine of equivalents and the other addressing the case law cited by the parties regarding the term "comprising." (Id. at 2-3

(discussing Mannesmann, 793 F.2d at 1282-1283; In re Crish, 393 F.3d at 1257; Bristol-Myers Squibb Co. v. Mylan Pharms. Inc., 2013 U.S. Dist. LEXIS 188207, at *23 (D. Del. Oct. 17, 2013); and Maxma v. ConocoPhillips, Inc., 2005 WL 1690611 (E.D. Tex. July 19, 2005))).

On February 27, 2018, the court issued its Memorandum construing the meaning of the Markush groups for the binder and disintegrant elements of claim 1. (D.I. 300). Relying primarily on Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp., 831 F.3d 1350 (Fed. Cir. 2016), the court found that "the Markush groups for the binder and disintegrant elements are closed to unrecited binders and disintegrants." (D.I. 300 at 6). Thus, there could be no literal infringement if the Defendants' ANDA product contained an unrecited (or unlisted) binder or disintegrant. (Id.). The court's Memorandum also stated that "Amgen is not precluded from relying on the doctrine of equivalents to prove that a defendant infringed the binder or disintegrant limitations, even though the Markush group for those elements are closed." (Id. at 9).

On March 6, 2018, Amgen filed its Motion for Reargument asserting that the court misunderstood its position on claim construction. (D.I. 323 at 1-2). Amgen now urged that the point of the Markush groups is not to determine literal infringement of a claim element, but to "define the binders and disintegrants considered in the weight percentage calculations." (Id.). According to Amgen:

> So long as the weight percentage is met by one of the listed binders or disintegrants, the presence of an additional excipient that functions as a binder or disintegrant does not take the Defendants' products outside the literal scope of the claims.

(Id.). In practice, claim 1 calls for "from about 1% to about 5% by weight of at least one binder selected from the group consisting of …." (D.I. 294-1, Ex. 7 at 4). Thus, under Amgen's

proposed construction, a hypothetical ANDA product using 4% of a listed binder and 6% of an unlisted binder would still literally infringe, even though it had 10% of binder total, because it had a listed binder within the "about 1% to about 5%" weight range. According to Amgen, the 6% of unlisted binder would be irrelevant. When asked where Amgen had previously presented this construction to the court, Amgen pointed to a single sentence in the February Letter that was in the middle of a paragraph discussing cases that construed the claim term "comprising." (D.I. 356 at 1072:7-10). "The 'consisting of' Markush group only limits the binders that may be used to satisfy the 'from about 1% to about 5% of at least one binder' claim element." (D.I. 298 at 3).

B. Standard of Review

"The decision to grant a motion for reargument lies within the discretion of the district court." Chemipal Ltd. v. Slim-Fast Nutritional Foods Int'l, Inc., 2005 WL 1384695, at *1 (D. Del. May 12, 2005). Such motions are granted "sparingly." D. Del. L.R. 7.1.5. A motion for reargument may only be granted if the court has "patently misunderstood a party, made a decision outside the adversarial issues presented by the parties, or made an error not of reasoning but of apprehension." Sussex Cty. Senior Serv., Inc. v. Carl J. Williams & Sons, Inc., 2000 WL 1726527, at *1 (D. Del. Mar. 31, 2000); Schering Corp. v. Amgen, Inc., 25 F. Supp. 2d 293, 295 (D. Del. 1998). A motion for reargument is not an opportunity to "accomplish repetition of arguments that were or should have been presented to the court previously." Karr v. Castle, 768 F. Supp. 1087, 1093 (D. Del. 1991).

C. Discussion

Contrary to Amgen's contentions, the court does not misunderstand its position on claim construction. (D.I. 323 at 1-2). Before the Motion for Reargument, Amgen's arguments

consistently focused on whether the Markush groups were "not closed sets" due to the term "comprising" in the preamble. (D.I. 294-1, Ex. 8 at 1; D.I. 294-1, Ex. 7 at 226; D.I. 323). Since filing the Motion for Reargument, Amgen has confirmed that "our position was and always has been that the 'comprising' at the beginning of claim 1 opens things up to things beyond the Markush groups." (D.I. 356 at 1064:13-16). This is the argument the court carefully considered and rejected in its February 27, 2018 Memorandum. (See, e.g., D.I. 300 at 4).

Amgen never fairly presented the proposed construction it now seeks, i.e., that the Markush groups "define the binders and disintegrants considered in the weight percentage calculations." (D.I. 323 at 2). The single sentence on which Amgen's Motion for Reargument rests was obscured in the middle of a paragraph analogizing the language of claim 1 to the language of patents a court construed as open to unrecited elements due to the term "comprising." (D.I. 298 at 3). Thus, Amgen's Motion for Reargument essentially raises a new argument. The court's colloquy with Amgen's counsel clearly confirms this point:

> THE COURT: Do you agree that the first time you suggested that construction was … in your motion for reargument?
>
> LAWYER: That is correct, Your Honor.

(D.I. 356 at 1070:17-23).

A new argument is not the proper subject of a motion for reargument. Davis v. Mountaire Farms, Inc., 2005 WL 1800054, at *1 (D. Del. July 29, 2005). "It is simply an attempt 'to argue new facts or issues that inexcusably were not [fairly] presented to the court in the matter previously decided.'" Id. (quoting Brambles USA, Inc. v. Blocker, 735 F. Supp. 1239, 1240 (D. Del. 1990)); Chemipal, 2005 WL 1384695, at *3 (denying a motion for reconsideration where plaintiff raised a new argument that "could have been, and thus certainly should have

been, presented in the first instance"). "On this ground alone, [the] motion for reconsideration should be denied." Ryan v. Asbestos Workers Union Local 42 Pension Fund, 2000 WL 1239958, at *8 (D. Del. Aug. 25, 2000).

Even if the court were to consider Amgen's new construction, however, it fails on the merits. This is because Amgen's claim construction requires the court to ignore the criticality of the weight ranges for the binder and disintegrant elements, which does not comport with the prosecution history. (D.I. 333 at 1).

When construing patent claims, the court considers "[t]he claims, the specification, and the prosecution history." Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995) (quoting Unique Concepts, Inc. v. Brown, 939 F.2d 1558, 1561 (Fed. Cir. 1991). As Amgen explained in the prosecution history, "the amount of binder is relevant" and "the ratio [of binder to diluent] is relevant."[5] (JTX 5 at -526).

The amendments in the prosecution history of the '405 patent further shows that Amgen acted consistent with its understanding that the weight ranges are critical to the invention. Amgen claimed the same specific weight ranges in every patent amendment, regardless of whether a Markush group was present or not. Specifically, in the amendments dated November

[5] Calcium-receptor active compounds, such as cinacalcet HCI, may be "insoluble or sparingly soluble in water" which "can result in low bioavailability of the active compound." (Id. at -520). According to Amgen, the inventive step in the '405 patent was the development of a pharmaceutical composition with cinacalcet HCI that had a rapid dissolution profile. (Id.). "The more rapid the dissolution was, the better." (Id. at -355). Testing by Amgen included in the prosecution history showed that the desired dissolution profile "can be obtained if the amount of diluent is at least 45% and the amount of binder is limited to at most 5%." (Id. at -526). Thus, "[t]he ranges for the components … are … not arbitrarily chosen, but lead to the described technical effects." (Id.; see also Id. at -354).

15, 2011 and December 15, 2014, which did not have Markush groups for the binder and disintegrant elements, Amgen claimed "from about 1% to about 5% by weight of at least one binder" and "from about 1% to about 10% by weight of at least one disintegrant." (JTX 5 at -258). In the Examiner's Amendment dated March 25, 2015, Amgen claimed those same weight ranges but added Markush groups. (Id. at -333 to -334). If Amgen is correct that the first Request for Continuing Examination dated June 23, 2015 withdrew the first Notice of Allowance dated March 25, 2015 and the Examiner's Amendment contained therein, the second Notice of Allowance dated August 18, 2015 allowed claims that kept the same weight ranges but eliminated the Markush groups for the binder and disintegrant elements. (D.I. 294-1, Ex. 7 at 128; JTX 5 at -345 to -347, -1064 to -1071). The third Notice of Allowance dated December 10, 2015, allowed claims that still kept those same specific weight ranges but added back the Markush groups. (Id. at -1092 to -1094, -1577 to -1583, and -1587 to -1595). Thus, the prosecution history demonstrates that the one invariable constant of the '405 patent was the specific weight ranges for the diluent, binder, and disintegrant elements. This suggests that the weight ranges in the '405 patent are critical to the invention and, therefore, not subject to a construction that results in their vitiation.

Amgen also argues that its claim construction is necessary to give meaning to the example in the '405 patent. (D.I. 323 at 7). The court is not persuaded. As the following table shows, if the court looked no further than the face of the patent, claim 1 covers the example:

Claim 1	Example
From about 10% to about 40% by weight of cinacalcet.	18.367% Cinacalcet HCI
From **about 45% to about 85%** by weight of a diluent selected from the group consisting of selected from the group consisting of **microcrystalline cellulose**, **starch**, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof;	33.378% **Pregelatinized Starch** 6.678% **Microcrystalline Cellulose** (intragranular) 34.300% **Microcrystalline Cellulose** (extragranular) **74.356%** Total
From **about 1% to about 5%** by weight of at least one binder selected from the group consisting of **povidone**, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof;	**2.044% Povidone**
From **about 1% to about 10%** by weight of at least one disintegrant selected from the group consisting of **crospovidine** (sic), sodium starch glycolate, croscarmellose sodium, and mixtures thereof….	**1.233% Crospovidone**

Amgen argues that claim 1 does not cover the example, because it was common knowledge to a person of ordinary skill in the art ("POSA") that pregelatinized starch could have one or more functions. (D.I. 323 at 8). According to Amgen, a POSA would read the pregelatinized starch in the example as a binder, but pregelatinized starch is not listed in the Markush group for binders. (Id.). Therefore, claim 1 needs to be open to unlisted binders. (Id.).

The '405 patent, however, does not teach that pregelatinized starch has more than one function. It teaches that pregelatinized starch has only one function – as a diluent. The '405 patent contains three Markush groups and each Markush group contains several members, but no member is present in more than one group. (D.I. 294-1, Ex. 7 at 4).

In addition, as Amgen stated in the prosecution history, "the skilled person realizes that binders are used in small amounts and diluents in big amounts." (JTX 5 at -351). The example contains 33.378% by weight of pregelatinized starch, which is a "big" amount when compared to claim 1's "about 5%" weight limit for binders. Finally, if a POSA treated the pregelatinized starch in the example as a binder, then the example would be left with an insufficient amount of diluent to meet the limitations of claim 1. It would have only 40.978% of diluent, when claim 1 requires a minimum of about 45% by weight of a diluent." (D.I. 324 at 5).

For all of these reasons, the patent teaches that the pregelatinized starch in the example is acting as a diluent, not a binder. Therefore, Amgen's argument regarding the example is without merit. (D.I. 323).

II. MOTION IN LIMINE

A. Standard of Review

"A district court judge is granted broad discretion in determining what is admissible under the Federal Rules of Evidence." Flickinger v. Toys R Us-Delaware, Inc., 492 F. App'x 217, 222, (3d Cir. 2012) (quoting Carden v. Westinghouse Elec. Corp., 850 F.2d 996, 1001 (3d Cir.1988)). When a party does not comply with its discovery obligations, the court considers the "Pennypack factors" in deciding whether to exclude the evidence. Those factors are:

> (1) the surprise or prejudice to the moving party; (2) the ability of the moving party to cure any such prejudice; (3) the extent to which allowing the testimony would disrupt the order and efficiency of trial; (4) bad faith or willfulness in failing to comply with the court's order; and (5) the importance of the testimony sought to be excluded.

Sheehan v. Del. & Hudson Ry. Co., 439 F. App'x 130, 132 (3d Cir. 2011) (citing Meyers v. Pennypack Woods Home Ownership Ass'n, 559 F.2d 894, 904–05 (3d Cir. 1977)).

B. Discussion

Zydus filed a Motion in Limine seeking an order precluding Amgen from asserting the doctrine of equivalents against it. (D.I. 307). Amgen filed a response the same day and then, unprompted, filed a supplemental response twenty-seven days later. (D.I. 301; D.I. 350). The supplemental response was unsolicited and filed without any procedural grounds permitting such filing. And all of the arguments in the supplemental response are based on facts that Amgen had in its possession at the time it filed its original response. There is no reason why Amgen could not have raised these arguments previously. Consequently, the court will disregard Amgen's supplemental response. (D.I. 350).

Zydus argues that Amgen should be precluded from asserting the doctrine of equivalents against it, because Amgen did not assert that theory before trial. (D.I. 308 at 1). Amgen does not dispute that, before trial, it only asserted literal infringement against Zydus. (D.I. 310 at 2 ("Prior to the [claim construction order], Amgen had asserted literal infringement by Zydus.")). Amgen makes several arguments, however, as to why it should now be permitted to assert this new theory.

First, Amgen argues that it has to assert a new infringement theory against Zydus, because Zydus "intends to raise a new non-infringement defense to literal infringement." (Id.). This is not accurate. Zydus raised the same non-infringement defenses at trial that it set forth in expert discovery. A review of discovery in this case supports this conclusion.

During discovery, Amgen's expert, Dr. Davies, opined that where other defendants used pregelatinized starch as a diluent, the cold water soluble portion functioned as a binder. (D.I. 353 at 169:18-23; Id. at 220:12-221:5; D.I. 354 at 250:21-251:8). Because claim 1 does not list

pregelatinized starch in the Markush group for binders, Dr. Davies further opined that the cold water soluble portion was equivalent to povidone, a listed binder. (D.I. 353 at 220:12-221:5; D.I. 354 at 250:21-251:8). Zydus' ANDA product uses pregelatinized starch as a diluent. (D.I. 353 at 169:17-18; D.I. 294-1, Ex. 7.1 at 200). Accordingly, Zydus's expert, Dr. Roth, adopted Dr. Davies' opinion that the cold water soluble portion of pregelatinized starch functioned as a binder, and then asserted that Zydus could not literally infringe, because it had an unlisted binder. (D.I. 356 at 909:18-22; Id. at 911:24-912:12). Amgen acknowledges that the reason it needs to assert the doctrine of equivalents against Zydus "is because their expert, Dr. Roth, accepted and incorporated all of Dr. Davies' opinions on this very issue." (D.I. 353 at 172:24-173:4). Thus, Amgen has been aware of Zydus' noninfringement theories since the exchange of expert reports. Zydus is not asserting new defenses to noninfringement, and Amgen cannot use that excuse to assert new theories of infringement.

Second, Amgen suggests there would be no prejudice in allowing it to now assert the doctrine of equivalents against Zydus, because Amgen will use the same evidence and expert opinions against Zydus that it has used against other defendants. (D.I. 310 at 2). The court disagrees that there will be no prejudice. There are multiple ways Zydus could have taken a different approach to litigation had Amgen timely asserted the doctrine of equivalents against it, from having its own expert opine on the theory to pursuing different avenues of discovery. (D.I. 353 at 170:8-171:7). As demonstrated at trial, none of the defendants to whom Amgen has asserted its theory regarding pregelatinized starch have responded with the same defenses. There is no reason to assume that Zydus would have adopted their arguments. The fact that other

defendants have had the opportunity to test Amgen's theories regarding pregelatinized starch does not cure the prejudice to Zydus.

Third, Amgen argues that the court's claim construction Memorandum, issued in the week before trial, left it with the belief that "it was free to assert infringement by equivalents" against any defendant. (D.I. 310 at 2). Amgen has unreasonably misconstrued the court's ruling. The operative Opinion does state that "Amgen is not precluded from relying on the doctrine of equivalents to prove that a defendant infringed the binder or disintegrant limitations, even though the Markush group for those elements are closed." (D.I. 300 at 8). But this ruling did not give Amgen the right to assert new infringement theories without proper notice. It simply stated that Amgen was not prevented from asserting infringement theories it had previously preserved.

Finally, Amgen argues that it "should be permitted to adjust its infringement theory and testimony to meet the constructions in the [claim construction Memorandum]," and asks for leave of the court to do so. (D.I. 310 at 2). Amgen, however, waited until the eve of trial to make this request, which left no time for Zydus to take any discovery that could have cured the prejudice against it. Amgen had several days to act after the court issued the Memorandum.[6] Amgen was asked why it did not alert Zydus shortly after receiving the Memorandum that it was going to expand the scope of its expert report based on the ruling, and replied that it "[did not] have a good reason for it." (D.I. 353 at 172:12-20). Given all of the above, Zydus' Motion in

[6] Amgen also did not have to wait until receiving the court's claim construction Memorandum to request relief. There were two weeks between the pre-trial conference and trial in which Amgen could have taken steps to assert the doctrine of equivalents against Zydus in case the court issued an unfavorable claim construction.

Limine is granted. Amgen is precluded from asserting a doctrine of equivalents theory against Zydus.

III. CONCLUSION

For the foregoing reasons, Amgen's Motion for Reargument of the Court's February 27, 2018 Memorandum and Order (D.I. 323) is denied. Zydus' Motion in Limine to preclude the assertion of the doctrine of equivalents against it (D.I. 307) is granted. An order consistent with this memorandum opinion will be entered.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AMGEN INC., Plaintiff, v. AMNEAL PHARMACEUTICALS LLC, et al., Defendants.	Civ. No. 16-853-MSG CONSOLIDATED

JUDGMENT

In this consolidated patent infringement action, plaintiff Amgen, Inc. ("Amgen") has asserted claims of infringement against Defendants Amneal Pharmaceuticals LLC and Amneal Pharmaceuticals of New York LLC (collectively, "Amneal") (*see* C.A. No. 16-925), Piramal Healthcare UK Ltd. ("Piramal") (*see* C.A. No. 17-713), and Watson Laboratories, Inc., Actavis, Inc., and Actavis Pharma, Inc. (collectively, "Watson") (*see* C.A. No. 16-855). A four-day bench trial on infringement was held between March 5, 2018 and March 9, 2018. (D.I. 375 at 2). For the reasons set forth in the court's Opinion and Order dated July 27, 2018 (D.I. 375; D.I. 376) and subsequent Order dated August 24, 2018 (D.I. 384);

IT IS HEREBY ORDERED AND ADJUDGED that:

1. A judgment of NON-INFRINGEMENT of claims 1-4, 6, 8-12, and 14-18 of the '405 patent is hereby entered in favor of Amneal and against Amgen;

2. A judgment of NON-INFRINGEMENT of claims 1-6 and 8-20 of the '405 patent is hereby entered in favor of Piramal and against Amgen; and

3. A judgment of NON-INFRINGEMENT of claims 1-6 and 8-20 of the '405 patent is

hereby entered in favor of Watson and against Amgen.

Dated: August 24, 2018

UNITED STATES DISTRICT JUDGE

(12) **United States Patent**
Lawrence et al.

(10) **Patent No.: US 9,375,405 B2**
(45) **Date of Patent: *Jun. 28, 2016**

(54) **RAPID DISSOLUTION FORMULATION OF A CALCIUM RECEPTOR-ACTIVE COMPOUND**

(75) Inventors: **Glen Gary Lawrence**, Thousand Oaks, CA (US); **Francisco J. Alvarez**, Newbury Park, CA (US); **Hung-Ren H. Lin**, Oak Park, CA (US); **Tzuchi R. Ju**, Vernon Hills, IL (US)

(73) Assignee: **Amgen, Inc.**, Thousand Oaks, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1190 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/942,646**

(22) Filed: **Nov. 9, 2010**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(60) Provisional application No. 60/502,219, filed on Sep. 12, 2003.

(51) **Int. Cl.**

A61K 31/135	(2006.01)
A61K 31/137	(2006.01)
A61K 31/00	(2006.01)
A61K 9/20	(2006.01)
A61K 9/28	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/00*** (2013.01); ***A61K 9/2077*** (2013.01); ***A61K 31/135*** (2013.01); ***A61K 31/137*** (2013.01); *A61K 9/2866* (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/135; A61K 31/137
USPC 514/275, 579, 607, 614, 646, 649; 424/434, 464, 465, 476, 490
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient, wherein the composition has a controlled dissolution profile. The present invention further relates to a method of manufacturing the pharmaceutical composition, as well as a method of treating a disease using the pharmaceutical composition.

23 Claims, 1 Drawing Sheet

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Equipment	Components	Unit Operation	Critical Process Controls
PMA 800L granulator	purified water and intra-granular components[a]	granulation[b]	water level, impeller speed, water spray rate
Comil (In-line)		wet mill	
Aeromatic MP6		fluid bed dry	
Quadro Mill 196S (Comil)		dry mill	
Gallay tote blender (650 L)	extra-granular components[c]	pre-blend	
Gallay tote blender (1000 L)	combine granulation mix A and B and extra-granular mix	final blend	blend time
Gallay tote blender (1000 L)	magnesium stearate	lubrication	
Unipress 27		compression[d]	tablet press speed, tablet weight, thickness, hardness, friability, disintegration time
3 X Vector Hi-Coater pan (3 spray guns) delivery (peristaltic pump)	color coat (Opadry® II), clear coat (Opadry® Clear), carnauba Wax	film coating and wax	spray rate, exhaust temperature
Ackley ink-based offset printer	Opacode® black	print	

[a] cinacalcet HCl, pregelatinized starch, microcrystalline cellulose, povidone, and crospovidone

[b] The granulation step to dry milling step is repeated to generate 2 bowls of wet granulation (Mix A and B).

[c] Extra-granular components are microcrystalline cellulose, crospovidone, and colloidal silicon dioxide

[d] Tooling dimension is dependent on tablet size and strength, (30 mg; 0.2372" x 0.3800" oval shape plain, 60 mg; 0.3000" x 0.4800" modified oval (double radius) plain, 90 mg; 0.3420" x 0.5480" modified oval (double radius) plain)

RAPID DISSOLUTION FORMULATION OF A CALCIUM RECEPTOR-ACTIVE COMPOUND

This application claims the benefit of priority of U.S. Provisional Patent Application No. 60/502,219, filed Sep. 12, 2003.

Calcium receptor-active compounds are known in the art. One example of a calcium receptor-active compound is cinacalcet HCl, which is described, for example, in U.S. Pat. No. 6,001,884. Such calcium receptor-active compounds may be insoluble or sparingly soluble in water, particularly in their non-ionized state. For example, cinacalcet has a solubility in water of less than about 1 μg/mL at neutral pH. The solubility of cinacalcet can reach about 1.6 mg/mL when the pH ranges from about 3 to about 5. However, when the pH is about 1, the solubility decreases to about 0.1 mg/mL. Such limited solubility can reduce the number of formulation and delivery options available for these calcium receptor-active compounds. Limited water solubility can also result in low bioavailability of the compounds.

There is therefore a need to maximize the dissolution of the calcium receptor-active compound from a dosage form, and potentially during in vivo exposure. There is also a need to improve the bioavailability of the calcium receptor-active compound during in vivo exposure.

One aspect of the present invention provides a pharmaceutical composition comprising at least one calcium receptor active compound in combination with at least one pharmaceutically acceptable carrier. Certain embodiments of the present invention are directed to a pharmaceutical composition with a defined dissolution profile.

The invention also provides a method of manufacturing the pharmaceutical composition to achieve the desired dissolution profile, as well as a method of treating a disease using the pharmaceutical composition. In addition, certain embodiments of the present invention are directed to a method for controlling dissolution rate of a formulation comprising the pharmaceutical composition.

According to one aspect of the invention, the invention provides a pharmaceutical composition comprising an effective dosage amount of at least one calcium receptor-active compound and at least one pharmaceutically acceptable excipient, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in United States Pharmacopeia (USP)—National Formulary (NF) (USP 26/NF 21), chapter 711 using a USP 2 apparatus at a temperature of 37° C.±0.5° C., and at a rotation speed of 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

According to another aspect of the invention, the invention provides a pharmaceutical composition comprising an effective dosage amount of at least one calcium receptor-active compound and at least one pharmaceutically acceptable excipient, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in USP 26/NF 21, chapter 711 using a USP 2 apparatus at a temperature of about 37° C., and at a rotation speed of about 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

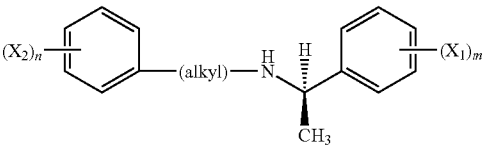
The invention also provides a method of controlling the dissolution rate of a formulation comprising an effective dosage amount of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient, the method

comprising producing the formulation in a granulator which has a volume ranging from about 1 L to about 2000 L, and contains water in a granulation level ranging from about 10% to about 50% relative to the weight of the dry powders in the granulator.

The calcium receptor-active compound useful in the claimed invention may be a calcimimetic compound or a calcilytic compound. As used herein, the term "calcimimetic compounds" refers to compounds that bind to a calcium receptor, and induce a conformational change that reduces the threshold for calcium receptor activation by the endogenous ligand Ca^{2+}, thereby reducing parathyroid hormone ("PTH") secretion. These calcimimetic compounds can also be considered allosteric modulators of the calcium receptor. As used herein, the term "calcilytic compounds" refers to compounds that act as calcium receptor antagonists, and stimulate PTH secretion.

The calcimimetic compounds and calcilytic compounds useful in the present invention include those disclosed in, for example, European Patent No. 933 354; International Publication Nos. WO 01/34562, WO 93/04373, WO 94/18959, WO 95/11221, WO 96/12697, WO 97/41090; U.S. Pat. Nos. 5,981,599, 6,001,884, 6,011,068, 6,031,003, 6,172,091, 6,211,244, 6,313,146, 6,342,532, 6,363,231, 6,432,656, and U.S. Patent Application Publication No. 2002/0107406. The calcimimetic compounds and/or calcilytic compounds disclosed in these patents and published applications are incorporated herein by reference.

In certain embodiments, the calcium receptor-active compounds are chosen from compounds of formula (I) and pharmaceutically acceptable salts thereof



wherein:

X_1 and X_2, which may be identical or different, are each a radical chosen from CH_3, CH_3O, CH_3CH_2O, Br, Cl, F, CF_3, CHF_2, CH_2F, CF_3O, CH_3S, OH, CH_2OH, $CONH_2$, CN, NO_2, CH_3CH_2, propyl, isopropyl, butyl, isobutyl, t-butyl, acetoxy, and acetyl radicals, or two of X_1 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical, or two of X_2 may together form an entity chosen from fused cycloaliphatic rings, fused aromatic rings, and a methylene dioxy radical; provided that X_2 is not a 3-t-butyl radical;

n ranges from 0 to 5;

m ranges from 1 to 5; and

the alkyl radical is chosen from C1-C3 alkyl radicals, which are optionally substituted with at least one group chosen from saturated and unsaturated, linear, branched, and cyclic C1-C9 alkyl groups, dihydroindolyl and thiodihydroindolyl groups, and 2-, 3-, and 4-piperid(in)yl groups; and the stereoisomers thereof.

Calcium receptor-active compounds useful in the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate,

glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, mandelate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 2-phenylpropionate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate, mesylate, and undecanoate. When compounds of the invention include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable salts for the carboxy group are well known to those skilled in the art and include, for example, alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. For additional examples of "pharmacologically acceptable salts," see infra and Berge et al., *J. Pharm. Sci.* 66:1 (1977). In certain embodiments of the invention salts of hydrochloride and salts of methanesulfonic acid can be used.

In some embodiments of the present invention, the calcium-receptor active compound can be chosen from cinacalcet, i.e., N-(1-(R)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl) phenyl]-1-aminopropane, cinacalcet HCl, and cinacalcet methanesulfonate. The cinacalcet HCl and cinacalcet methanesulfonate can be in various forms, such as amorphous powders, crystalline powders, and mixtures thereof. For example, the crystalline powders can be in forms including polymorphs, psuedopolymorphs, crystal habits, micromeretics, and particle morphology.

The therapeutically effective amount of the calcium receptor-active compound in the compositions disclosed herein ranges from about 1 mg to about 360 mg, for example from about 5 mg to about 240 mg, or from about 20 mg to about 100 mg. As used herein, the "therapeutically effective amount" is an amount that changes in a desired manner at least one of the calcium level, the phosphorus level, the PTH level, and the calcium phosphorus product in a subject. In some embodiments, the therapeutically effective amount of cinacalcet HCl in the composition disclosed herein can be chosen from about 5 mg, about 15 mg, about 30 mg, about 50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, or about 360 mg.

While it may be possible to administer a compound of the invention alone, the compound administered will normally be present as an active ingredient in a pharmaceutical composition. Thus, a pharmaceutical composition of the invention may comprise a therapeutically effective amount of at least one calcium receptor-active compound, or an effective dosage amount of at least one calcium receptor-active compound.

As used herein, an "effective dosage amount" is an amount that provides a therapeutically effective amount of the at least one calcium receptor active compound when provided as a single dose, in multiple doses, or as a partial dose. Thus, an effective dosage amount of the at least one calcium receptor active compound of the invention includes an amount less than, equal to or greater than an effective amount of the compound; for example, a pharmaceutical composition in which two or more unit dosages, such as in tablets, capsules and the like, are required to administer an effective amount of the compound, or alternatively, a multidose pharmaceutical composition, such as powders, liquids and the like, in which an effective amount of the at least one calcium receptor-active compound is administered by administering a portion of the composition.

Alternatively, a pharmaceutical composition in which two or more unit dosages, such as in tablets, capsules and the like, are required to administer an effective amount of the at least one calcium receptor active compound may be administered

in less than an effective amount for one or more periods of time (i.e., a once-a-day administration, and a twice-a-day administration), for example to ascertain the effective dose for an individual subject, to desensitize an individual subject to potential side effects, to permit effective dosing readjustment or depletion of one or more other therapeutics administered to an individual subject, and/or the like.

The effective dosage amount of the pharmaceutical composition disclosed herein ranges from about 1 mg to about 360 mg from a unit dosage form, for example about 5 mg, about 15 mg, about 30 mg, about 50 mg, about 60 mg, about 75 mg, about 90 mg, about 120 mg, about 150 mg, about 180 mg, about 210 mg, about 240 mg, about 300 mg, or about 360 mg from a unit dosage form.

In some embodiments of the present invention, the compositions disclosed herein comprise a therapeutically effective amount of cinacalcet HCl for the treatment of hyperparathyroidism, such as primary hyperparathyroidism and secondary hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium-phosphorus product. For example, in certain embodiments, the cinacalcet HCl can be present in an amount ranging from about 1% to about 70%, such as from about 5% to about 40%, from about 10% to about 30%, or from about 15% to about 20%, by weight relative to the total weight of the composition.

The compositions of the invention may contain one or more active ingredients in addition to the calcium receptor-active compound. The additional active ingredient may be another calcium receptor-active compound, or it may be an active ingredient having a different therapeutic activity. Examples of such additional active ingredients include, for example, vitamins and their analogs, such as vitamin D and analogs thereof, antibiotics, and cardiovascular agents.

The cinacalcet HCl or other calcium receptor-active compound that can be used in the composition is typically present in the form of particles. These particles can have a particle D_{50} of, for example, less than or equal to about 50 μm. As used herein, the "particle D_{50}" is the particle size of the active pharmaceutical ingredient at the 50^{th} percentile of a particle size distribution. According to certain embodiments of the invention, the active pharmaceutical ingredient in the formulation has a particle D_{50} that is less than the granule D_{50} of the formulation, discussed in detail below.

The particle D_{50} of the cinacalcet HCl particles can be determined by one of ordinary skill in the art using known light scattering techniques. In one embodiment of the invention, the particle D_{50} of the cinacalcet HCl particles is determined by using a particle size analyzer, such as a Malvern Mastersizer analyzer, that uses a laser to scan a suspension of particles. The particles diffract the incoming light to detectors: smaller particles diffract light at larger angles, while larger particles diffract light at smaller angles. The light intensities observed at each detector are translated into a particle size distribution based on the diameter of a sphere that has an equivalent volume to that of the measured particles.

Specifically, the particle size distribution of the active pharmaceutical ingredient, for example, cinacalcet HCl, can be determined according to the following procedure. The following instrument conditions in a Malvern Mastersizer particle size analyzer are specified in its software:

Refractive Index Sample	1.630
Absorptive Index	0.1
Refractive Index Dispersant	1.375
Analysis model	General purpose spherical
Calculation sensitivity	Enhanced

-continued

Measurement snaps and time	20,000 snaps over 20 seconds
Background snaps and time	20,000 snaps over 20 seconds
Stir speed	1750 rpm

While stirring, about 170 mL of a dispersion of about 0.1% sorbitan trioleate (for example Span 85®, available from Kishida Chemical) in hexane ("dispersant-B"), is added to the sampling unit, and the laser is aligned to take a background measurement of the dispersant-B.

The entire suspension containing the cinacalcet HCl is added until a suitable obscuration range ranging from about 10 to about 20% is obtained. The sample is measured after the obscuration value has stabilized. After the measurement, the system is drained and rinsed once with about 170 mL of dispersant-B, the dispersant-B is drained, and the sampling unit is refilled with about 170 mL of dispersant-B. The measurement are repeated two more times with different riffled fractions. The riffling is performed on large samples to obtain small representative particle size fractions about 15 mg in size.

The Obscuration, D(v,0.1), D(v,0.5), D(v,0.9) values are then calculated from these measurements. The average, standard deviation, and relative standard deviation (RSD) of the D(v,0.1), D(v,0.5), D(v,0.9) values is also calculated. The RSD (%) is calculated as follows:

$$RSD\ (\%) = \frac{100}{X}\left[\frac{\sum_{i=1}^{N}(X_i - \overline{X})^2}{N-1}\right]^{\frac{1}{2}}$$

where X, is an individual measurement in a set of N measurements and is the arithmetic mean of the set.

The composition disclosed herein can be in various forms, for example, in granular form. The granules that can be used in the present invention can have a granule D_{50} ranging from about 50 μm to about 150 μm, such as from about 80 μm to about 130 μm. As defined herein, the "granule D_{50}" is the particle size of the composition at the 50^{th} percentile of a particle size distribution. The granule D_{50} can readily be determined by one of ordinary skill in the art using sieve analysis techniques. Specifically, the granule D_{50} is determined according to the following procedure.

Approximately 100 g of sample is added to sieve shaker equipped with 40 mesh, 60 mesh, 80 mesh, 100 mesh, 140 mesh, 200 mesh, 325 mesh, and the bottom pan. The sieve shaker is then turned on for about 10 minutes to separate the sample according to particle size. Each sieve is weighed to determine the amount of sample retained on each sieve and the bottom pan. The individual sieve weight is normalized to generate sieve weight fraction. The individual sieve weight fraction is calculated by dividing each sieve weight with the sum of all sieve weights.

$$\text{Weight Fraction of each sieve} = \frac{\text{Weight of each sieve}}{\text{Sum of all sieves}}$$

Before the particle size calculation, the mean size range must be determined for each sieve and the bottom pan. This mean size of each sieve screen represents the mean particle size retained on the screen. The mean size of each sieve screen is determined by the hole size of the screen (lower limit) and one sieve size larger (upper limit). In the case of the 40 mesh sieve screen, the hole size of about 1410 μm is used as an upper limit. Table 1 set forth below shows the particle size range of any retained material on each screen and the mean of the particle size range.

TABLE 1

Screens	Hole size of each screen (μm)	Particle size range of retained material on each screen (μm)	Median particle size of the screen (μm)
40 mesh	425	425-1410	918
60 mesh	250	250-424	337
80 mesh	180	180-249	215
100 mesh	150	150-179	165
140 mesh	106	106-149	128
200 mesh	75	75-105	90
325 mesh	45	45-74	60
Bottom pan	0	1-44	23

The weight fraction of each sieve is added to generate cumulative frequency distribution starting from the bottom pan to 40 mesh screen. Once the cumulative frequency distribution is generated, the corresponding particle size at 10 percentile (D_{10}), 50-percentile (D_{50}), and 90-percentile (D_{90}) are determined. The particle size of the corresponding percentile is determined by linear interpolation between two consecutive data from the cumulative frequency distribution. For example, particle size of 50-percentile (D_{50}) is interpolated by,

$$D_{50}(\mu m) = \frac{[(50 - X_n) * d_{n+1} + (X_{n+1} - 50) * d_n]}{(X_{n+1} - X_n)}$$

where,

X_n=cumulative quantity of sample that is just below 50-percentile (in %);

d_n=mean of the particle size range from the sieve screen where X_n occurs (in mm);

X_{n+1}=next cumulative quantity of sample that is above 50-percentile (in %).

d_{n+1}=mean of the particle size range from the sieve screen where X_{n+1} occurs (in mm).

According to all embodiments of the present invention, the particle size of active pharmaceutical ingredient is measured according to light scattering techniques, and the particle size of the granules of composition is measured according to sieve analysis.

The compositions disclosed herein can be in a form chosen from, for example, tablets, capsules, and powders. The tablets can be made by pressing the granules into the form of tablets. The capsules can also be made using the granules.

The at least one pharmaceutically acceptable excipient can be chosen from, for example, diluents such as starch, microcrystalline cellulose, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins; binders such as povidone, hydroxypropyl methylcellulose, dihydroxy propylcellulose, and sodium carboxyl methylcellulose; and disintegrants such as crospovidone, sodium starch glycolate, croscarmellose sodium, and mixtures of any of the foregoing. The at least one pharmaceutically acceptable excipient can further be chosen from lubricants such as magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, hygrogenated vegetable oil,

glycerine fumarate and glidants such as colloidal silicon dioxide, and mixtures thereof. In some embodiments of the present invention, the at least one pharmaceutically acceptable excipient is chosen from microcrystalline cellulose, starch, talc, povidone, crospovidone, magnesium stearate, colloidal silicon dioxide, sodium dodecyl sulfate, and mixtures of any of the foregoing. The excipients of the present invention, can be intragranular, intergranular, or mixtures thereof.

In some embodiments of the present invention, the composition and/or the granules within the composition can comprise microcrystalline cellulose and starch in a weight ratio ranging from about 1:1 to about 15:1. For example, in the composition, the weight ratio of the microcrystalline cellulose and starch can range from about 1:1 to about 15:1, such as about 10:1, and in the granules within the composition, the weight ratio of the microcrystalline cellulose and starch can range from about 1:1 to about 10:1, such as about 5:1.

The microcrystalline cellulose can be present in an amount ranging from about 25% to about 85%, for example from about 50% to about 80%, or from about 60% to about 75% by weight relative to the total weight of the composition. The starch can be present in an amount ranging from about 5% to about 35%, for example, from about 5% to about 25%, or from about 5% to about 10% by weight relative to the total weight of the composition.

The compositions disclosed herein can further comprise at least one ingredient chosen from coating materials that are known in the art such as, for example, hydroxypropyl methylcellulose.

Certain compositions can comprise:

(a) from about 10% to about 40% by weight of a calcium receptor-active compound chosen from cinacalcet HCl and cinacalcet methanesulfonate;

(b) from about 45% to about 85% by weight of at least one diluent;

(c) from about 1% to about 5% by weight of at least one binder; and

(d) from about 1% to about 10% by weight of at least one disintegrant;

wherein the percentage by weight is relative to the total weight of the composition. The compositions can further comprise from about 0.05% to about 5% by weight, relative to the total weight of the composition, of at least one additive chosen from glidants, lubricants, and adherents. The composition can additionally comprise from about 1% to about 6% by weight of at least one coating material, relative to the total weight of the composition.

In another embodiment, the composition disclosed herein comprises:

(a) from about 10% to about 40% by weight of cinacalcet HCl;

(b) from about 5% to about 10% by weight of starch;

(c) from about 40% to about 75% by weight of microcrystalline cellulose;

(d) from about 1% to about 5% by weight of povidone; and

(e) from about 1% to about 10% by weight of crospovidone;

wherein the percentage by weight is relative to the total weight of the composition.

The povidone can be present in an amount ranging from about 1% to about 5%, for example, from about 1% to about 3% by weight relative to the total weight of the composition. The crospovidone can be present in an amount ranging from about 1% to about 10%, for example from about 3% to about 6%, by weight relative to the total weight of the composition.

The composition can further comprise from about 0.05% to about 5% by weight, relative to the total weight of the composition, of at least one additive chosen from colloidal silicon dioxide, magnesium stearate, talc, and the like, and mixtures of any of the foregoing. In certain embodiments of the invention, the composition comprises from about 0.05% to about 1.5% of colloidal silicon dioxide, from about 0.05% to about 1.5% of magnesium stearate, from about 0.05% to about 1.5% of talc, or mixtures of any of the foregoing. The composition can even further comprise from about 1% to about 6% by weight of at least one coating material, relative to the total weight of the composition.

As mentioned above, the compositions of certain embodiments of the present invention have a dissolution profile that results in about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition no later that about 30 minutes from the start of a dissolution test that is conducted in 0.05 N HCl in a U.S.P. 2 apparatus at a temperature of 37° C.±0.5° C. at a rotation speed of 75 r.p.m. The dissolution test is conducted using a USP 2 apparatus, and according to the dissolution protocol described in USP 26/NF 21, chapter 711, which is incorporated herein by reference. According to this embodiment using this dissolution protocol, a stated volume of the dissolution medium (±1%) is placed in the vessel of the USP 2 apparatus, the apparatus is assembled, the dissolution medium is equilibrated to 37° C.±0.5° C., the thermometer is removed, the dosage form is placed in the vessel, and the amount of active pharmaceutical ingredient that is released as a function of time is measured.

According to another embodiment of the invention, a stated volume of the dissolution medium is placed in the vessel of the USP 2 apparatus, the apparatus is assembled, the dissolution medium is equilibrated to about 37° C., the thermometer is removed, the dosage form is placed in the vessel, and the amount of active pharmaceutical ingredient that is released as a function of time is measured.

The dissolution profile represents the percentage of the active pharmaceutical ingredient released based on a target amount of the active pharmaceutical ingredient in the formulation. As used herein "target amount" refers to the amount of active pharmaceutical ingredient in each formulation. In certain embodiments, the target amount refers to the label amount and/or label claim.

USP 26/NF 21, chapter 905, defines a protocol used to determine the dosage-unit conformity according to the present invention, and this content uniformity protocol is incorporated herein by reference. According to this protocol, the content uniformity is determined by measuring the amount of active pharmaceutical ingredient in 10 dosage unit samples, and calculating whether the amount of active pharmaceutical ingredient in all the dosage unit samples falls within a range of 85% to 115% of the target amount. If one dosage unit sample is outside the range of 85% to 115% of the target amount and no unit is outside a range of 75% to 125% of the target amount, or if the Relative Standard Deviation (RSD), which is the sample standard deviation expressed as a percentage of the mean, is not greater than 6%, then 20 additional dosage unit samples are tested. After treating at least 30 dosage units, the content uniformity requirement is met if not more than one dosage unit sample is outside the range of 85% to 115% of the target amount, and no unit is outside a range of 75% to 125% of the target amount, and the RSD of the at least 30 dosage units does not exceed 7.8%.

In certain embodiments, the dissolution profile of the compositions disclosed herein can result in, for example, at least about 50%, at least about 70%, at least about 75%, or at least

about 85%, of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test. In certain embodiments, the dissolution profile of the compositions disclosed herein can comprise at most about 125%, for example at most about 115%, at most about 110%, or at most about 100% of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test. In additional embodiments, the dissolution profile of the compositions disclosed herein can comprise from about 50% to about 125%, for example from about 70% to about 110%, of the target amount of the calcium receptor-active compound being released from the composition no later than about 30 minutes from the start of the test.

Other embodiments of the present invention are directed to a method of making a pharmaceutical composition comprising:

(a) forming a granule comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and

(b) controlling the particle size of the granule such that from about 50% to about 125% of a target amount of calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37° C.±0.5° C., and a rotation speed of 75 r.p.m.

Further embodiments of the present invention are directed to a method of making a pharmaceutical composition comprising:

(b) forming a granule comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and

(b) controlling the particle size of the granule such that from about 50% to about 125% of a target amount of calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37° C., and a rotation speed of about 75 r.p.m.

The granule can be formed by any known process, such as high wet shear granulation, low wet shear granulation, fluid bed granulation, rotary granulation, extrusion-spheronization, dry granulation, roller compaction, and the like.

The particle size of the granule of the composition can be controlled by various factors. In certain embodiments of the present invention, the particle size of the granule of the composition can be controlled by the amount of water added to the materials present in a granulator. For example, a desired particle size of the granule can be achieved when the granulator has a volume ranging from about 1 L to about 1200 L, such as from about 65 L to about 1200 L, or from about 300 L to about 800 L, and the amount of water added ranges from about 20% to about 40%, such as from about 30% to about 36%, relative to the amount of dry powders present in the granulator to form the granules.

The granulator's impeller tip speed can also affect the particle size of the granules. In some embodiments, the impeller tip speed, measured in meters per second (m/s), can range from about 5 m/s to about 10 m/s, such as from about 7 m/s to about 9 m/s.

Other embodiments of the present invention are directed to a method of making a pharmaceutical composition comprising

(a) forming a composition comprising a therapeutically effective amount of particles of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and

(b) controlling the particle size of the calcium receptor-active compound such that from about 50% to about 125% of a target amount of the calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37° C.±0.5° C., and a rotation speed of 75 r.p.m.

Additional embodiments of the present invention are directed to a method of making a pharmaceutical composition comprising

(a) forming a composition comprising a therapeutically effective amount of particles of a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein; and

(b) controlling the particle size of the calcium receptor-active compound such that from about 50% to about 125% of a target amount of the calcium receptor-active compound is released from the composition no later than about 30 minutes from the start of a test in 0.05 N HCl according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37° C., and a rotation speed of about 75 r.p.m.

The size of the particles is controlled during the production of the active pharmaceutical ingredient, for example, by use of a milling step, or a controlled crystallization process. For example, the active pharmaceutical ingredient can be milled using a stainless steel hammer mill with 5 mm screen and 12 hammers forward at a mill speed of 8100±100 rpm, with the feed speed is set at 90±10 rpm.

Yet other embodiments of the present invention are directed to a method for the treatment of a disease or disorder that can be treated by altering a subject's calcium receptor activity. In some embodiments, a method for the treatment of a disease chosen from hyperparathyroidism, such as primary hyperparathyroidism and secondary hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium-phosphorus product comprises administering to a patient, such as human, an effective dosage amount of a pharmaceutical composition comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in a USP 2 apparatus at a temperature of 37° C.±0.5° C., and at a rotation speed of 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition in no later than about 30 minutes from the start of the test.

A further embodiment of the present invention is directed to a method for the treatment of a disease chosen from hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium-phosphorus product comprises administering to a patient, such as human, an effective dosage amount of a pharmaceutical composition comprising a calcium receptor-active compound and at least one pharmaceutically acceptable excipient as disclosed herein, wherein the composition has a dissolution profile in 0.05 N HCl, measured according to a dissolution test conducted in a USP 2 apparatus at a temperature of about 37° C., and at a rotation speed of about 75 r.p.m., which comprises from about 50% to about 125% of a target amount of the calcium receptor-active compound being released from the composition in no later than about 30 minutes from the start of the test.

Reference will now be made to the following examples which are not intended to limit the invention. To the contrary,

it will be appreciated that various alternatives, modifications, and equivalents may be included within the spirit and scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**: A process Flow diagram showing a process by which 30-, 60- and 90-mg tablets of active pharmaceutical ingredient are prepared.

EXAMPLES

Three pharmaceutical formulations with target amounts of 30 mg, 60 mg, and 90 mg active pharmaceutical ingredient with the following components were prepared:

	Weight % (w/w)	30 mg Tablet Amount (mg)	60 mg Tablet Amount (mg)	90 mg Tablet Amount (mg)
Cinacalcet HCl	18.367	33.06	66.12	99.18
Pregelatinized starch (Starch 1500)	33.378	60.08	120.16	180.24
Microcrystalline cellulose (Avicel PH102)	6.678	12.02	24.04	36.06
Povidone (Plasdone K29/32)	2.044	3.68	7.36	11.04
Crospovidone (Polyplasdone XL)	1.233	2.22	4.44	6.66
Purified Water[1]	—	—	—	—
Microcrystalline cellulose (Avicel PH102)	34.300	61.74	123.48	185.22
Magnesium stearate	0.500	0.90	1.80	2.70
Colloidal silicon dioxide (Colloidal anhydrous silica) (Cab-O-Sil M5P)	0.500	0.90	1.80	2.70
Crospovidone (Polyplasdone XL)	3.000	5.40	10.80	16.20
Core Tablet	100.000	180.00	360.00	540.00
Purified Water[1]	—	—	—	—
Opadry ® II (colored film former)	4.000	7.20	14.40	21.60
Purified Water[1]	—	—	—	—
Opadry ® Clear (clear film former)	1.500	2.70	5.40	8.10
Carnauba Wax Powder	0.010	0.018	0.036	0.054
Opacode ® Ink (Black)[2] 1	—	—	—	—

[1]The purified Water was removed during processing.
[2]Trace quantities of ink were applied to the coated tablet.

The wet granulation process was conducted in a PMA 800 L high-shear granulator with water serving as the granulation fluid. The cinacalcet HCl and the intra-granulation excipients (pregelatinized starch, microcrystalline cellulose, povidone, and crospovidone) were dry-mixed for 1 to 2 minutes with an impeller speed set point at 116±10 rpm, followed by granulation with 30.0% to 36.0% w/w water (based on intra-granular lot size; target was 34.9% w/w) with an impeller speed set point at 116±10 rpm and at a slow or fast chopper speed (target was slow speed). During the granulation process water was delivered at 9.8±0.5 kg/min.

Following granulation, the mixture was wet-milled using an in-line Comil equipped with a 0.375" (0.953 cm) opening screen and an impeller speed set point at 1400±50 rpm. The mixture was then discharged into a fluid-bed dryer.

After completion of the wet-milling process, the granulation mixture was dried in an Aeromatic MP6 fluid bed dryer with an inlet temperature set point at 70°±5° C. When the outlet temperature reached 37° C. to 41° C., samples were taken to determine moisture levels by loss on drying (LOD). The granules were dried until the average moisture levels reached 1.0% to 2.5%.

The dried granulation mixture was milled through a Quadro Mill 196S (Comil) equipped with a 0.055" (0.140 cm) opening screen at an impeller speed of 1650±50 rpm into a 1000 L Gallay tote.

Except for magnesium stearate, the extra-granular excipients were blended in a 650 L Gallay tote blender for 7±1 minutes at 12±1 rpm. This mixture was further blended with the dry-milled granulation in a 1000 L Gallay tote blender for 15±5 minutes at 12±1 rpm, and then for 6±1 minutes at 12±1 rpm after magnesium stearate was added for lubrication.

The final lubricated blend was compressed into tablets containing 30-, 60-, or 90 mg of the free base equivalent of active cinacalcet HCl using a Unipress 27 tablet press set to a speed of 2000±300 tablets per minute and equipped with a force feeder. Throughout the compression operation, individual tablet weights (target weights of 180, 360, and 540 mg for 30-, 60-, and 90-mg tablets, respectively), the average weight of 10 tablets, tablet hardness and thickness were monitored at pre-determined intervals.

The color-coating suspension and clear-coating solution were prepared by slowly adding either the Opadry® II (green) or Opadry® Clear into purified water while mixing until uniform (≥45 minutes). The color suspension and clear solution deaerated for ≥45 minutes before the spraying process began, and were used within a pre-determined time limit.

Each lot was film-coated with color and clear coats in a Vector Hi-Coater 48" pan. The color-coating suspension was applied onto a moving core tablet bed (pan speed=4 to 7 rpm) and a spray rate of 250±50 grams per minute per 3 guns. The distance between the spray guns and the tablet bed was approximately 8" (20 cm) to 11" (28 cm), and the air volume was 600±200 ft^3 per minute (17.1±5.7 m^3 per minute) with a pan pressure differential maintained between −0.1" (−0.25 cm) to −0.3" (−0.76 cm) of water. Supply air temperature was adjusted to 80±10° C. to maintain an exhaust temperature of 41±3° C.

When the clear-coating application was completed, the heater and the air supply was turned off and the wax was spread evenly over the moving tablet bed (after it reached ≤37° C.) with a pan speed of 4 to 7 rpm. The tablets were rotated for 5±1 minutes, and after the supply air and exhaust fan were turned on, the tablets were rotated for an additional 5±1 minutes with a pan speed of 4 to 7 rpm and supply air of 600±200 ft^3 per minute (17.1±5.7 m^3 per minute). The pan was jogged until the tablet bed temperature reached ≤30° C.

An Ackley ink-based offset printer was used to produce 2-sided printed tablets.

The dissolution profile of the three formulations were measured according the dissolution protocol described in the USP 26/NF 21, chapter 711 using a USP 2 apparatus at a temperature of about 37° C., and at a rotation speed of about 75 r.p.m. The dissolution profile of the formulations in which at least about 75% of the cinacalcet HCl was released from the composition in no later than about 30 minutes from the start of the test is set forth in Table 2.

TABLE 2

Time (min)	30 mg Tablet	60 mg Tablet	90 mg Tablet
15	85.3	81.9	80.8
30	95.2	93.8	93.4
45	97.7	97.7	97.9
60	98.7	98.8	99.8

The content uniformity of the three formulations were measured in accordance with USP 26/NF 21, chapter 905,

described in detail above. The content uniformity and for each of the three formulations is set forth in Table 3.

TABLE 3

	30 mg Tablet		60 mg Tablet		90 mg Tablet	
Container	Mean (10 tablets)	% RSD	Mean (10 tablets)	% RSD	Mean (10 tablets)	% RSD
1 (beg.)	98.5	0.8	96.7	1.6	99.7	1.2
5	98.8	0.8	98.5	0.8	100.7	0.9
11	98.5	0.6	98.3	1.0	99.9	0.7
16	98.3	0.8	97.6	1.3	99.9	0.5
22	98.3	1.0	96.3	1.8	100.7	0.9
end	98.0	0.6	95.8	1.9	99.3	0.8

What is claimed is:

1. A pharmaceutical composition comprising:

(a) from about 10% to about 40% by weight of cinacalcet HCl in an amount of from about 20 mg to about 100 mg;

(b) from about 45% to about 85% by weight of a diluent selected from the group consisting of microcrystalline cellulose, starch, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof,

(c) from about 1% to about 5% by weight of at least one binder selected from the group consisting of povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof; and

(d) from about 1% to 10% by weight of at least one disintegrant selected from the group consisting of crospovidine, sodium starch glycolate, croscarmellose sodium, and mixtures thereof,

wherein the percentage by weight is relative to the total weight of the composition, and wherein the composition is for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

2. The composition according to claim **1**, further comprising at least one excipient selected from the group consisting of lubricants and clear and color coating materials.

3. The composition according to claim **1**, further comprising from about 1% to about 6% by weight of at least one coating material selected from the group consisting of clear and color coating materials wherein the percentage by weight is relative to the total weight of the composition.

4. The composition according to claim **1**, further comprising from about 0.05% to about 5% of at least one additive selected from the group consisting of glidants, lubricants and adherents, wherein the percentage by weight is relative to the total weight of the composition.

5. The composition according to claim **1**, wherein the at least one binder is povidone.

6. The composition according to claim **1**, wherein the at least one disintegrant is crospovidone.

7. The composition according to claim **6** wherein the form of the cinacalcet HCl is selected from the group consisting of needle-shape particles, rod-shape particles, plate-shaped particles, and mixtures thereof.

8. The composition according to claim **1**, wherein the cinacalcet HCl is in a form selected from the group consisting of amorphous powders, crystalline particles, and mixtures thereof.

9. The composition according to claim **8** wherein the particle D_{50} of the cinacalcet HCl particles is less than or equal to about 50 μm.

10. The composition according to claim **9**, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 50 μm to about 150 μm.

11. The composition according to claim **9**, wherein the granules have a granule D_{50} measured using a sieve analysis ranging from about 80 μm to about 130 μm.

12. The composition according to claim **11**, wherein the crospovidone is present intergranularly.

13. The composition according to claim **11**, wherein the crospovidone is present intragranularly.

14. The composition according to claim **9**, wherein the disintegrant is crospovidone and the crospovidone is present intergranularly, intragranularly, or a combination thereof.

15. The composition according to claim **1** wherein the composition comprises granules.

16. The composition according to claim **1** further comprising from about 0.05% to about 1.5% by weight of colloidal silicon dioxide relative to the total weight of the composition.

17. The composition according to claim **1** further comprising from about 0.05% to about 1.5% by weight of magnesium stearate relative to the total weight of the composition.

18. The composition according to claim **1**, wherein the hyperparathyroidism is primary hyperparathyroidism or secondary hyperparathyroidism.

19. The composition according to claim **1**, wherein the diluent is microcrystalline cellulose or starch.

20. A pharmaceutical composition comprising:

(a) from about 10% to about 40% by weight of cinacalcet HCl in an amount of from about 20 mg to about 100 mg;

(b) from about 45% to about 85% by weight of a diluent selected from the group consisting of microcrystalline cellulose, starch, dicalcium phosphate, lactose, sorbitol, mannitol, sucrose, methyl dextrins, and mixtures thereof,

(c) from about 1% to about 5% by weight of at least one binder selected from the group consisting of povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethylcellulose, and mixtures thereof; and

(d) from about 1% to 10% by weight of at least one disintegrant selected from the group consisting of crospovidine, sodium starch glycolate, croscarmellose sodium, and mixtures thereof,

wherein the disintegrant is at least present intragranularly and wherein the composition is for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

21. A pharmaceutical composition comprising:

(a) from about 10% to about 40% by weight of cinacalcet HCl in an amount of from about 20 mg to about 100 mg;

(b) from about 5% to about 10% by weight of starch;

(b) from about 40% to about 75% by weight of microcrystalline cellulose,

(c) from about 1% to about 5% by weight of povidone, and

(d) from about 1% to 10% by weight of crospovidone,

wherein the percentage by weight is relative to the total weight of the composition, and wherein the composition is for the treatment of at least one of hyperparathyroidism, hyperphosphonia, hypercalcemia, and elevated calcium phosphorus product.

22. The composition according to claim **21** further comprising from about 0.05% to about 1.5% by weight of colloidal silicon dioxide relative to the total weight of the composition.

23. The composition according to claim **21** further comprising from about 0.05% to about 1.5% by weight of magnesium stearate relative to the total weight of the composition.

* * * * *

ADD-1 through ADD-42 Removed Due To Confidential Material

CERTIFICATE OF SERVICE

I hereby certify that on June 24, 2019, a true and correct copy of the foregoing was timely filed with the Clerk of the Court using the appellate CM/ECF system. I further certify that I caused a copy of the confidential version to be served on all parties by email at the email addresses listed below.

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 32(a)(7)(B) and the Rules of this Court, because it contains 11,781 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii).

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